GENERIC ENTRY IN PRESCRIPTION MEDICINES IN THE EU:

MAIN CHARACTERISTICS, DETERMINANTS AND EFFECTS*

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1. Introduction

On 8 July 2009 the European Commission adopted the Final Report on its competition inquiry into the pharmaceutical sector[1]. The aim of competition inquiries is to allow the Commission to gain a more complete understanding of sectors where it believes that competition problems may be present.

One of the objectives of the inquiry was to examine the reasons for observed delays in the entry of generic medicines to the markets of prescription medicines after loss of exclusivity by the originator company. The inquiry concentrated on those practices that originator incumbent companies may use to block or delay such entry: e.g., concluding settlement agreements with potential generic entrants ("pay-to-delay"), using the patent system unduly to extend protection on the product, and intervening at the level of national marketing authorisation bodies and pricing and reimbursement bodies with a view to delay entry after the product's loss of exclusivity. The Commission collected and analysed a great deal of information for this purpose, including internal strategy documents of companies, to gain a better insight into the companies' general market behaviour.

The Chief Economist Team (CET) conducted an extensive quantitative analysis aimed at analysing the extent and timing of generic entry in European markets, the level of generic penetration and the effect of such penetration on the average price of drugs. Such analysis was based on data covering a very comprehensive sample of prescription medicines facing loss of exclusivity in the period between 2000 and 2007, selected on the basis of the overall turnover generated. The data used were in part collected from pharmaceutical companies in the context of the sector inquiry, in part provided by IMS Health, a provider of pharmaceutical data services.[2]

The CET contribution, as well as the whole inquiry, also devoted particular attention to the regulatory framework in place in the different Member States with respect to the introduction of bioequivalent medicines into the market and generic substitution. Information about the introduction and possible modification over time of specific policies aimed at fostering generic entry was collected for all the 27 Member States and for the period under scrutiny.

Section 2 of this paper provides a description of the data used by the CET in the analysis and presents descriptive statistics on the pattern, timing and effect of generic entry at the level of Member States and on the aggregate EU level. Section 3 provides the main results of the econometric analyses undertaken by the CET in the context of the pharmaceutical sector

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1 Available at http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/index.html.

2 Data and other information from IMS Health (IMS), a provider of pharmaceutical data services, which are cited or used in this paper (including the empirical analysis performed by the Commission) were obtained by the Commission pursuant to Article 18 of Council Regulation 1/2003. IMS has not acted as an advisor, expert, or consultant in connection with this paper or, more generally, in connection with the pharmaceutical sector inquiry. Further references to IMS in this report should be understood in the same way.

inquiry. Section 3.1 describes the analysis of the main determinants of the pattern of generic entry in terms of the occurrence and the number of entrants. Section 3.2 explores the main determinants of time to entry. Section 3.3 describes the analysis of the main determinants of the effect of generic entry in terms of prices and market penetration. Finally, Section 3.4 analyses the effects of generic entry on other INNs[3] present in the ATC4 class.

2. Data description and descriptive analysis

2.1. Data and selection of INNs

The data used by the CET in the present work stems from two main sources.

First, an extensive data set was received from pharmaceutical companies in the context of the sector inquiry. All data from the companies were gathered for each of the 27 EU Member States, except for price data, which covered only ten countries: Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Spain and the United Kingdom.

Second, the Commission has used data requested from IMS Health. IMS data were obtained for all 27 Member States. The data obtained from IMS included, for the period 2000 – 2007 and for each company active in the INN concerned, monthly data on sales (local currency), volumes, prices and discounts (local currency) at the pack level, as well as loss of exclusivity and launch dates. For some Member States, IMS data were also available as regards the level of promotional activity at the brand level (on a quarterly basis). The emphasis has been given to sales and prices at the ex-manufacturer level, as they directly relate to the companies being the focus of the sector inquiry. Finally, for the ten countries mentioned above, IMS data were also obtained for all INNs belonging to ATC4 classes, within which loss of exclusivity took place in the period 2000 – 2007.

Both data sets were merged to create a comprehensive set of information about INNs which lost exclusivity between 2000 and 2007. It went through the following cleaning process. To eliminate possible inconsistencies, a number of companies were asked for data corrections and additional information on the presence of SPCs and data protection. Further, in a number of cases entry dates did not reflect entry by independent generic companies, but rather the launch of a company's own generic product or the launch of a product by companies authorised to do so by the originator company, e.g. as part of a distribution or licence agreement (see below). These entry dates were corrected to reflect entry of independent generic producers.

For each INN, the date of loss of exclusivity in the country concerned was defined as earlier of the two: the date at which the first product based on the INN lost patent protection (including Supplementary Protection Certificate) or the date at which the INN seized to be protected by data exclusivity.[4] This applied to all INNs for which this information was

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[3] "INN" is the International Non-proprietary Name for pharmaceutical substances. A combination product and each of the related mono-products are viewed as separate INNs.

[4] During the public consultation which followed the publication of the preliminary report, it was submitted that for the purposes of measuring delays to generic entry caused by the behaviour of originator companies, the loss of patent protection (or SPC protection) cannot be compared with the loss of data

provided by the companies. IMS only reported a single date (month and year) for the date of loss of exclusivity, but its definition of loss of exclusivity is based on the same principles.[5] Finally, in a number of cases, a given INN is used for distinct medical indications and is part of several distinct ATC classes. These cases have been treated separately as the loss of exclusivity and/or entry date for a given INN may differ across ATC.

The date of first generic entry was established on the basis of the first occurrence of sales by generic companies as recorded in the IMS sales data set, combined with information provided by the companies.

Consumption volumes of the various formulations relating to given INNs were converted into DDD (Daily Defined Dosage) in order to compare volume measures across different products (formulations) based on the same INN. This conversion was made using a data set obtained from the World Health Organisation. For the small number of formulations for which this information was not available, volumes in mg were used to the extent possible for the volume analysis at INN level.

Information on the regulatory framework in the various Member States was compiled on the basis of the Öbig report of 2006[6], the answers given by the authorities of the Member States to the Commission questionnaire of July 2008, information from the Pharma Forum, as well as other sources.[7]

Sample selection

The selection of the sample was pursued with the objective of obtaining the broadest possible view on the INNs facing loss of exclusivity in the period 2000-2007. Three criteria were used in the sample selection process: (i) loss of exclusivity in the period 2000-2007, (ii) total turnover generated by the INN, (iii) occurrence of possible generic entry in the period 2000-2007. Due to data availability, the selection was done for INNs sold in three Member States (France, Germany and the United Kingdom) in the period 2000-2007.

The first list of INNs selected were the 75 top-selling INNs that faced the loss of exclusivity (e.g. patent/IP expiry, data exclusivity) in the period 2000 – 2007 in France, Germany and the UK. In each of the three Member States, this list represented well over 90% of value sales of all INNs that faced loss of exclusivity in the period 2000 – 2007. The combination of the top

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protection given that generic companies were, during the reference period 2000 – 2007, only able to submit abridged applications for marketing authorisation to the competent authorities after the moment of loss data protection. However, the concept of time to entry is not confined to delays to generic entry caused by the behaviour of originator companies, but also comprises other factors such as the time that generic companies need for standard regulatory procedures in the country concerned (including requests relating to the pricing and reimbursement status). In any event, the number of instances (INNs and countries) in which loss of data protection came after patent expiry (including SPC protection) was 52, out of a total of 713 for which it was possible to make the comparison. It appears, therefore, that the impact of these cases is rather limited on the descriptive statistics.

5 For a description of the determination of the loss of exclusivity date by IMS, see CRA International, *Factors Affecting Generic Entry in Europe*, June 2008.

6 Öbig - Österreichisches Bundesinstitut Für Gesundheitswesen, *Surveying, Assessing and Analysing the Pharmaceutical Sector in the 25 EU Member States*, 2006.

7 Information was coded for each year between 2000 and 2007, taking into account possible evolutions in the different regulatory systems.

75 molecules in each of these Member States provided a final list of 128 INNs. In this paper, this list is referred to as "E75".

The second group of INNs was chosen from the list of the 50 top-selling INNs (whether protected or not) for each of the three Member States mentioned above. In total, this led to the identification of 90 INNs (of which 61 INNs were not part of the E75 list). It is referred to as "T50".

The third group of INNs was selected by choosing the 50 top-selling INNs having faced (possible) first generic entry in each of the selected countries. This led to the identification of 95 INNs (30 new INNs in comparison with the E75 and T50 lists mentioned above). Finally, the list contained a number of INNs that might be of interest in the light of other market information available to the Commission.

The combination of these three lists, with a view to obtaining a sample of INNs likely to be representative for the EU as a whole, makes up the final list of 219 INNs presented in table D (annex).

The main part of the analysis was performed on the basis of the "E75" list of INNs for which the Commission requested information from the companies.

For each of the Member States, the relevant sample was defined as the national subset of the E75 list, i.e. those INNs that (i) were effectively sold in that Member State and (ii) that faced loss of exclusivity in the period 2000 – 2007 in that Member State.

As the result, based on the IMS data set, the national subsets of INNs in the various Member States contained the following numbers of INNs.[8]

Table 1: Number of INNs on the E75 list relevant to each Member State

AT	68	**DE**	82	**NL**	25*
BE	75	**EL**	38	**PL**	-
BG	-	**HU**	-	**PT**	35
CZ	15	**IE**	55	**RO**	-
CY	-	**IT**	71	**SK**	-
DK	63	**LV**	-	**SI**	-
EE	-	**LT**	-	**SP**	51
FI	56	**LU**	-	**SE**	71
FR	93	**MT**	-	**UK**	84

Source: IMS data

As is clear from the above table, there are major disparities between the subsets of molecules that were subject to analysis. This is a natural consequence of significant disparities between

[8] The dashes (-) in the table relate to the fact that, as indicated above under "Data sources", the IMS data set did not contain expiry dates for these countries. (*) The fact that the number of expiring INNs for the Netherlands is somewhat low is related to the fact that data for the Netherlands are available only as of April 2002.

the national markets for pharmaceutical products in the EU.[9,10] The differences are explained in part by the fact that the set of INNs sold in each country differs. Further, the differences relate to the period considered and the fact that INNs may have different loss of exclusivity dates in different Member States. For a given Member State, if an INN lost exclusivity before the year 2000 or after 2007, it was excluded from the sample. Consequently, the requirements (i) and (ii) mentioned in the previous paragraph resulted in subsets of molecules that were different (in size and composition) among the various Member States.[11]

After merging company information with IMS data set, the number of INNs that could be used for the analysis in a number of countries changed to a mild extent.[12] The merged data set led to national subsets of INNs in the various Member States with the following numbers of INNs:

Table 2: Number of INNs on the E75 list relevant to each Member State

AT	61	**DE**	75	**NL**	25
BE	73	**EL**	38	**PL**	5
BG	14	**HU**	17	**PT**	35
CZ	15	**IE**	59	**RO**	11
CY	-	**IT**	73	**SK**	5
DK	63	**LV**	3	**SI**	6
EE	1	**LT**	4	**SP**	51
FI	48	**LU**	41	**SE**	76
FR	91	**MT**	-	**UK**	83

Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Only a few INNs were available for study in Slovakia, Slovenia, Poland, Latvia, Lithuania, Estonia, Cyprus and Malta. A contributing factor to the relatively low number of observations may be that few INNs may have effectively faced loss of exclusivity in the relevant period 2000 – 2007 in the countries concerned. However, a substantial number of companies

9 For similar observations, see CRA International, *Factors Affecting Generic Entry in Europe*, June 2008. CRA observes that of the 271 molecules that lost protection in the period 2000 – 2007 in one of the five largest national markets for pharmaceutical consumption in the EU (namely France, Germany, Italy, Spain, and United Kingdom) only 30 of them lost protection (in the same time frame, 2000-2007) in all five countries.

10 A factor that may also have contributed to the disparities may be that, as set out above under "Data sources", IMS expiry dates were sometimes only available for some of the relevant products within the countries, not for all products.

11 Focusing on products with the majority of their sales in the retail segment, CRA (2008) reports that the total number of products losing exclusivity in the period 2000-2007 was 105 in the UK, 143 in France, 114 in Germany, 106 in Spain and 141 in Italy. In each of these countries, the top 50 of the products losing exclusivity in the period 2000 – 2007 (in terms of value) accounted for over 85-90% of sales of all products losing exclusivity. CRA International, *Factors Affecting Generic Entry in Europe*, June 2008 (p. 23-24).

12 In the public consultations, it was noted that the number of INNs went slightly down in some countries. It is primarily because by applying company information the loss of exclusivity date was revised to a date falling outside the reference period 2000 – 2007. Further additional data cleaning led some INNs to be removed from the lists in some countries.

appeared unable to provide comprehensive information on the patent expiry date in these countries (many entries contained "N/A"). Further, the process of merging the company data with the IMS data turned out – from a technical perspective – less successful than for the other Member States. For this reason, Section 2.2 does not contain descriptive statistics for these countries.

The number of available observations (INNs) for Romania and Bulgaria, who became Member States in 2007, is also small. Further, there were data issues in the information provided for these countries. For this reason, Section 2.2 does not contain descriptive statistics for these two countries.

Correspondingly, the analysis was based on 17 countries, i.e. all EU Member States with the exception of Slovakia, Slovenia, Poland, Latvia, Lithuania, Estonia, Cyprus, Malta, Romania and Bulgaria.

The various types of analysis further differed in terms of data requirements. The regression analyses involved the simultaneous use of price data, volume data (in DDD), dates (date of loss of exclusivity, entry date) and qualitative information (product characteristics, characteristics of the regulatory environment). For six INNs, such comprehensive information was not available and therefore they were not used for the regression analysis.

Ultimately, the principal data set used for the regression analyses was based on 1085 observations in total (cross-sectional, by country-INN-ATC4), relating to 17 countries, 122 INNs and 924 country-INN pairs.

The analysis of substitution within ATC4 classes presented in section 3.4 was performed on the data available in 9 countries (Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Spain and the United Kingdom), i.e. all countries for which information on ATC4 classes was obtained from IMS with the exception of Poland (see above).

Measures Analysed

All EU statistics (entry rates, market shares, price indices, etc.) presented below are calculated taking into account the relative importance of the individual Member States as measured by the sales of the relevant INNs in the Member State concerned, either in the year prior to expiry (for establishing shares of generic entry, average time to entry and generic penetration) or in the year 2007 (for the indices that track the development of prices or volumes over longer time periods).

The rate used for the conversion of exchange rates is the average exchange rate in the year 2007.[13]

Descriptive statistics on the impact of generic entry are mostly presented both as a “head count” measure (where within each country each INN in counted as equal) and as a weighted measure (where within each country each INN receives a weight to account for its relative

[13] For consistency, prices and values in the data set were expressed in Euro terms for all countries. In order to properly identify developments in local currency prices and values in a given country over time, it was decided to apply a fixed conversion rate (relating to 2007), not contemporaneous, fluctuating rates.

importance).[14] Two types of weights are used for the latter purpose, depending on the context. For the purposes of establishing shares of generic entry, average time to entry and generic penetration, the weight is the sales value of an INN in the year before the loss of exclusivity. This weight is constant over time. By contrast, for the indices that track the development of prices over longer time periods, the weight used is the contemporary value sales of each INN sold in the month concerned. The use of contemporary weights (as opposed to constant weights, e.g. related to a fixed year) avoids problems one might encounter in relation to months where a given product is in fact non-available. The same approach is used for tracking volume indices over time.

When descriptive statistics were given by size class, the following approach was used. First, the 128 INNs on the E75 list were divided into five classes, with class one referring to the 20% of lowest-selling INNs in terms of EU sales value in 2007, class two to the next lowest 20%, etc. Class five thus refers to the 20% of highest-selling INNs on the E75 list. Then, for each INN, the relevant statistic in each country was obtained and weighted using country weights. Finally, within each size class, the weighted average was taken over all INNs in that class.

For the average price indices, the index level is set to 1 (i.e. unity) six months prior to the end of the exclusivity period. The benchmark was taken 6 months prior to the end of the exclusivity period instead of at the very moment exclusivity ended in order not to let incidental price cuts or small errors in the date of expiry influence the benchmark price level.

The same approach is used for the volume indices.

Treatment of Early Entries

The measurement of time to entry was complicated by the fact that in the IMS data set there was a number of instances, where generic products appeared to have entered before the loss of exclusivity of the INN in the country concerned. For those INNs, for which the entry date appeared to be just preceding the loss of exclusivity, the small time gap can be interpreted as a measurement error. The INNs with a longer time gap are more difficult to interpret. These instances may relate to cases where the companies made a mistake when providing the date of loss of exclusivity, where the IMS data set records the date incorrectly or where there was an "early" entry by a generic firm, i.e. entry before the reported date of loss of exclusivity.

The accuracy of the entry dates was improved using information on independent generic entry from the companies. Whenever the originator company indicated a later date for the first independent entry than the presumed entry date on the basis of IMS data, this later date was used as the date of the first independent generic entry.

Where the dates continued to point to early entry, the observations were further compared with a data set prepared by CRA and IMS in the course of the sector inquiry.[15] Where this

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[14] As mentioned above, in a number of cases, INNs are used for distinct medical indications and are part of several distinct ATC classes. These cases have been treated separately as the loss of exclusivity and/or entry date for a given INN may differ across ATC, except in the case of headcount measures (as the importance of individual INNs would be inflated when it is part of multiple ATC classes).

[15] Data set used for the preparation of the report *Competition in the off-patent market post generic entry*, CRA International and IMS, September 2008; report prepared for EFPIA.

data set gave a more plausible date of loss of exclusivity and/or entry date, this date was used. Where the INN was not considered as expiring in the country concerned in the period 2000-2007, the country-INN pair was dropped from the analysis. For the still remaining cases with negative time to entry, the following procedure was used.

Where the negative time to entry was less than or equal to three months ("small negatives"), the time to entry was taken to be zero, on the basis that these cases may represent a small measurement error. This related to 55 cases (country-INN pairs).

Where the negative time to entry was more than three months ("substantial negatives"), the time to entry was also put to zero. This related to 39 cases (country-INN pairs). In view of the limited number of cases, such treatment of these observations is not per se problematic for the analysis, but its correctness depends on certain assumptions. For the so-called controlled entries (e.g. companies entering via distribution agreement or licence – see below), it would have to be assumed that these entrants turn effectively independent at the loss of exclusivity (because they are no longer restricted by patents), which is not necessarily the case. In cases of "early entry" due to an incorrectly specified loss of exclusivity date, it is not clear whether entry really took place early (i.e. before the date of loss of exclusivity), took place at the first moment the opportunity arose (i.e. at loss of exclusivity), or took place later (i.e. after the real moment of loss of exclusivity). For the purpose of obtaining conservative estimates and not overstating the time to entry for generic companies, the Commission services opted for the interpretation that entry took place at the first moment the opportunity arose (i.e. at the loss of exclusivity).

In the regression analysis, the cases involving "substantial negative" time to entry were flagged (using dummies) and analysed further. Further robustness checks suggest that the results are insensitive to the method used (see below).

Information on company agreements further shed light on some of the remaining substantial negatives. A number of supply/distribution and settlement agreements whereby originator companies allowed early entry to a generic company were used to interpret significant negative delays. These cases, 20 in total, were interpreted as a form of controlled entry. In the subsequent regression analyses, they have been specifically flagged with a dummy variable.

The above procedures for treating early entries were tested for robustness (both as regards the descriptive statistics and the regression results). Checking the robustness of the results vis-à-vis the above handling of early entries was done by

- running the regression analysis both with and without the observations with the negative time to entry;

- changing the number of months above which an entry is regarded as substantial negative time to entry (e.g. taking 6 months as a threshold) and running the analysis without country-INN pairs exhibiting a relatively substantial negative time to entry;

- using a dummy variable to indicate whether or not the country-INN pair is a substantial negative time to entry.

These tests confirmed the robustness of the results towards the applied procedures.

2.2. Descriptive analysis

This section provides detailed descriptive statistics and graphs on generic entry and its effects in the data set at disposal. Given the purpose of the analysis, the sample used is "E75". The sample or sub-sample used in any of the calculations in nevertheless reported on top of each graph and table.

2.2.1. Extent of generic entry

Table 3 shows, for the EU as a whole[16], the share of INNs in the sample that faced generic entry over the period 2000 – 2007. All shares are presented both as a head count (where within each country each INN is counted as one; left-hand column) and in value terms (where within each country weights are given to the INN in relation to their sales value in the year before loss of exclusivity; right-hand column).

Table 3: Share of INNs that faced generic entry following loss of exclusivity (EU average; sample: E75-list)

	Entry share (head count)	Value share entry
Entire sample; entire period	66%	85%
Measured one year after loss of exclusivity (entire sample)	47%	70%
Measured one year after loss of exclusivity (INNs expired in 2000-2006)	46%	69%
Measured two years after loss of exclusivity (INNs expired in 2000-2005)	54%	80%

Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

The first row in the table gives the occurrence of entry for the entire sample of 128 INNs on the E75-list, irrespective of when in the period the INN lost exclusivity or generic entry took place. As can be seen, the share of INNs in the overall sample that faced generic entry at any point in time over the period 2000 – 2007 is about 66% in number terms and about 85% in value terms.

These shares may be somewhat difficult to interpret, however, in that not all INNs are in an equal position. For instance, if those INNs lost exclusivity early in the period 2000 – 2007, that left a long time for entry to occur within the period under investigation. By contrast, for INNs which lost exclusivity late in the period (e.g. in autumn of 2007), little time is left for entry to occur and – even if they were relatively quick – instances of generic entry might not be counted for these INNs. For this reason, the table also indicates the shares of INNs for which entry took place within one year, both for the entire sample (second row, mainly for comparison) and the sample which lost exclusivity up to 2006 (third row). It also indicates for

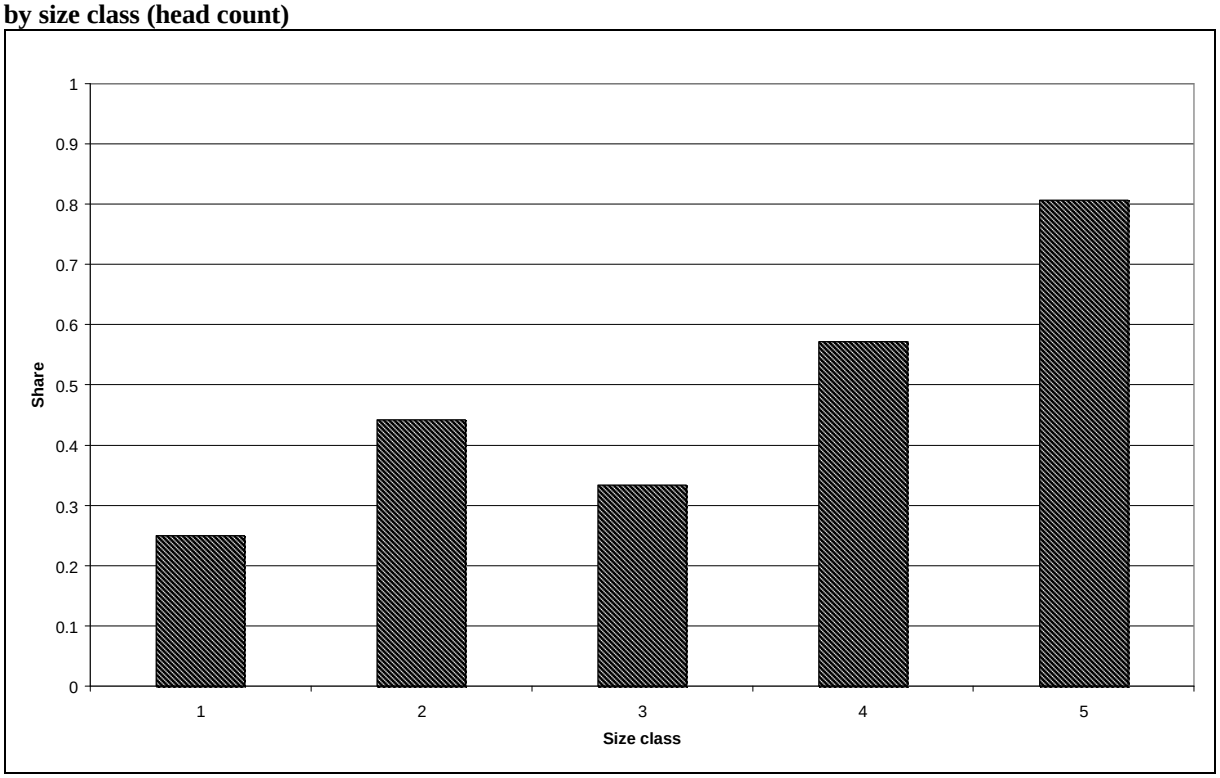
[16] All EU averages in this section are calculated taking into account the relative weight of the individual Member States, i.e. measured by sales of the relevant INNs in the Member State concerned, either in the year prior to expiry (for establishing shares of generic entry, average time to entry and generic penetration) or in the year 2007 (for the indices that track the development of prices or volumes over longer time periods).

this sample, the shares of INNs for which entry took place within two years (for loss of exclusivity up to 2005).

The table shows that, focusing on patents which expired between 2000 and 2006 followed by entry within one year, the share of INNs that faced generic entry is about 46%. However, taking into account the importance of the INNs (in terms of sales), the entry share is higher, at 69%.

This last finding suggests that generic entry tends to concentrate especially on INNs with a high sales value. This pattern can also be seen to some extent in Figure 1 below, which sets out the share of generic entry for individual size classes. The set of INNs is split into five size classes, with class 1 containing the 20% of smallest INNs (in terms of their sales value in the year prior to expiry), class 2 the next smallest 20%, etc. Class 5 therefore contains the 20% of largest-selling INNs. On average, the share of generic entry appears higher for the larger size classes than for the smaller ones. This can be explained by higher incentives for the generics to enter. Obviously, from the perspective of consumer welfare, generic entry without delay for this category is most valuable.

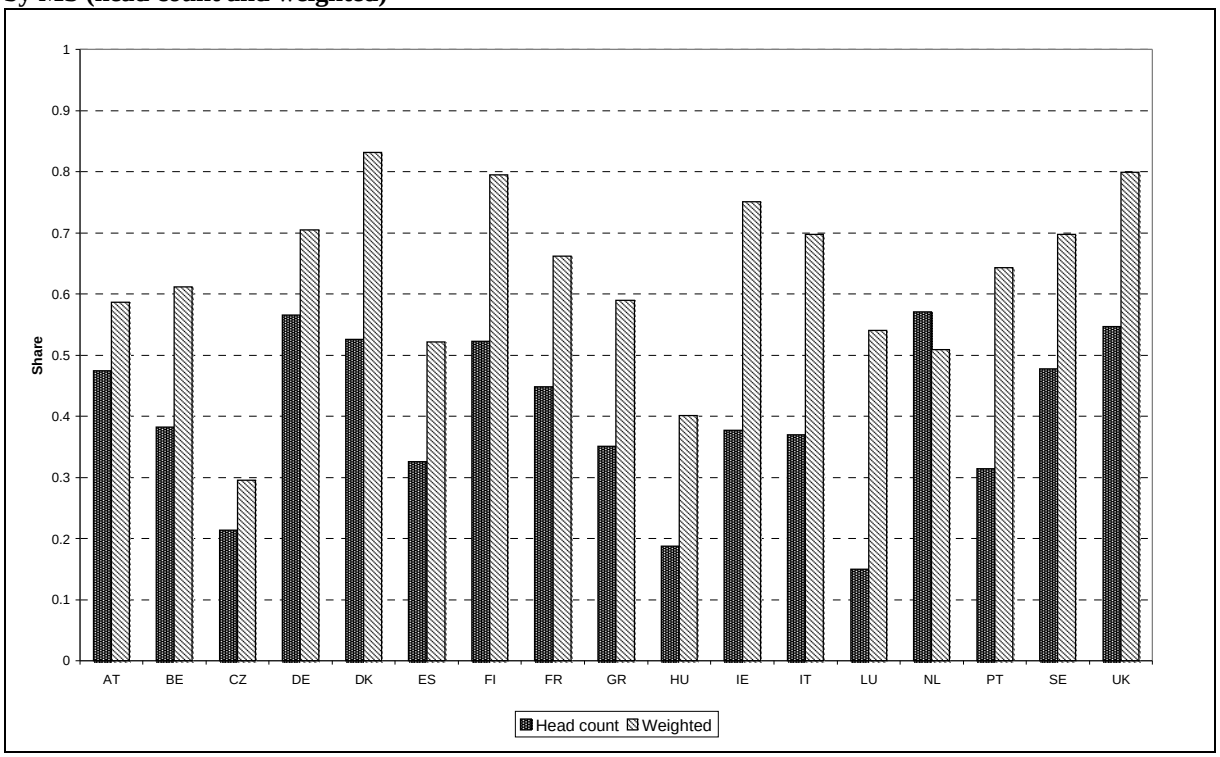
Figure 1: Share of INNs which expired between 2000 and 2006, followed by generic entry within one year, by size class (head count)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data). Class 1 contains the 20% of the smallest INNs (in terms of sales value), class 2 the next smallest 20%, etc. Class 5 contains the 20% of largest-selling INNs.

The EU averages indicated above hide considerable variation between the EU Member States. Figure 2 provides an overview of the share of entry in a range of countries, both as a head count of INNs and with the INNs weighted by value. The figure shows that in the sample investigated, generic entry is most pervasive in Germany, Denmark, Finland, the Netherlands and the UK, with entry shares within the first year above 50% both in number and value terms.

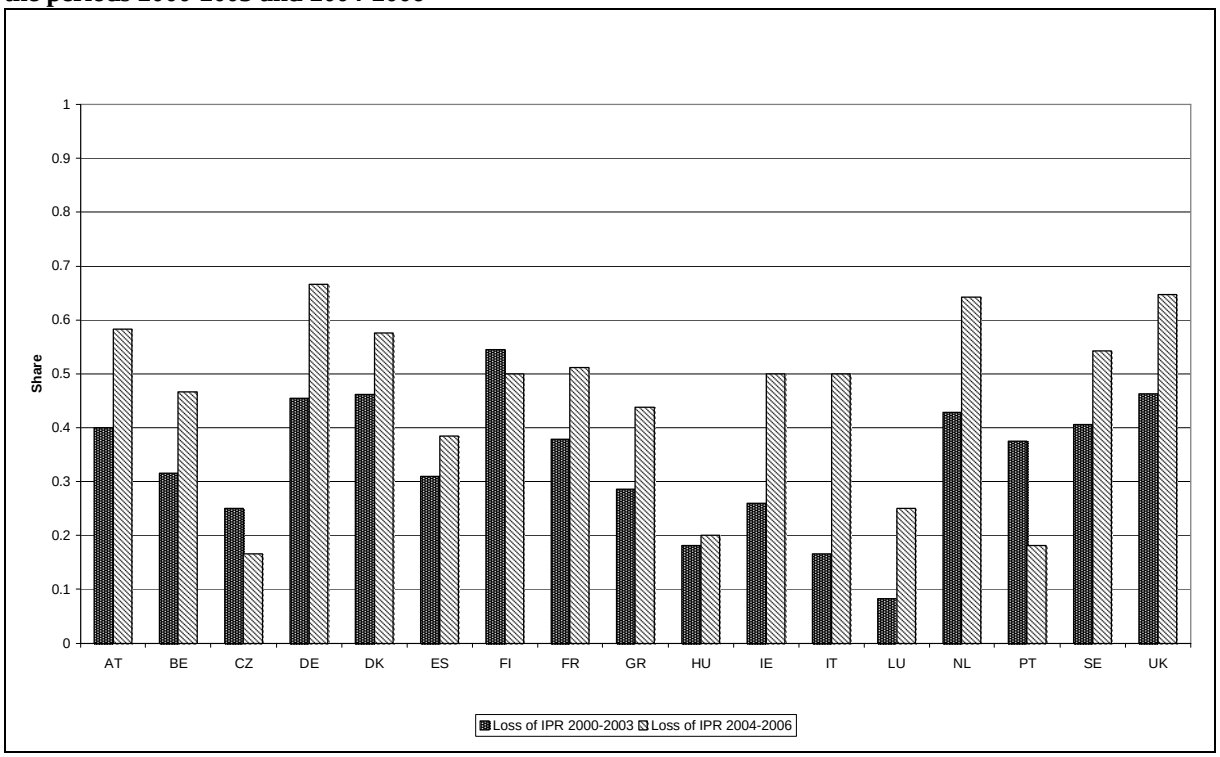
Figure 2: Share of INNs which expired between 2000 and 2006, followed by generic entry within one year, by MS (head count and weighted)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data). Statistics for other countries not available

Another interesting aspect is whether the generic entry has changed over the period in question. Figure 3 presents the share of INNs that faced generic entry for a number of countries, drawing a distinction between INNs which experienced LoE in the period 2000 – 2003 and in the period 2004 – 2006.

Figure 3: Share of INNs which expired followed by generic entry within one year, by MS (head count), for the periods 2000-2003 and 2004-2006



Source: Pharmaceutical Sector Inquiry (partially based on IMS data).

As can be seen in the above figure, the share of expiring INNs followed by generic entry within one year has in most countries increased somewhat over the period 2000 – 2007, although there are some exceptions.

2.2.2. Time to entry

Table 4 provides an overview of the average gap between the time when the INN in question lost exclusivity and the first generic entry into that INN ("time to entry"). The average time to entry is presented both as a head count (within each country each INN in counted as one; left-hand column) and within each country weighting the INN in relation to their sales levels in the year before LoE (right-hand column).[17]

Table 4: Average time to entry following loss of exclusivity (in months; EU average; sample: E75-list; expiries in 2000-2006); INNs facing entry

	Time to entry (head count)	Time to entry (with INNs weighted by value)
Time to entry (sample: E75)	12.9	7.9

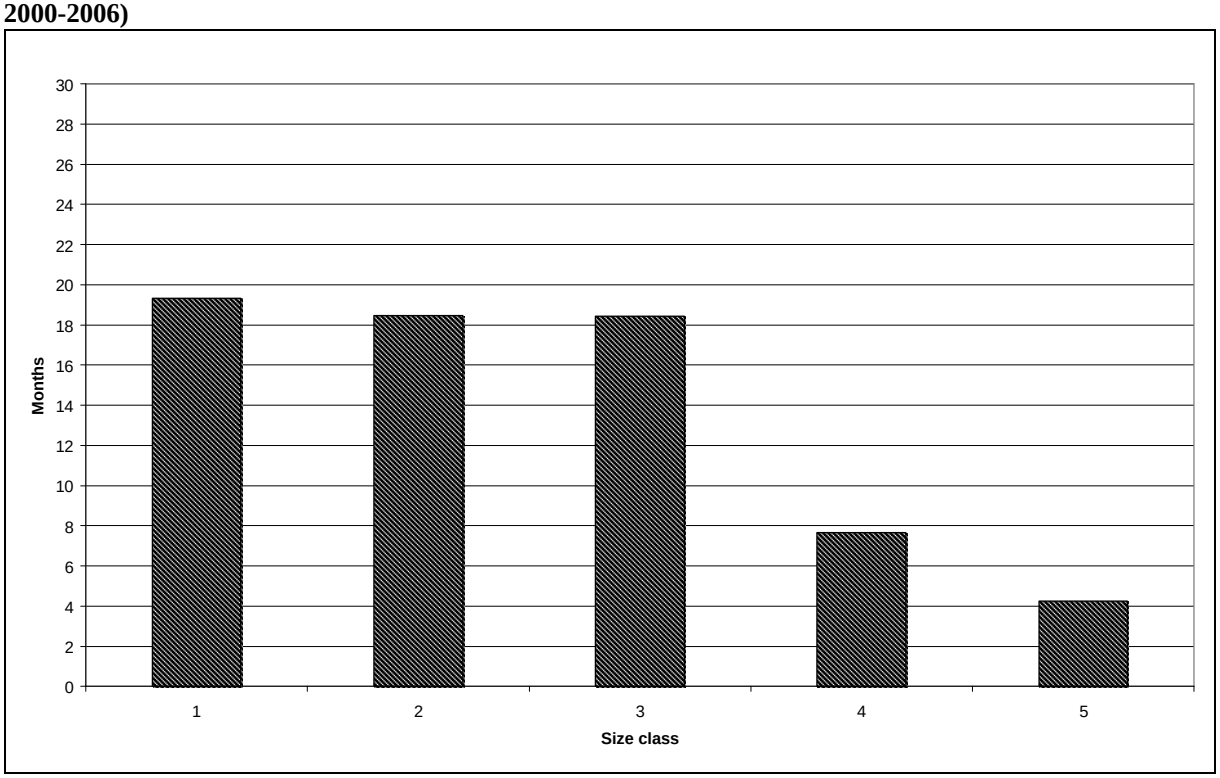
Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

The average time to entry is about thirteen months in absolute terms, whereas it is more than seven months in weighted value terms.

The table suggests that it takes less time for high value products to be faced with generic entry. As mentioned earlier, this finding is not surprising considering that top selling INNs are normally also the most attractive to enter. The conclusion is further confirmed by the figure below setting out the time to entry for individual size classes. The set of INNs is split up into five size classes, where class 1 contains the 20% of smallest INNs (in terms of sales value in the year prior to expiry), class 2 the next smallest 20%, etc. By and large, the average time to entry appears to be smaller for the larger INNs (as measured by sales in the year prior to expiry). However, even for the top selling category it still took about four months on a weighted average basis before entry took place. In individual cases in this category, the time to entry ranged from 0 months (no delay) to over 50 months.

[17] The period of expiries is restricted to 2000 – 2006. When calculating the average time to entry on a collection of expiring INNs, one needs to bear in mind that not all INNs are in an equal position. For instance, for all INNs that expired towards the end of the period 2000 – 2007 and for which entry can be observed, the time to entry is necessarily short. Taking these late observations into account would not give a representative estimate (a biased estimate) of the average time to entry of the sample of INNs under investigation.

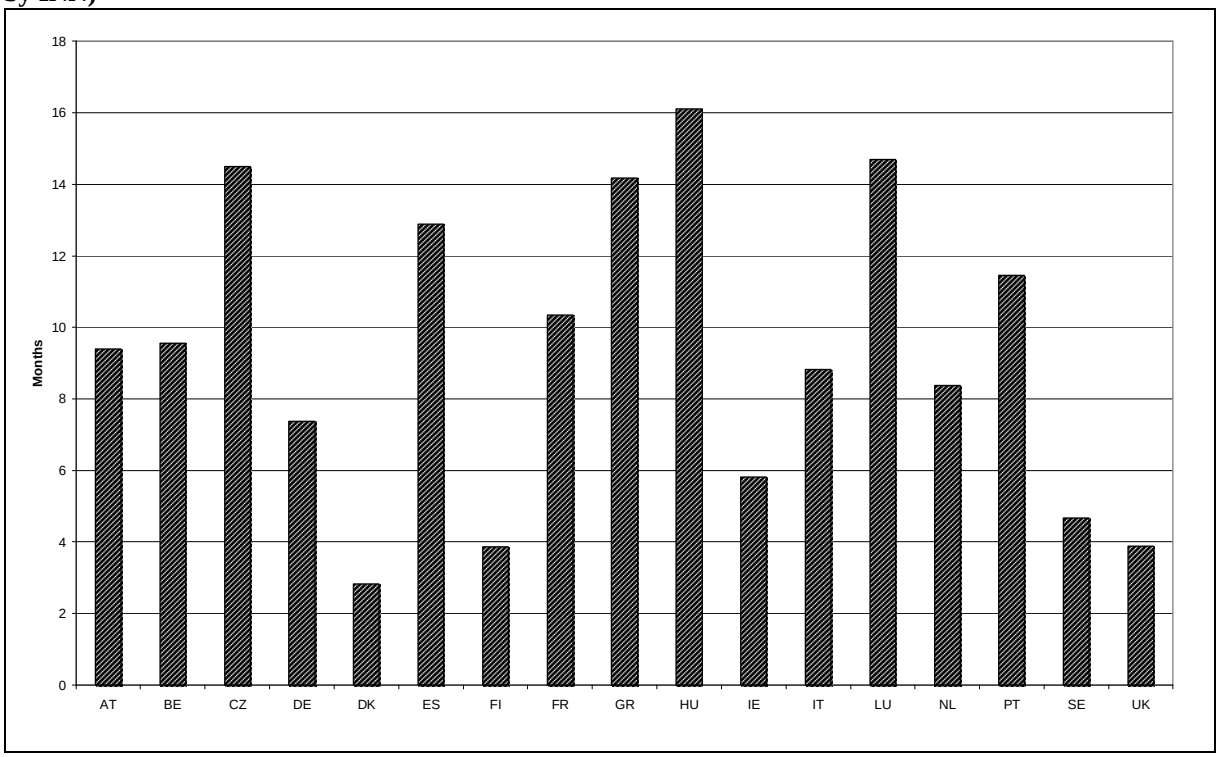
Figure 4: Average time to entry following LoE, by size class (EU average); sample: E75-list; expiries in 2000-2006)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data). Class 1 contains the 20% of smallest INNs (in terms of EU sales value), class 2 the next smallest 20%, etc. Class 5 contains the 20% largest selling INNs.

There are equally considerable differences in time to entry between the EU Member States. Figure 5shows the average time to entry in a range of countries. It is relatively short in Denmark, Finland, Ireland, Sweden and the UK but exceeds half a year, on average, in Austria, Belgium, the Czech Republic, Germany, Spain, France, Greece, Hungary, Italy, Luxemburg, the Netherlands and Portugal.

Figure 5: Average time to entry following LoE, by country (sample: E75 list; LoE in 2000-2006; weighted by INN)



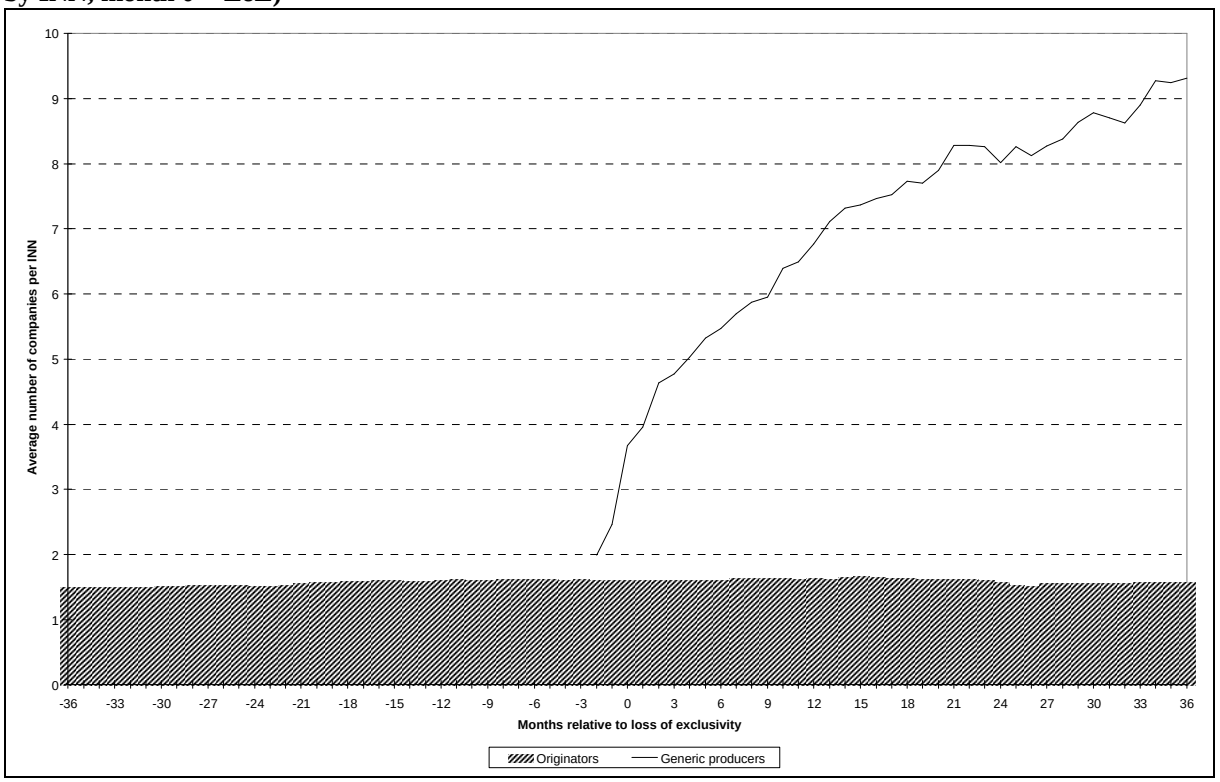
Source: Pharmaceutical Sector Inquiry (partially based on IMS data).

Over the period, there appears to be a gradual decline in the time to entry for expiring INNs. It is, however, difficult to provide meaningful descriptive statistics in this respect, given that the choice of time horizon (the time one allows for expiry to take place) heavily influences any resulting statistic.

2.2.3. Number of generic entrants

The third aspect of the extent of entry is the number of generic companies that enter if and when entry takes place. Figure 6 charts the trend in the number of companies active per INN over time.

Figure 6: Number of companies active per INN per MS (sample: E75 list; all instances of entry; weighted by INN, month 0 = LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Before entry, the average number of companies per INN per Member State remains stable at about 1.5, normally comprising the originator firm itself and/or the companies which have obtained a licence to produce and sell the INN concerned.[18]

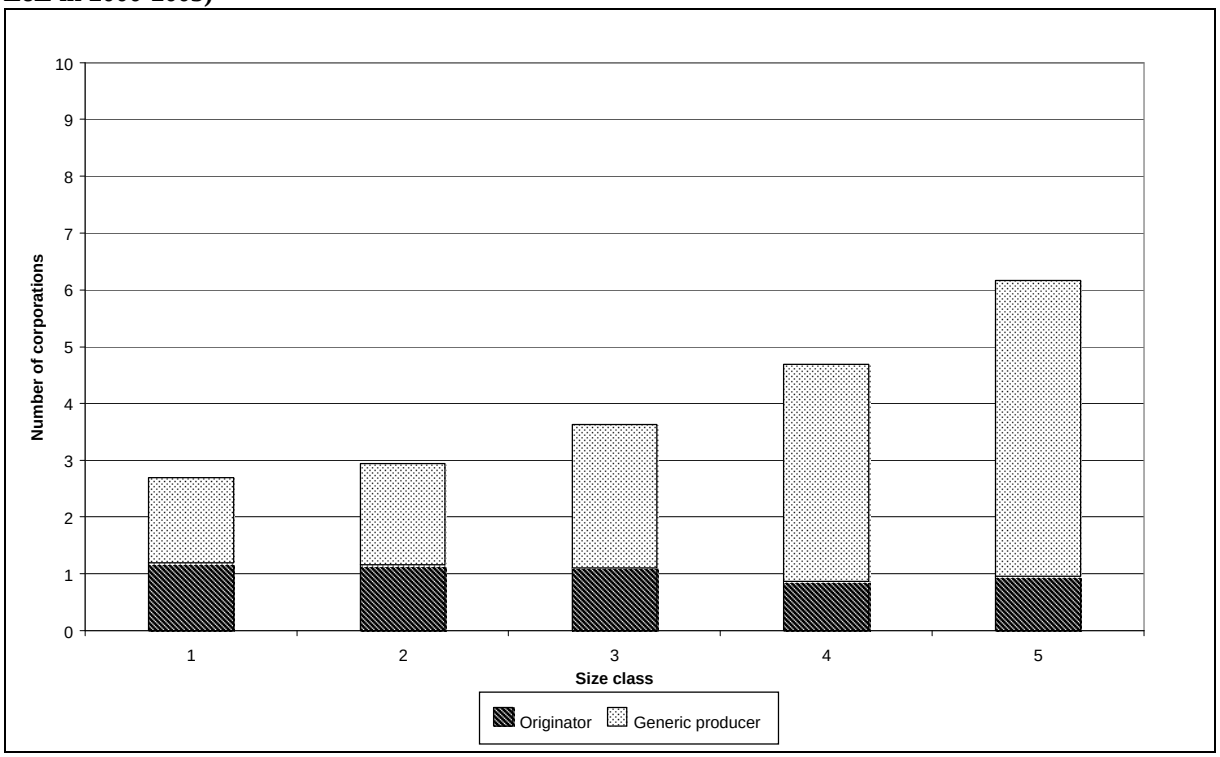
One thing which is clear from the figure above is that the LoE leads to a considerable increase in the number of companies selling products incorporating the INN concerned. On average, after one year following the LoE, about four to five generic companies appear to be present in the market. Within three years following the LoE the ratio of generic companies to originators is about 6:1.

As with the share of INNs that faces generic entry following LoE, the number of generic firms entering also increases as a function of the value of the market as measured by the sales of the INN in question. This is borne out by Figure 7.

There is also quite some variation when it comes to the number of companies active per INN across the various Member States. This is visible in Figure 8.

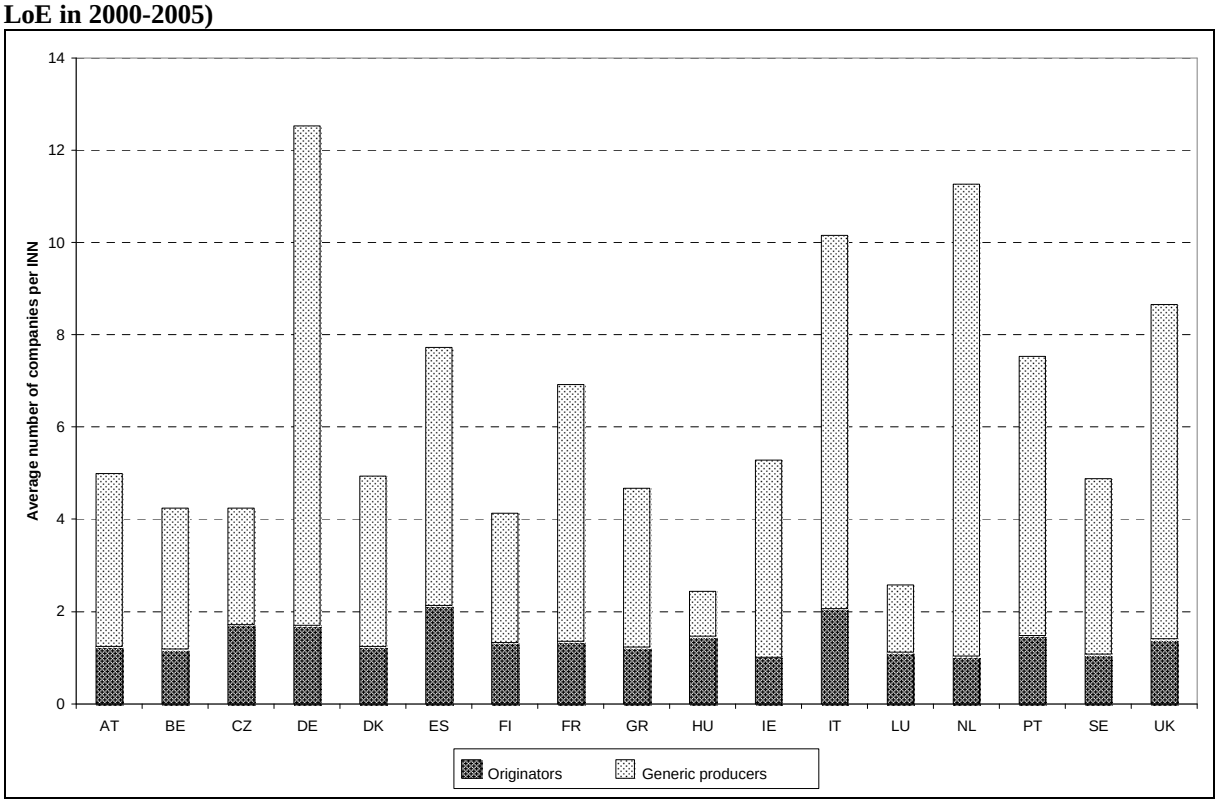
[18] A small proportion of "other" companies can also be observed prior to the loss of exclusivity. These may relate to INNs for which the company status had not been fully established or recorded in the IMS data set, but also to possible "early" entries by generic firms, i.e. entries before the date of loss of exclusivity.

Figure 7: Number of companies active per INN per MS within two years, per size class (sample: E75 list; LoE in 2000-2005)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data). Class 1 contains the 20% of smallest INNs (in terms of EU sales value), class 2 the next smallest 20%, etc. Class 5 contains the 20% top selling INNs.

Figure 8: Number of companies active per INN per MS within two years, per size class (sample: E75 list; LoE in 2000-2005)

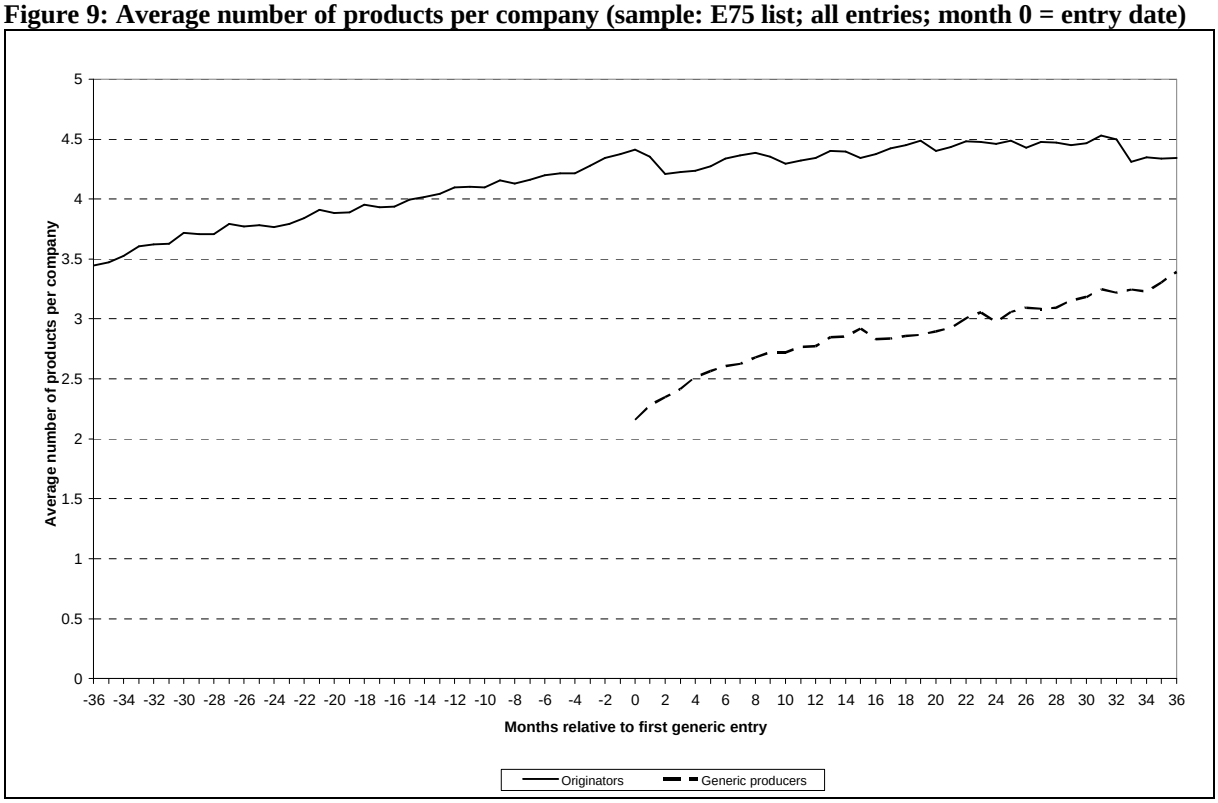


Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

It is striking to see that in the pharmaceuticals markets of Germany, the Netherlands, Portugal, Spain, the UK, France and Italy a high number of generic producers is present in the market. The generic segment of the pharmaceuticals market in these countries appears therefore rather fragmented.

The above findings are also borne out by the regression analysis presented in the second part of the paper. Among other things, the value of the market per capita at the point of LoE and the size of the country's population are important drivers of the number of generic entrants, holding other factors constant. Another interesting aspect is the number of formulations which generic companies enter with when they enter. The figure below plots the average number of formulations generic companies sell over time alongside, the same average for originator companies for the purpose of comparison[19].

Figure 9: Average number of products per company (sample: E75 list; all entries; month 0 = entry date)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Generic companies generally appear to enter with about 2 to 2.5 products (formulations) per INN (EU average). This is smaller than the number of products with which originator companies are typically active (about 3.5 to 4). There are two main explanations for this. First, if and when a generic company enters a certain INN, it makes sense to focus on the commercially most attractive formulations, and to leave aside formulations that sell less (e.g. niche products). Second, typically, while the INN loses exclusivity insofar as the first formulation loses exclusivity, there are still other formulations that remain exclusive and that only the originator firm or its licensees can sell.

[19] In the calculation of this number, each single formulation (for instance, a tablet of a certain strength) is counted as one, regardless of whether or not it is sold under more than one brand name.

2.2.4. Effects of generic entry

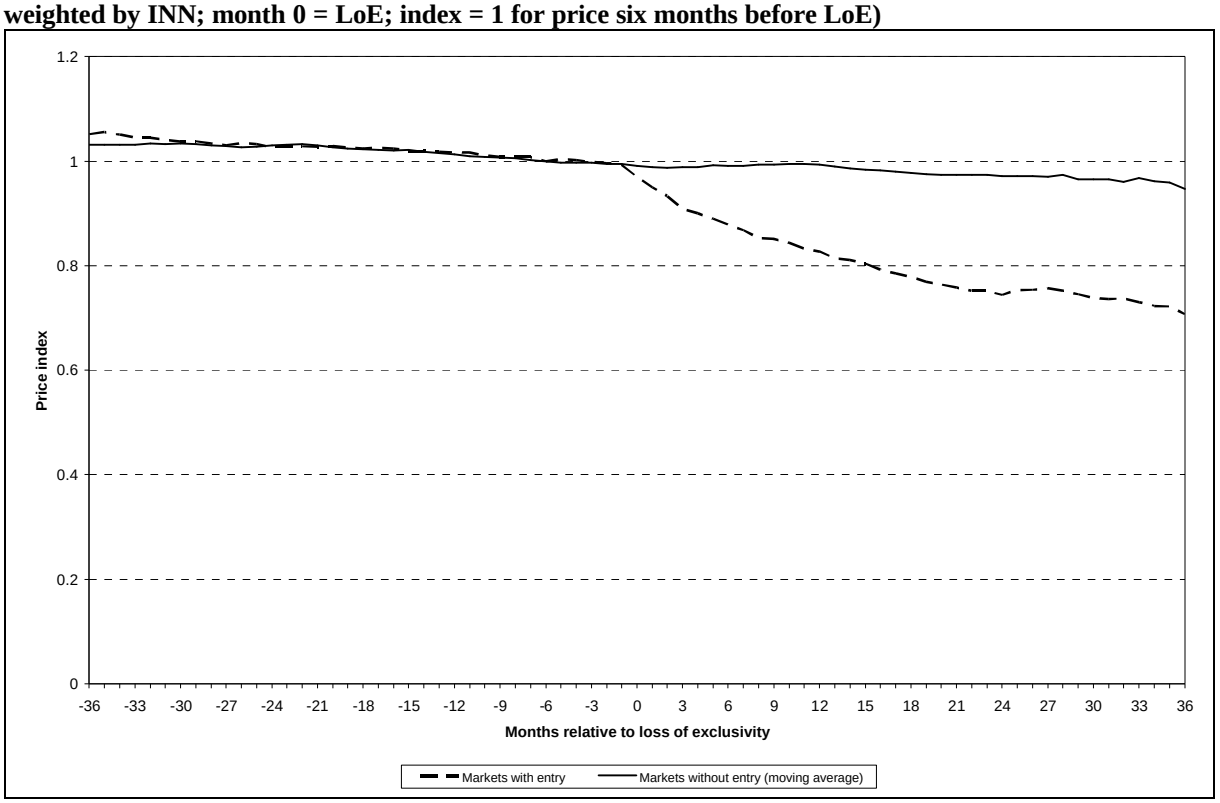
Generic entry into a pharmaceuticals market can have a profound effect as it changes the market from one in which only one firm could sell the product(s) concerned (possibly via licensees) into one where more sources of supply become available for the product. The most direct effect is likely to be on the average price level of the product(s) concerned and the sales volumes of the originator. But other products can also be affected, both products under the INN that remain patent-protected and products based on other INNs but competing with the product(s) that lost exclusivity.

This section first looks into the effects on prices for the INN concerned. It then turns to the effects on volumes, both the total volume of products sold and the volume sold by originators and generics respectively. Finally, it addresses, for a limited number of INNs, the effects of generic entry on possible substitute for the product that lost exclusivity.

2.2.4.1. Effects on prices

The first measure considered is the average price of the products sold under the INN. This average price is constructed as an index, which is set at one shortly (six months) prior to the end of the exclusivity period. Figure 10 plots the development over time of the average price index separately for expiring INNs with generic entry and without generic entry.

Figure 10: Development of average price index for INNs with and without generic entry (sample: E75 list; weighted by INN; month 0 = LoE; index = 1 for price six months before LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

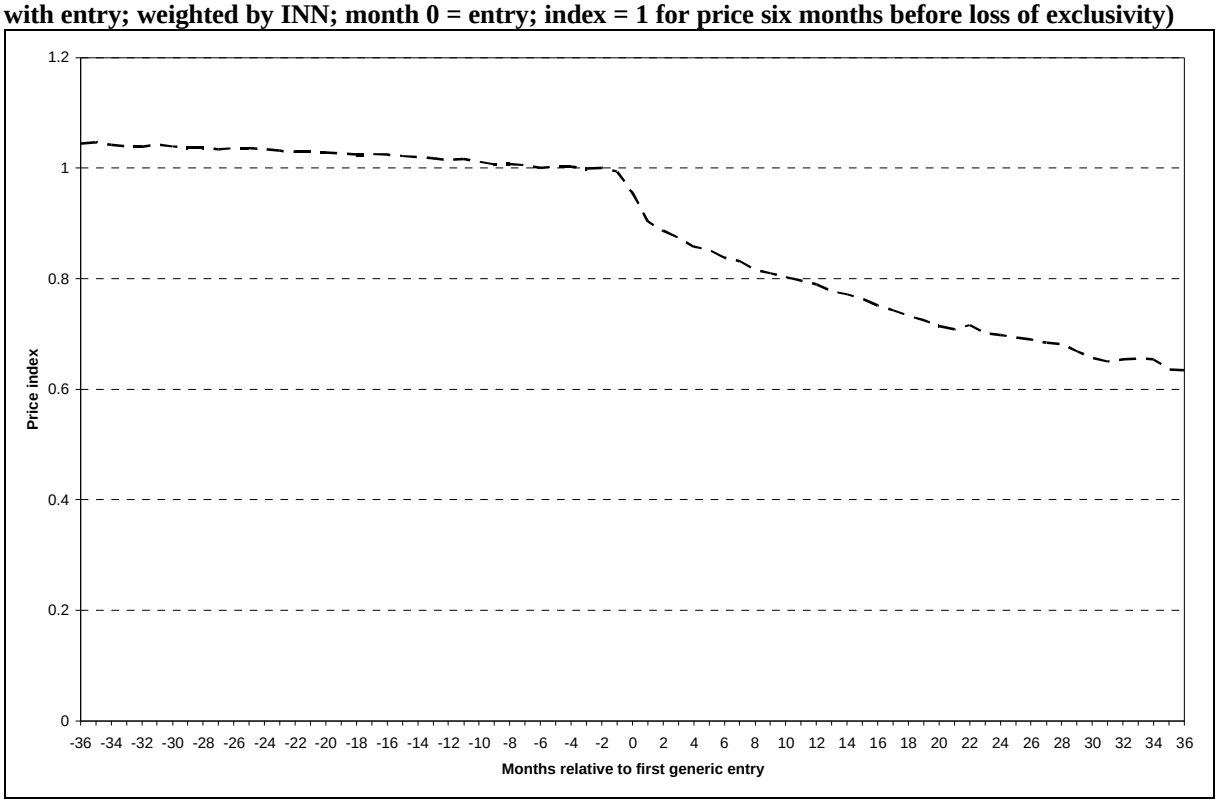
Comparison of the two lines clearly shows that the average price index drops considerably on markets with generic entry, but not on markets without. In markets with entry, average prices dropped by almost 20% after the first year following LoE and about 25% after two years. In

rare cases, for some medicines in some Member States, the decrease in the average price index was as high as 80-90%.

Of course, it must be borne in mind that entry will not take place immediately on LoE for every INN (see "data and selection of INNs" above). The gradual drop in levels observed in Figure 10 is therefore the result of the combination of average price levels coming down quickly in those markets, where entry took place quickly and average price levels coming down later because entry took longer.

A different picture emerges when not the date at which the INNs lost exclusivity, but the date of first generic entry is taken as the reference point. The resulting price development is illustrated in Figure 11.

Figure 11: Development of average price index for INNs with generic entry (sample: E75 list; all INNs with entry; weighted by INN; month 0 = entry; index = 1 for price six months before loss of exclusivity)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

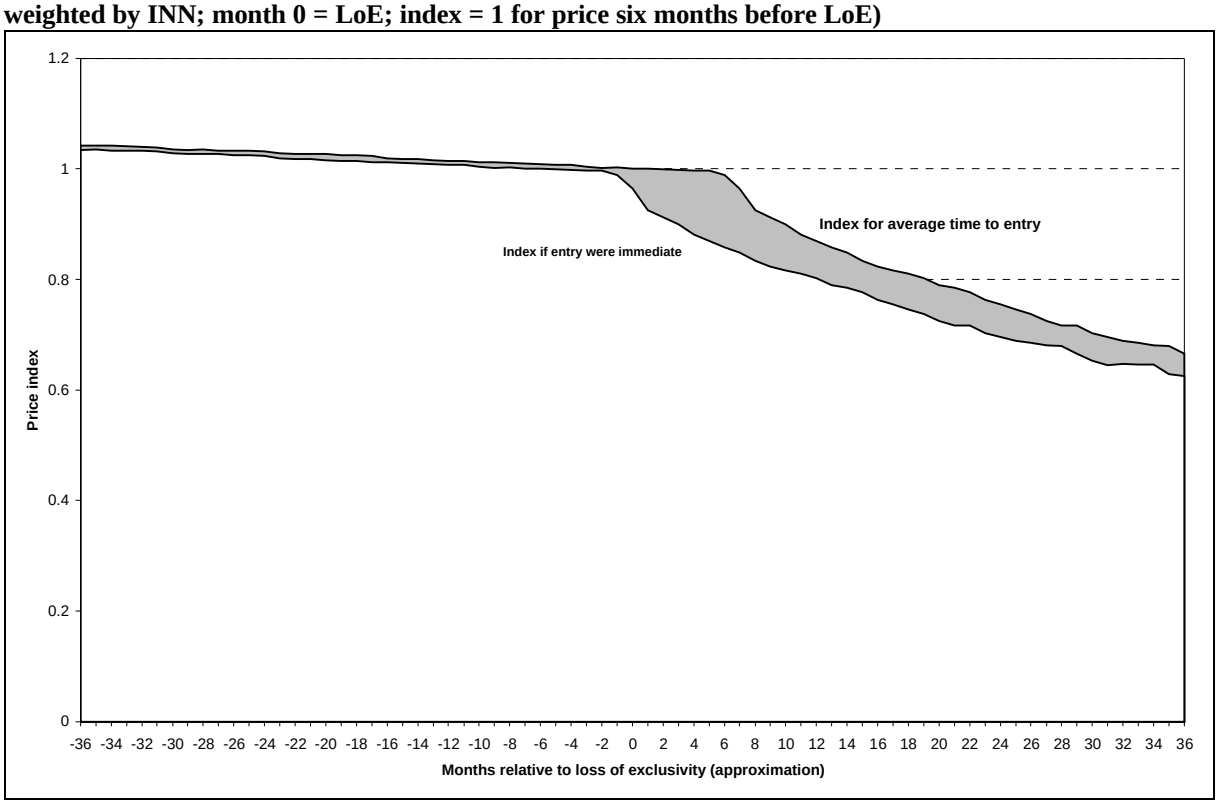
Taking the date of entry as the reference point, the decreases in average prices emerge a little more clearly. The difference can be observed in the form of a somewhat sharper average price decrease in the month of entry, with the differences between the two graphs diminishing after one year.

Figure 11 can also be used to obtain an impression of the additional savings that might have accrued to health systems in the period 2000 – 2007 if entry following LoE had been immediate, rather than occurring with a delay.[20] In Table 4 above, it was observed that the average time to entry in the sample of INNs under consideration exceeded seven months (weighted average). Figure 12 presents two lines, both depicting a development of the average price index following first generic entry. The two lines have identical shapes, the only

[20] The sample is again restricted to INNs expiring in the period 2000 – 2006. See footnote 17.

difference is that the line on the left ("Index if entry were immediate") assumes that for all INNs in the sample the first generic company enters at the time the INN lost exclusivity, whereas the line on the right ("Index for average time to entry") assumes that all INNs faced first generic entry only after seven months following LoE.

Figure 12: Development of average price indices if entry were immediate and for generic entry after seven months following LoE (approximation; sample: E75 list; expiries in 2000 – 2006; all INNs with entry; weighted by INN; month 0 = LoE; index = 1 for price six months before LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

At each month along the horizontal axis, the vertical difference between the two lines can be interpreted as (an approximation of) the difference between the price index that applied, in an average sense, in reality and the average price index that would have applied had entry taken place seven months earlier. By summing up these monthly differences over a longer period (see the grey area in Figure 12[21]), one obtains an estimate of the total potential savings that could have been obtained had generic entry taken place earlier, evaluated at constant consumption volumes.[22] Taking the volumes in the year prior to expiry as a benchmark,[23] the

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21 Note that Figure 12 only displays a time window of 36 months before and 36 months after loss of exclusivity, of which only the period after loss of exclusivity matters for the purpose of calculating the costs of delayed generic entry. In reality, however, the relevant horizon extends beyond the 36 months following loss of exclusivity displayed in the Figure 12, as all INNs expiring up to December 2004 have a horizon exceeding 36 months. In the calculations for the period 2000 – 2007 presented subsequently in this section this aspect is taken into account.

22 The comparison of price indices only allows for making meaningful statements about possible cost savings when these are evaluated at constant volumes.

23 The sales in the year before expiry have been approximated by taking 12 times the sales in the month of expiry.

cost of the average time to entry on the E75 sample under consideration can, for the entire period 2000 – 2007, be roughly estimated at € 3 billion (at retail prices).[24]

In the public consultation following the publication of the preliminary report, a number of questions have been raised as to the way the figure has been calculated. It should be noted that the figure is a composite figure. It relates to an estimate of the missed savings of the list of 128 INNs under consideration (E75 list) in the Member States for which observations were available. Each of these INNs expired at different times during the period 2000-2007. All calculations relate to the period between LoE and December 2007, a period which differs in length for each of the INNs and countries. Missed savings in the period 2000 – 2007 in relation to expiries from the period before 2000 are not taken into account. Nor are missed savings in relation to the list of INNs under consideration materialising after 2007.

In order to appraise the impact of these potential savings, these savings should be compared with the aggregate expenditure and savings on medicines for originator and generic products, on the sample investigated. These figures can again be measured, for each INN and country pair for the period between the date of LoE and December 2007. By considering the price index before expiry (equal to 1) with the price index as it developed over time with an average time to entry of seven months, the aggregate savings derived over the period between LoE and December 2007 due to generic entry can be estimated at about € 15 billion (white area A in Figure 13), at constant (pre-expiry) volumes. The aggregate expenditure (value sales) in the period between LoE and 2007, net of these savings, is in the order of € 50 billion (grey area B, including shaded surface). Therefore, the € 3 billion in savings should be compared to a universe worth an approximate € 50 billion. Had entry been immediate following LoE, this expenditure could have been € 3 billion (or 5%) lower (indicated by the shaded surface).[25] Compared to the actual savings of € 15 billion, it can be concluded that savings could have been 20% higher than they actually were.

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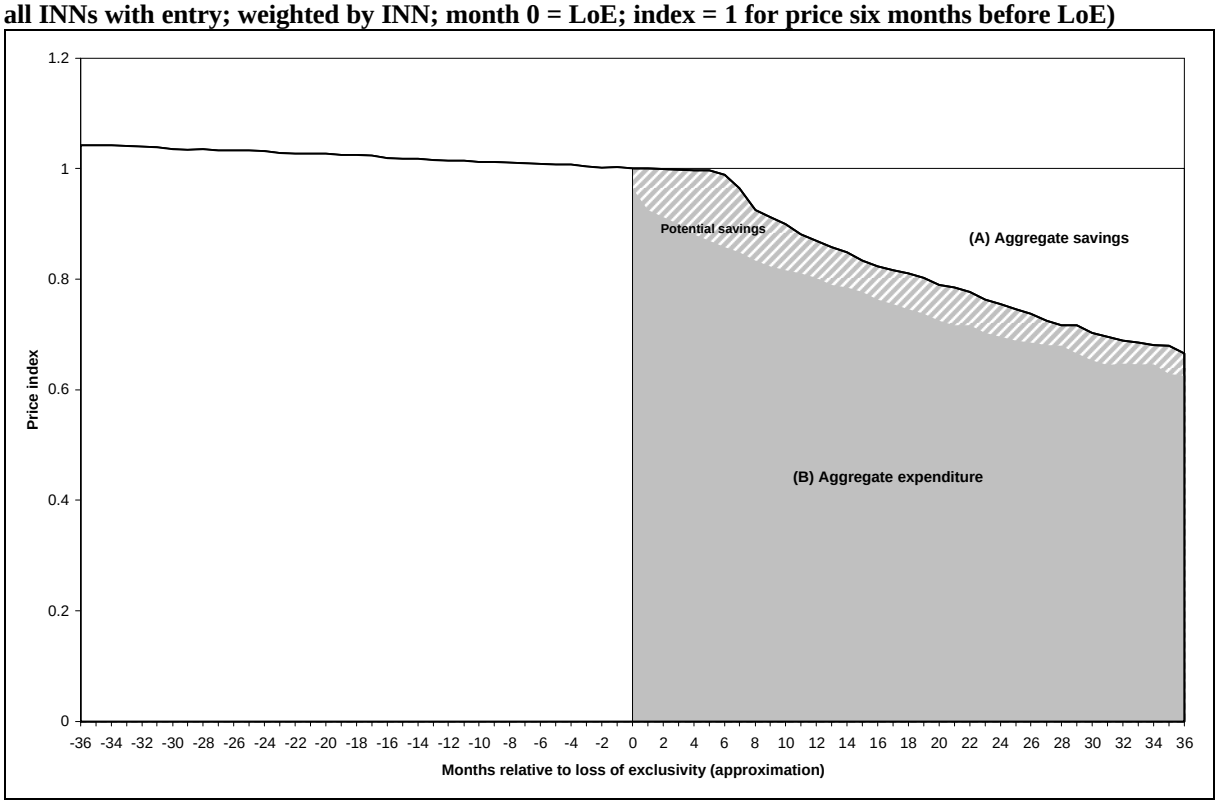
[24] This estimate is based on 17 Member States only, where sufficient observations were available; for further details on methodology, see above under "data and selection of INNs".

[25] It should be noted that the total expenditure on prescription medicine at retail level amounted to € 190 billion in 2007 in the EU. Of these sales approximately € 93 billion (or 49%) are sales of products not (or no longer) benefiting from patent protection. Of the aggregate expenditure of € 50 billion (post expiry, at constant volumes), about € 10 billion relates to 2007. This number is thus considerably smaller as it relates to a specific subset of the prescription medicines, namely those that faced loss of exclusivity in the reference period 2000 – 2007.

Figure 13: Aggregate value sales, aggregate savings for generic entry after seven months following LoE and potential savings if entry were immediate. (approximation; sample: E75 list; expiries in 2000 – 2006; all INNs with entry; weighted by INN; month 0 = LoE; index = 1 for price six months before LoE)



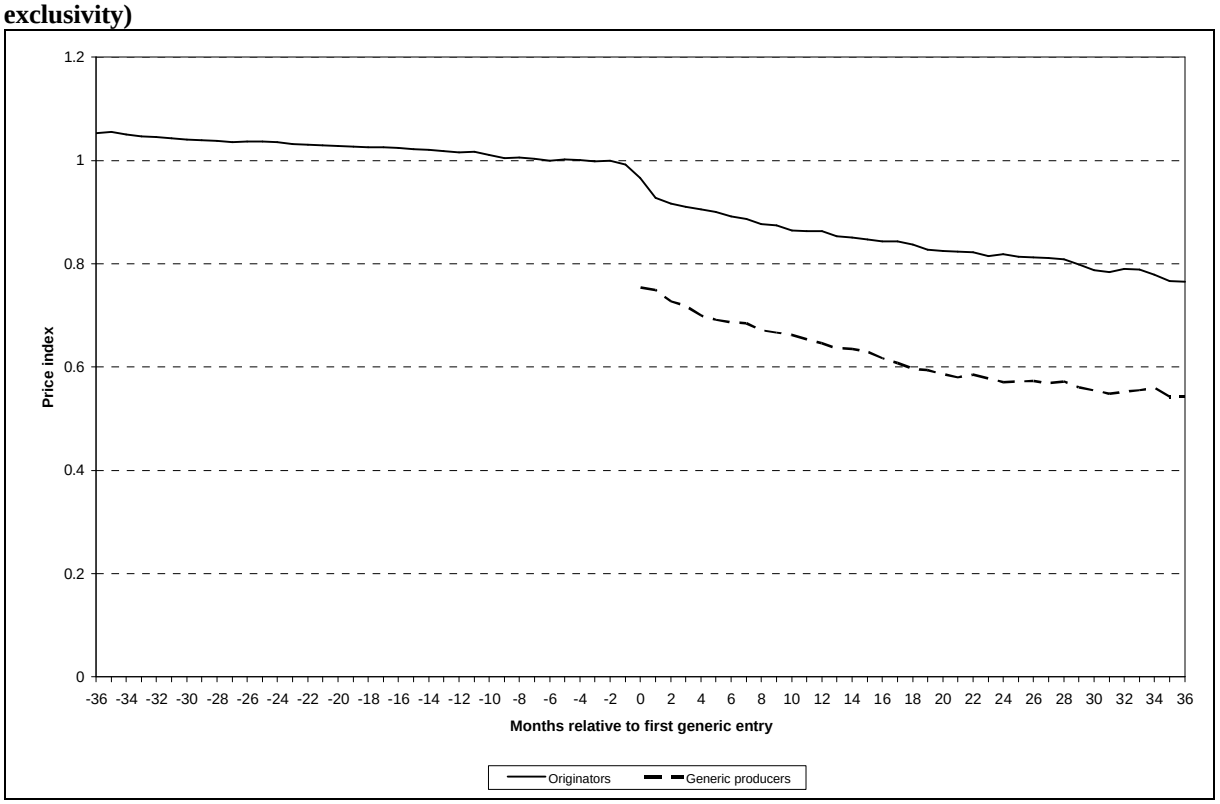
Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

It should be noted that the figure of € 3 billion is likely to provide a lower bound of the potential savings due to earlier entry. Likewise, the figure of € 15 billion probably represents a lower bound on total savings due to generic entry. After all, the E75 list of molecules contains many, but not all expiries in all Member States.[26] Further, the above calculations have been made at constant volumes. As will be described in further detail in the second part of this paper (section 3.4), INNs that turn generic may attract demand away from (expensive) substitute INNs that are still patent protected.

It seems reasonable to expect a different pricing behaviour between originator and generic producers. One might expect average generic price to be significantly lower than the originator one. Another issue relates to the reaction of originator companies in their pricing strategy when facing generic entry. While in general originator producers might be expected to adapt their price to the generic one, they may well decide to take advantage of the brand recognition of their product and focus on a subset of loyal "consumer", willing to pay a higher price than the one of generics. The following figure provides an overview of the level of development of these separate indices over time.

[26] As described in detail above, the list of E75 molecules represents over 90% of the value of all expiries in France, Germany, and the UK in the period 2000 – 2007, however. It is likely to comprise the vast majority of expiries in other Member States as well.

Figure 14: Development of originator and generic price indices for INNs with generic entry (sample: E75 list, all INNs with entry; weighted by INN; month 0 = entry; index = 1 for price six months before loss of exclusivity)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Figure 14 shows that generics typically come onto the market at a price that is about 25% lower than the price of the originator products prior to LoE. In other words, the generic:originator price ratio on entry is about 0.75. Over time, the generic-originator price ratio drops to about 0.55. Also the price levels of the originator products for INNs facing generic entry appear to decrease, albeit to a lesser extent.

Also the price levels of the originator products for INNs facing generic entry appear to decrease, albeit to a lesser extent. This may be related to a range of factors. For those products that lost exclusivity, there may have been a price response by originator companies in the face of increased (generic) competition. The presence of price regulation, which in some countries obliges originators to keep the prices of their products within a certain range from the lowest priced (generic) products, may also have played a role. At the same time, originator companies may have continued to enjoy a certain degree of brand recognition or loyalty on the part of patients and doctors, allowing them to charge a higher price than generic companies.[27]

These EU averages reported so far hide considerable variation between the EU Member States. Figure 15 and Figure 16 provide an overview of the price impact in a range of countries, measured one year after entry and two years after entry, respectively.

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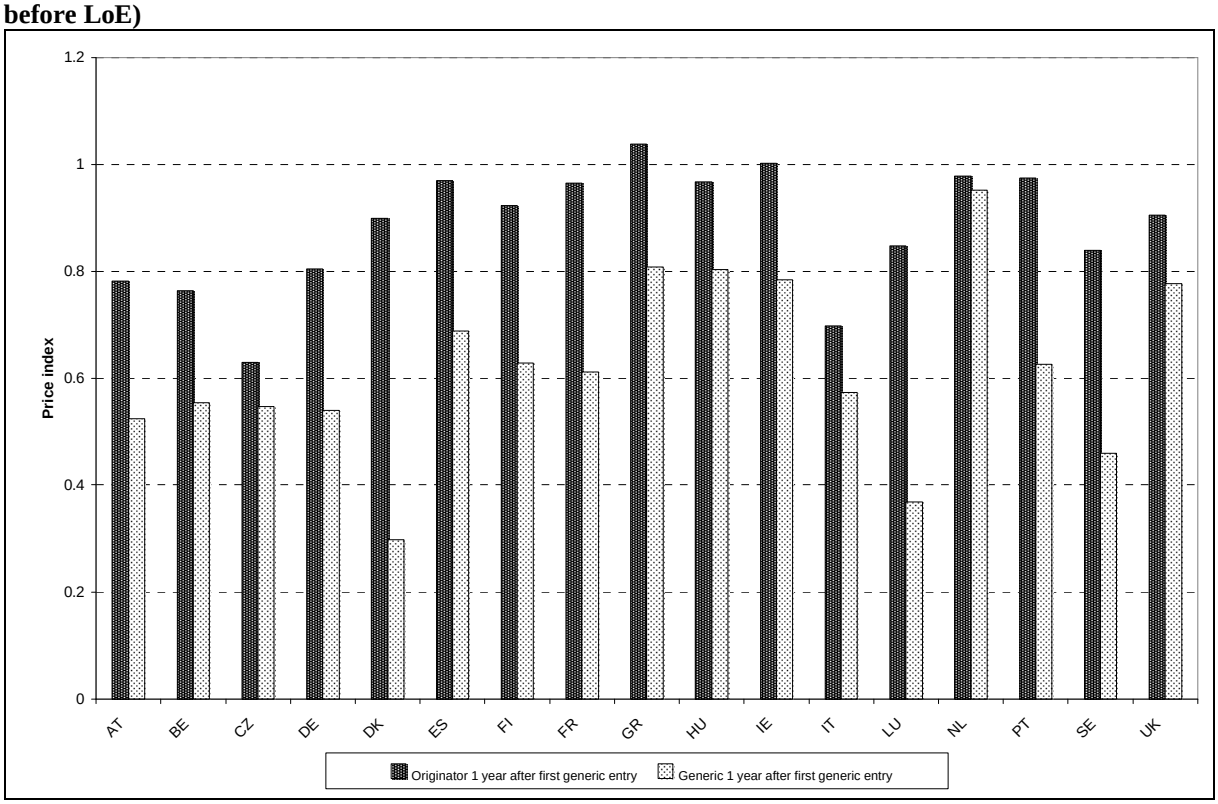
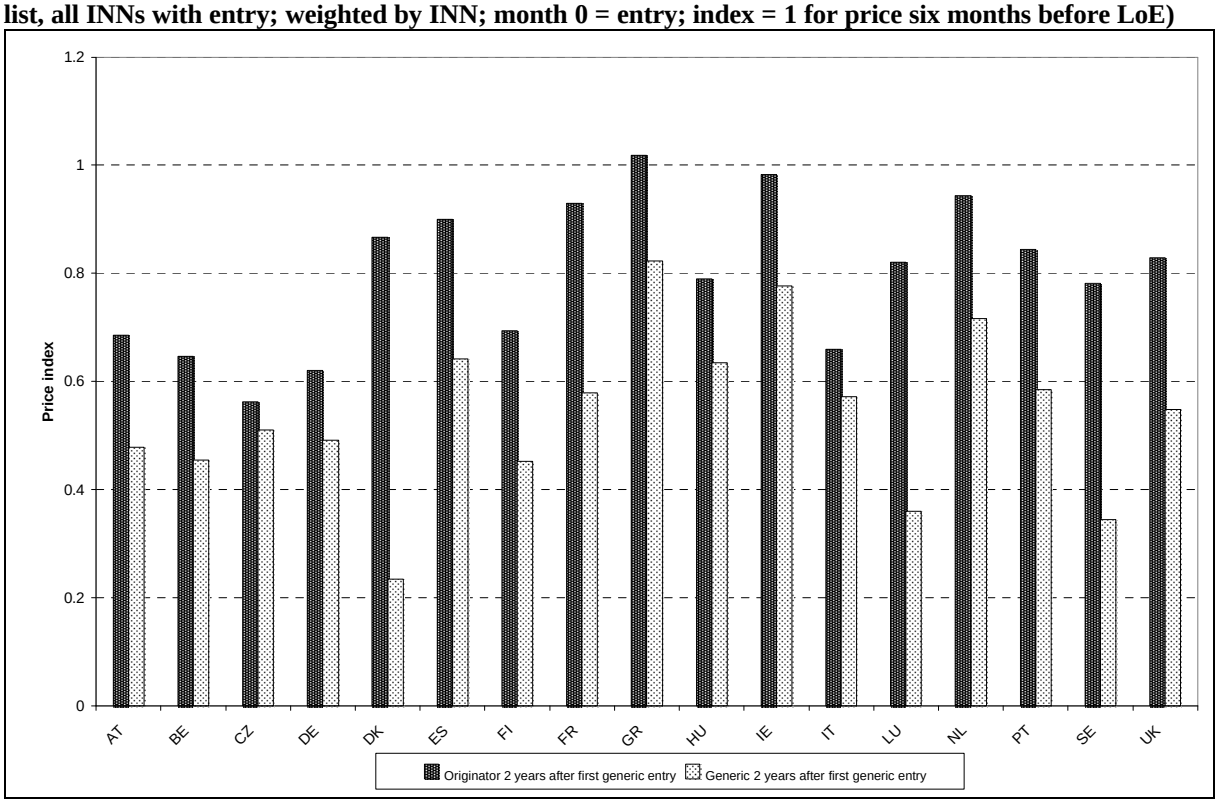
[27] Further, not all products belonging to a given INN of an originator company may have lost exclusivity at the same time, allowing an originator company to continue to charge mark-ups on these exclusive products. It should be noted that the price index for originator companies displayed in Figure 24 is a composite index of all products sold by the originator companies under the INNs concerned.

Figure 15: Development of originator and generic prices in the first year, by country (sample: E75 list, LoE in 2000-2005; all INNs with entry; weighted by INN; month 0 = entry; index = 1 for price six months before LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data).

Figure 16: Development of originator and generic prices in the first two years, by country (sample: E75 list, all INNs with entry; weighted by INN; month 0 = entry; index = 1 for price six months before LoE)

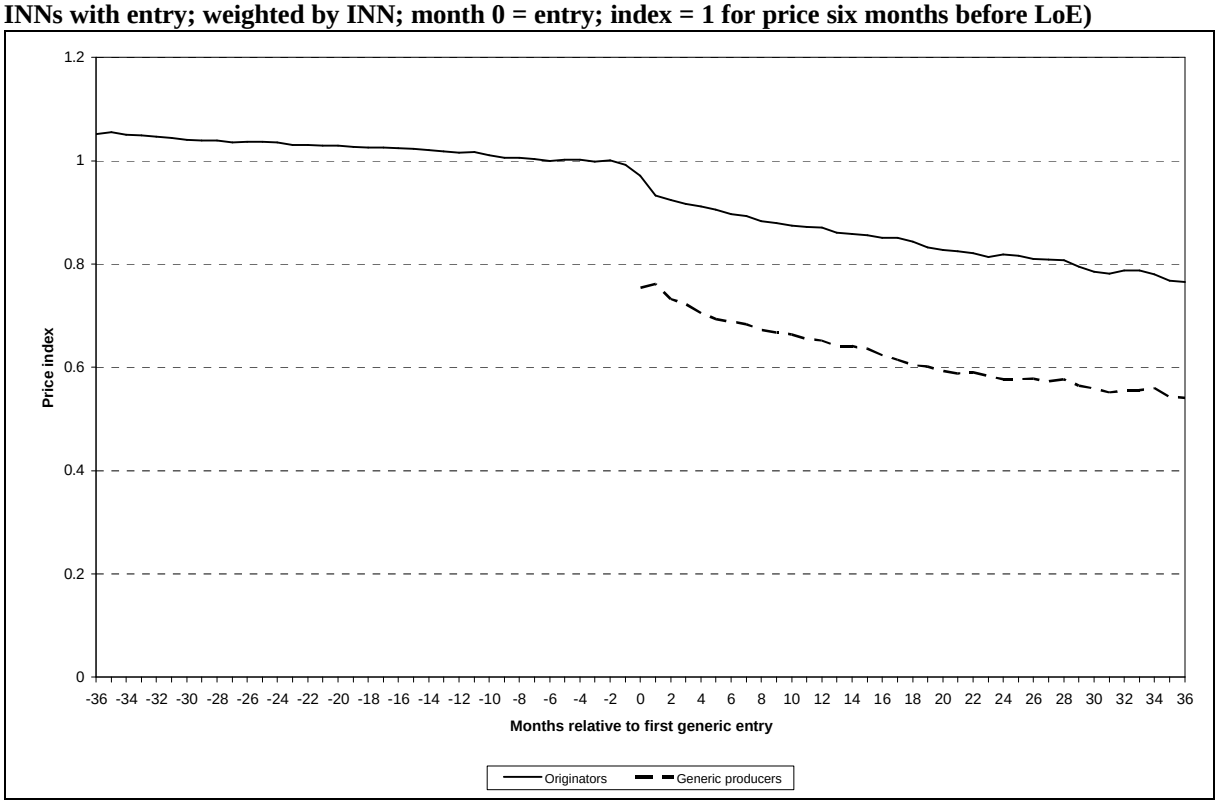


Source: Pharmaceutical Sector Inquiry (partially based on IMS data).

The charts show that generic entry leads to the biggest generic price decreases in countries such as Sweden, Finland, Denmark, Austria, Germany, Belgium and Luxemburg. In each of these countries average generic prices after two years appear to be more than 50% below the price of the originator price prior to LoE. In Sweden, Denmark and Luxemburg price drops of this nature are typically achieved within the first year of entry already. Also within Member States, there was quite some variation among the various INNs.

The indices reported so far relate to the prices of all products sold under the INN. The originator index may include products that have lost exclusivity and products that are still protected. An alternative way to present the impact of generic entry on prices is to consider only the prices of originator products (formulations) which have been exposed to generic entry. This is presented in Figure 17. Although this measure is more focused than the average indices described earlier, it is not necessarily more accurate or informative. It provides a different perspective. After all, as part of the life cycle strategy for INNs, originator companies may well have succeeded in shifting some of the demand towards formulations of the INN that still benefit from exclusivity (including second generation products) or even to other (exclusive) INNs altogether.

Figure 17: Trends in originator and generic prices for products with generic entry (sample: E75 list, all INNs with entry; weighted by INN; month 0 = entry; index = 1 for price six months before LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

2.2.4.2. Effects on volumes

The second main dimension in which generic entry may have an impact is on the volume of products sold and the market shares of the originator and generic companies.

The combined market share of the generic companies is often referred to as the "generic penetration rate". The higher the penetration rate, the greater the savings for the health system are likely to be (for a given market size).

Table 5 presents, for the EU as a whole, the generic penetration rate for the INNs in the E75 sample covered by this report that faced generic entry. The penetration rate is measured one year and two years after LoE. Once again the set of INNs is limited in order to allow enough time to lapse before measuring the impact of generic entry. It is given in both volume [28] and value terms (right-hand column).

Table 5: Generic penetration (EU average; sample: E75 list, all INNs with entry; weighted by INN)

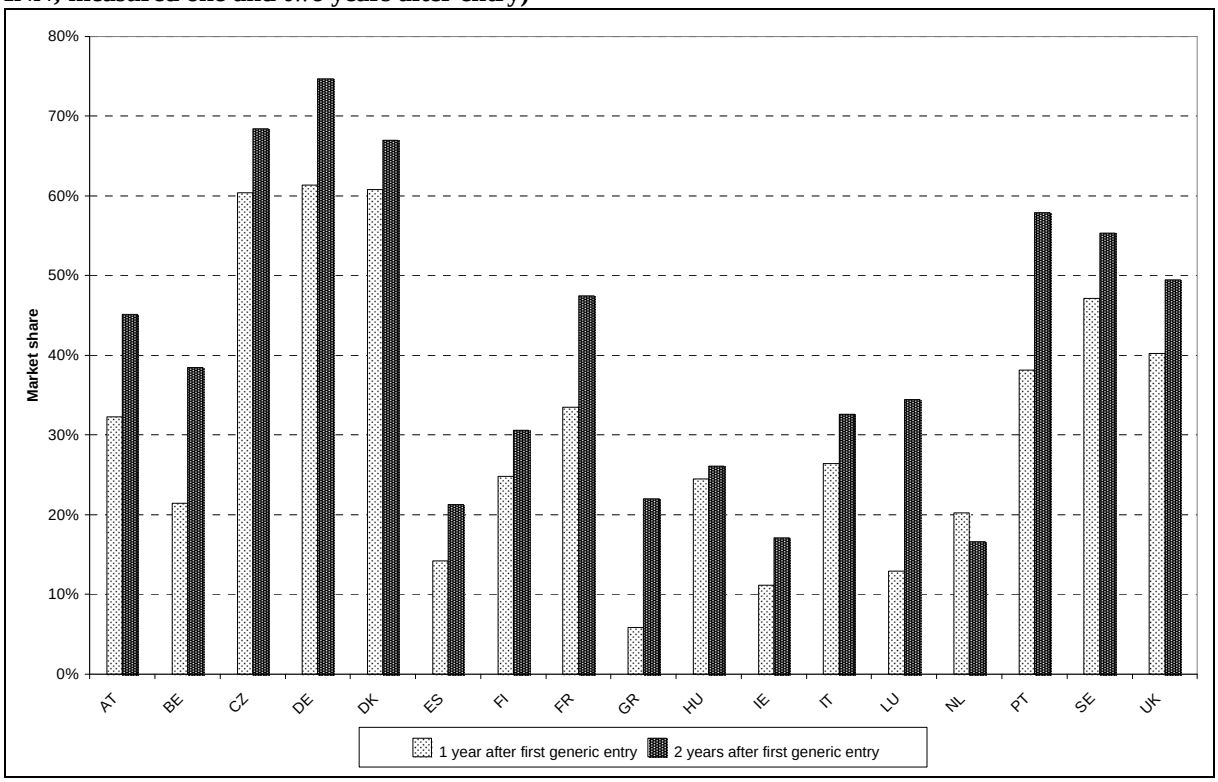
	Generic penetration rate (volumes)	Generic penetration rate (value)
Measured one year after first generic entry (INNs expired in 2006 or earlier)	30%	25%
Measured two years after first generic entry (INNS expired in 2005 or earlier)	45%	38%

Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Again, there is considerable variation between the individual Member States. Figure 18 and Figure 19 show the generic penetration rate in a number of countries, again measured one year and two years after LoE, by volume and value respectively.

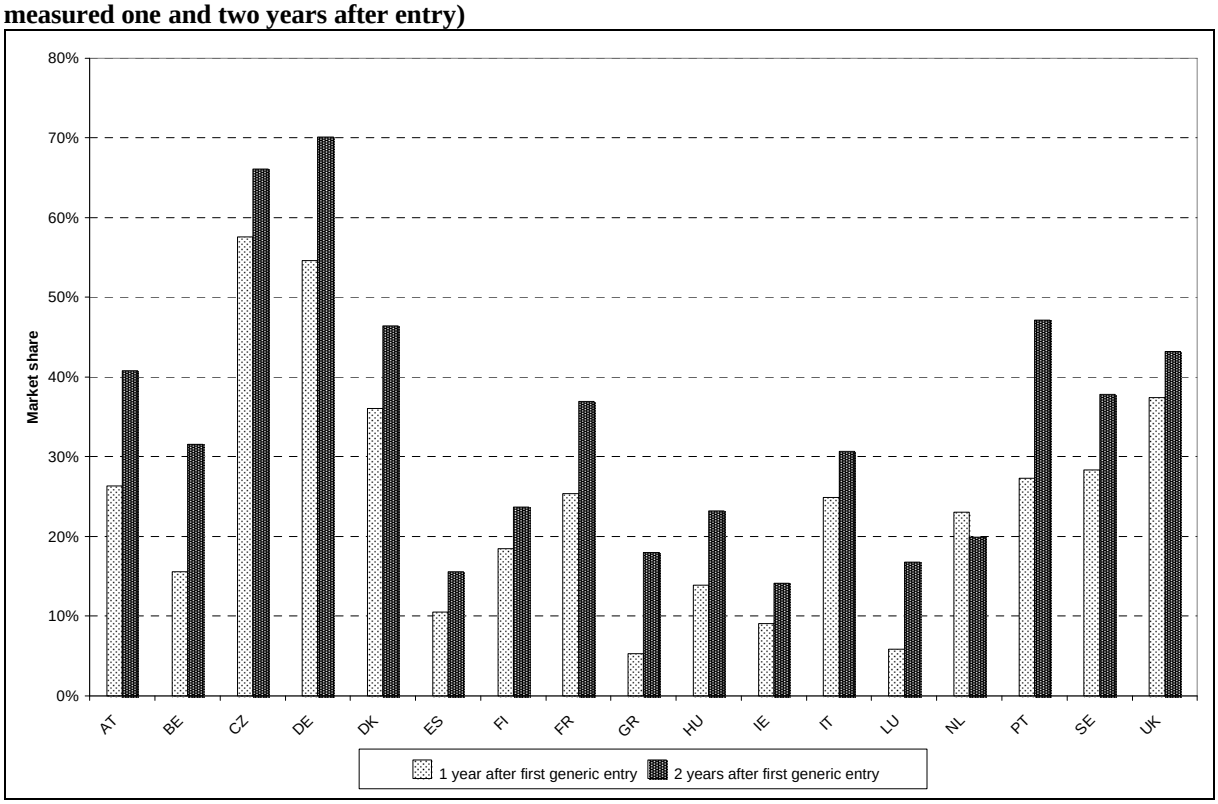
[28] For this volume index, IMS data on Standard Units are used in order to be able to aggregate consumption across different types of formulation (tablets, capsules, injections, etc.)

Figure 18: Generic penetration by volume, by MS (sample: E75 list, all INNs with entry; weighted by INN; measured one and two years after entry)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data).

Figure 19: Generic penetration by value, by MS (sample: E75 list, all INNs with entry; weighted by INN; measured one and two years after entry)

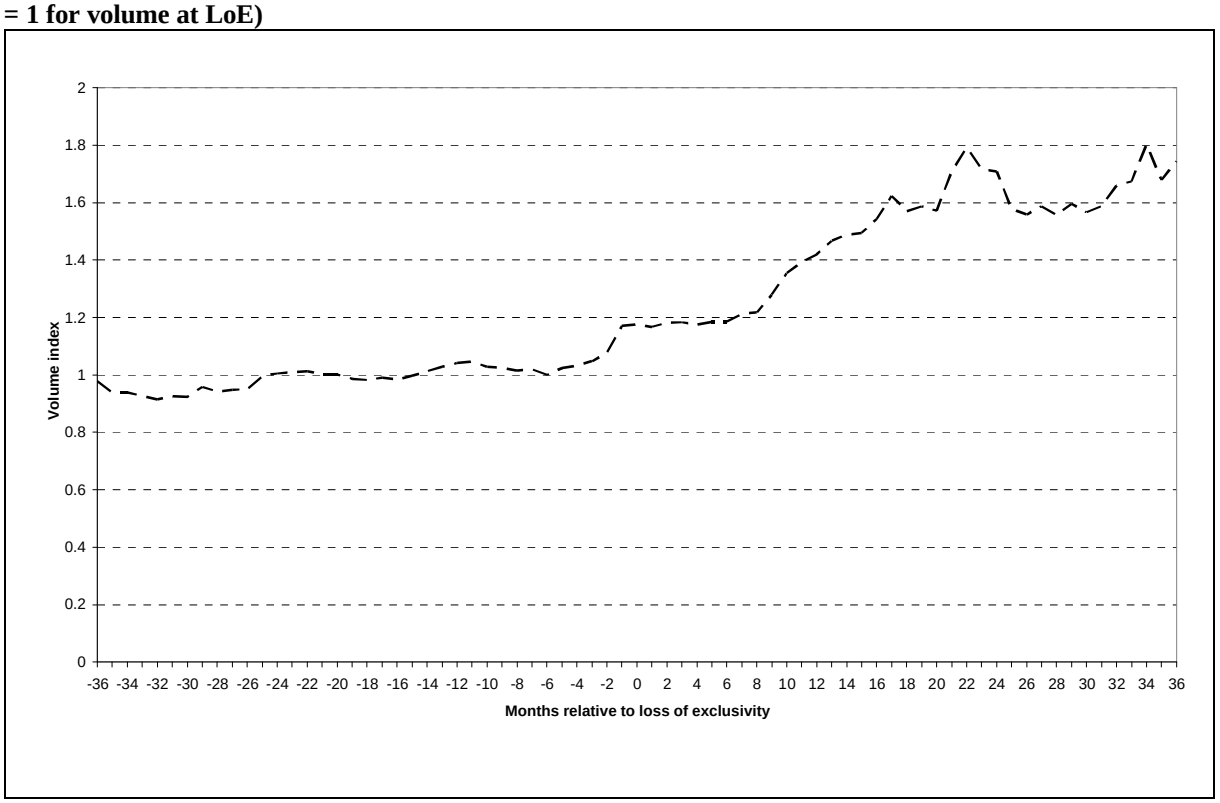


Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Measured by volume and value entry by generic companies appears to have had a very strong effect in Germany, the Czech Republic, Denmark and the UK. In Germany and the Czech Republic, generic companies built up a more than 50% share by value and volumes already within the first year. Measured only by volume, Denmark also shows a market share of generic companies exceeding 50% within the first year after entry.

Generic entry – especially when it is accompanied by significant price reductions – may also lead to an increase in overall consumption of the medicine. Figure 20 plots the development of the overall volume over time by considering an index, which is set at a level equal to one (1) six months prior to the end of the exclusivity period[29].

Figure 20: Volume effects of generic entry (sample: E75 list; all INNs with entry; weighted by INN; index = 1 for volume at LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

In the three years before the LoE, the consumption volume index remained fairly close to the 1.0 benchmark, but after generic entry the volumes consumed started to rise steadily. This may be partly related to the fact that the lower prices for the INNs losing exclusivity draws demand away from substitute products based on other INNs. This phenomenon is analysed in greater detail in the next section.

[29] The measure is taken six months before entry.

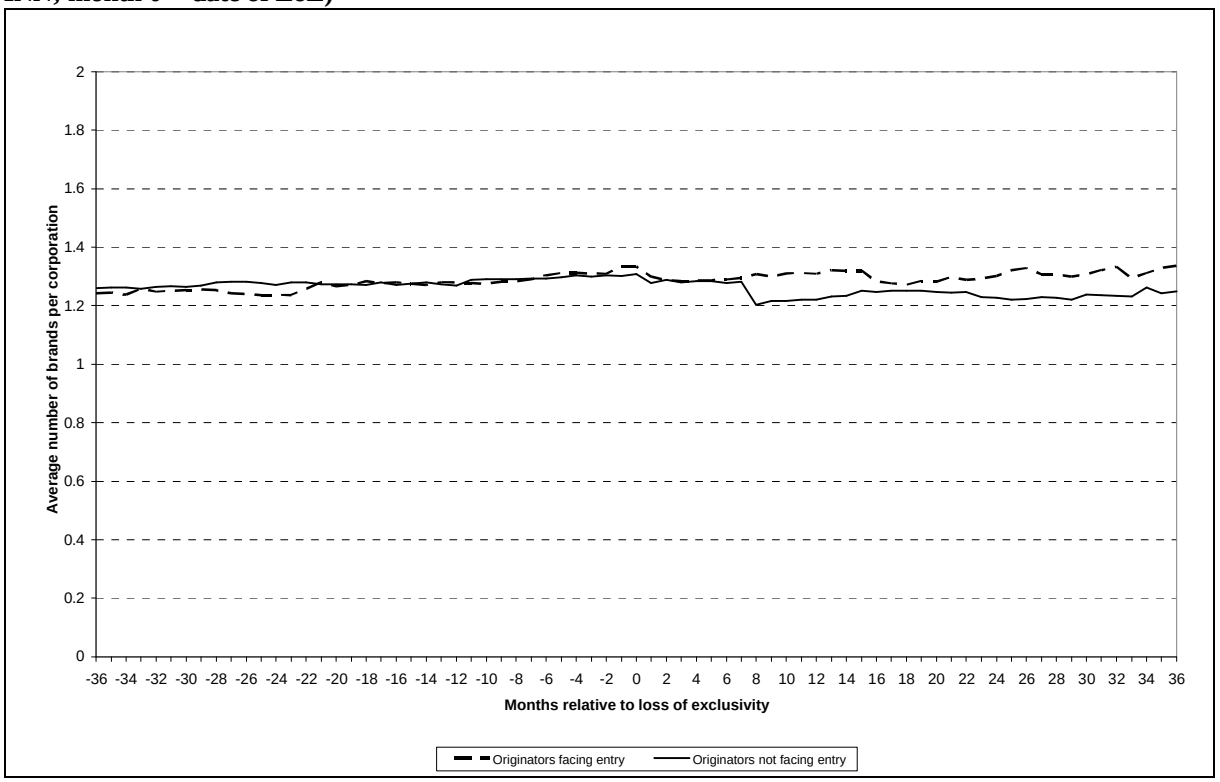
2.2.5. Responses of originators

As indicated above and presented in the pharmaceutical sector inquiry report, there are a number of ways in which the originator can anticipate or react to the entry of generics into the market. For instance, the originator can react in the form of product proliferation, advertising, pricing or litigation.

The first interesting point is how the product and brand portfolios develop over time. Figure 21 and Figure 22 below show the average number of brands per company and the average number of formulations per brand over time, respectively, differentiating between cases with and without generic entry.

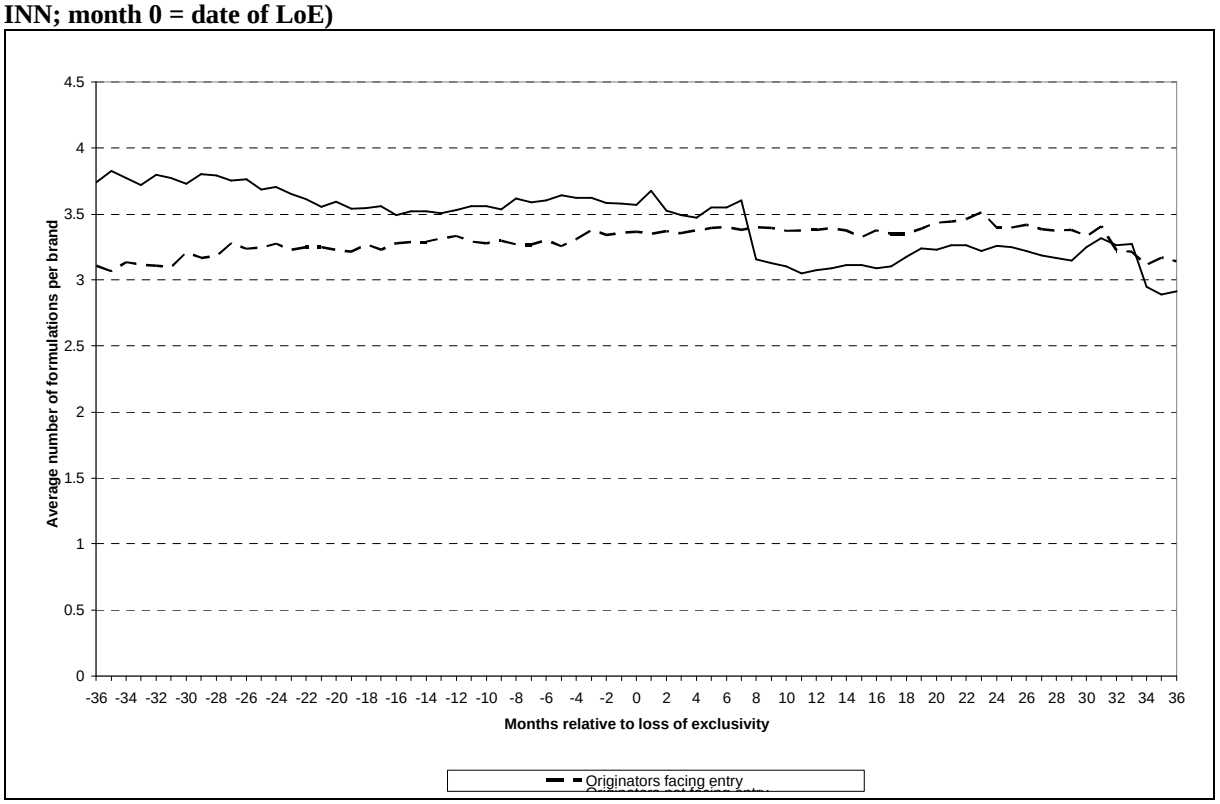
In terms of number of brands per corporation there appears to be little difference between originators facing entry and not facing entry. Nor do there appear to be major developments over time in this respect, although a very slight increase might be observed in the number of brands per company in the period leading up to LoE in those instances where entry took place. The average number of formulations per brand before LoE appears to show an increase in those instances where entry took place, whereas a relative decline in the number is visible in instances without entry. One tentative conclusion is that in the period before the INNs lose exclusivity, originator firms facing the prospect of entry have a tendency to increase the number of formulations per brand in anticipation of future generic entry.

Figure 21: Average number of brands per company (sample: E75 list; all INNs with entry; weighted by INN; month 0 = date of LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Figure 22: Average number of products per brand (sample: E75 list; all INNs with entry; weighted by INN; month 0 = date of LoE)



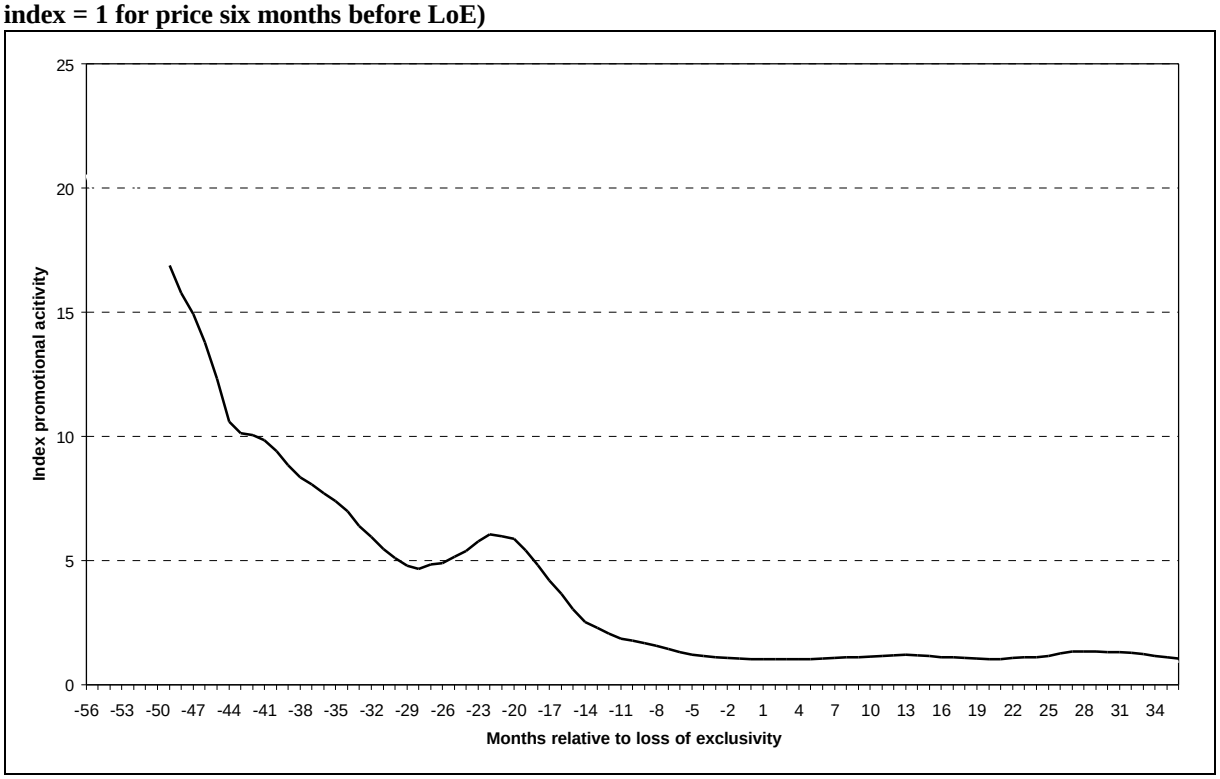
Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

Promotional activities (e.g. in the form of detailing activities, sales representatives informing doctors, advertisement) are another tool that may be used to influence the demand for

individual products. In particular, as indicated in the other sections of this report, it makes sense to divert promotional expenditure away from products that have lost exclusivity to products that are still protected.

The below graph presents the development over time of promotional activity. It appears that already well before the time of loss of exclusivity promotional activities decrease significantly. Around the time of loss of exclusivity, these activities stand at less than 10% of the level attained four years earlier. There is quite some variation across countries and INNs, however.

Figure 23: Promotional activity over time (sample: E75 list; weighted by INN; month 0 = date of LoE; index = 1 for price six months before LoE)



Source: Pharmaceutical Sector Inquiry (partially based on IMS data)

3. Econometric analysis

This part of the paper presents the econometric analyses undertaken by the CET. While Section 3.1 describes the analysis of the main determinants of the pattern of generic entry in terms of occurrence and number of entrants, Section 3.2 explores the main determinants of the time to entry. Section 3.3 describes the analysis of some of the main determinants of the effect of generic entry in terms of prices and shares of sales. Finally, Section 3.4 analyses the effects of generic entry on other INNs present in the ATC4 class.

The set of characteristics and potential determinants considered is presented in tables A – C (annex). Table A sets out the list of INN characteristics used in the regression analysis. Table B sets out the list of characteristics of the regulatory environment. Table C contains other control variables used in the analysis. Finally, table D lists the 219 INNs included in the data set.

3.1. Extent of Generic Entry: Occurrence of Entry and Number of Entrants

3.1.1. Introduction

The econometric analysis presented in this Section attempts to identify the main determinants of the pattern of generic entry observed in the data on the basis of a set of characteristics of the INN and the regulatory environment in the different countries.

The two models presented below analyse how this set of characteristics may affect (a) the probability of observing the entry of a generic in the market and (b) the scope of generic entry in terms of total number of generic producers entering the market. These two aspects are clearly related to each other, but nevertheless provide a different perspective on the issue of generic entry. For instance, a specific kind of price regulation in a country may make entry attractive for early generic entrants, at the disadvantage of later entrants, thereby reducing the number of entrants observed. Another example might be the case in which generic entry takes place under the control of the originator producer (e.g. via a distribution, license or settlement agreement). This constitutes a positive realization of generic entry, but may negatively impact upon the number of additional entrants.

Each INN in the data set is observed for a determined time period 2000 – 2007. For each of the INNs a specific loss of exclusivity date has been identified in a specific month in the period. However, it is important to compare like with like. Applying the analysis to the data as they stand, looking at the event of entry or the number of entrants at the end of the period, may give a distorted picture, since very different time horizons are available for the different INNs. Therefore, for the purpose of the analysis the two dependent variables of interest are recorded (a) one year after loss of exclusivity and (b) two years after loss of exclusivity.[30] At

[30] Estimation can also be carried out with a longer term perspective, taking into account the difference in time period during which each INN is observed since the moment of loss of exclusivity ("exposure time").

the same time, the relevant samples are adjusted accordingly, to INNs with loss of exclusivity in the period 2000 – 2006 and the period 2000 – 2005, respectively.

In order to test for the different determinants that either enhance or reduce generic entry, the entry decision by generic producers is modelled in the period around of loss of exclusivity, when the possibility to enter opens up. For this purpose, a number of explanatory variables have been included as measured at the moment of expiry.[31]

3.1.2. Methodological Framework

The fact of observing the entry of at least one generic entrant for an INN in a certain country is best analysed in econometrics using a binary outcome model, which takes into account the discreteness of the dependent variable (entry vs. no entry). Under distributional assumptions on the probability of the event of interest[32], the focus is on the conditional effect of each of a set of covariates or regressors (e.g. potential determinants) on the probability of observing entry of a generic company.[33]

The second model presented focuses on the number of generic entrants observed one and two years after loss of exclusivity (count data model).[34] The model is estimated assuming a negative binomial distribution of the dependent variable[35] and computing the marginal effect of each of the determinants on the dependent variable.

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31 For the variables available on a monthly basis, such as total revenue generated by the INN or price, the value six months before patent expiry has been used. For those variables for which information on an annual basis is collected, such as the regulation in place in the different countries, the characteristics in the year of loss of exclusivity have been used.

32 The most commonly used are the logistic distribution and the standard normal. The first case leads to what is called the logit model, the latter to the probit model. Given the similarity of the two distributions, the use of either of the two assumptions usually leads to very similar results.

33 Formally, let p_i denote the probability of observing entry of a generic company and x the vector of regressors to be tested on their impact on this probability. The model estimates the conditional probability as $p_i = Prob[y_i =1 | x_i] = F (x_i'* \bullet)$, where $\bullet$ is the vector of model coefficients and F is the cumulative distribution function of the logistic distribution (in the logit model) or of the normal distribution (in the probit model).

34 One could also consider, as an intermediate solution between the two models presented, the estimation of an ordered probit model. Such a model, using a setting which is an extension of the one of the probit model, would estimate the impact of the regressors on the entry of each additional generic producer with respect to the situation in which entry is not observed. For the sake of completeness, this model was tested and the results are fully consistent with those presented for probit and count data (see 1.3).

35 The Poisson distribution is the most commonly used distributional form for the count data model. In the Poisson distribution, the probability mass function of yi, the number of generic entrants observed, conditional on x_i, the regressors, is given by $p_i = Pr [y_i = y | x_i] = [(exp (- \bullet_i) * \bullet_i^y) / y!]$ where $\bullet_i \bullet exp(x_i' * \bullet)$. This distribution has the burdensome implication that the mean and variance of the distribution have to coincide; this property is known as equidispersion. In the present case the data do not fulfil this requirement, i.e. the sample variance of the number of generic entrants after 1-2 years is higher than its mean. For this reason the negative binomial is preferred, since it allows more flexibility in the distribution of the dependent variable. For a comprehensive discussion of the different properties of these models, see M. Verbeek, *A guide to modern econometrics*, John Wiley and sons Ltd. (2004), section 7.3.1.

As a natural consequence of the models chosen (involving a specification of the distribution function), the maximum likelihood estimation method was used.

In binary models, as well as in count data models, the coefficients cannot in principle be interpreted in as straightforward a way as for instance in ordinary least squares. Only the sign of this effect can be identified and interpreted. Further, the results can be recalculated in way that makes the coefficients interpretable also in terms of magnitude, so it provides a measure of the marginal effect of each of the covariates on the outcome. In Table 6 this modification has been applied to all the specifications presented.[36]

To obtain robust estimates, different sets of variables have been tested as potential explanatory factors. Many of them, even if potentially interesting from an economic perspective, were dropped since they were available only for a sub-sample of INN/countries.[37] To provide the more general results possible with respect to the molecules included in the E75 list for which statistics were provided, the choice was made to only include regressors which did not cause any further restriction in the sample.

The data set used includes the small number of INN/countries for which entry of the first generic appeared to take place before the date of loss of exclusivity. For consistency, the analysis was replicated on a restricted sample excluding the problematic early entries. The results for these estimates are presented for each specification and are consistent with the ones based on the full data set.

To control for the heterogeneity of INNs and countries in the sample, heteroskedasticity robust standard errors were used in all the specifications. The constant was also always included (not reported in the tables).

3.1.3. Regression Results

Table 6 reports the main results for the regressions for the probability of observing entry after one year and after two years. Each of the model variants 1 - 2 presents the same specification estimated on the complete data set and on the one obtained excluding early entries. In the regressions presented, attention was restricted to a subset of variables which fulfilled the statistical requirements for simultaneous inclusion in the regressions (i.e. the variables were not highly collinear).

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[36] Particular care should be taken in the interpretation of the coefficients. In binary models, the marginal effect of the change in one regressor on the probability of observing a positive outcome in the dependent variable can be obtained by differentiating the cumulative distribution function with respect to the regressor of interest: $\partial p_i / \partial x_{ij} = F'(x_i'\beta)\beta_j$, where $F'(z)=\partial F(z)/\partial z$. The marginal effect of each of the regressors changes with the point at which this effect is measured, i.e. the value of the other regressors present in the specification. The most common way is to compute the marginal effect at the sample average. This is what was done in the present case. Cf. Cameron A. C. and P. K. Trivedi, *Microeconomics, Methods and Applications*, Cambridge University Press (2005), section 1.4.3. In the case of a count data model, as for any model with exponential conditional mean, the coefficients need to be converted, taking the exponential, in order to give a measure of the marginal effect of each of the regressors, called incidence ratio. This modification was not applied to the coefficients presented in table 7.

[37] The variables referring to the ATC4 category of each INN were available only for certain countries. The same applies to the variable promotional expenditure.

Most standard controls (table A) seem to be statistically significant and robust across specifications. The value sales of the original drug prior to loss of exclusivity included in per capita terms, seem to be a clear driver of generic entry. At the same time, also the geographical size of the market, taken into account by the population of the country, seems to attract early entry of generic producers.

On average, INNs for which a high number of different formulations are present tend to attract more entry than others. The negative coefficient for the price prior to loss of exclusivity may suggest that, controlling for the revenue generated by the originator product, generic companies tends to enter in those medicines which might be the less complicated to produce. [38]

The results also show an improvement over time in terms of generic entry to markets, both in the short term and in the longer term perspective. The probability of observing the first generic entry within the first year increases on average by 5% for each year.[39]

For what concerns the regulatory variables (Table B) the full set of variables was tested.

Policies involving compulsory substitution of generic products by pharmacists seem to positively affect the probability or entry. The coefficient found is positive and statistically significant in all the specifications.[40]

The presence of price caps appears to negatively affect the probability or entry, at least in the short run. The other regulatory variables included do not seem to show coefficients that are statistically significant in a stable manner.

The regressions include a number of additional control variables (Table C). The first is a control variable for the presence of a generic entry controlled by the originator company. The variable takes the value one for the case in which an entry took place either as the result of a distribution agreement between originator and generic producer, or in the context of a settlement. The coefficient is positive and statistically significant.[41] In cases in which a

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[38] The price of the product might also be interpreted as a proxy for the importance of sales of highly expensive formulations within the INN, which are on average more difficult to replicate. It is further important not to confuse a unit price of the product with a profit margin on that product. These are two different economic values.

[39] This figure should be interpreted with care since the relevant time window for the first generic entry (i.e. one year) overlaps to a large extent with the average time to entry calculated at a head count. Therefore a very small downward change over time in the values situated in the proximity of the central point (here one year) may have an important impact on the presented probability. The possible presence of multicollinearity between the *expiry year* and *pre-expiry value* was checked (so as to see whether INNs expiring later in the period also tend to have higher sales values and therefore attract more entry), but the correlation coefficient is lower than 0.2.

[40] A slightly modified version of this specification was also tested, including of the interaction between *compulsory_substit* and *physicians_encourage_gen.* When these two policies take place at the same time, i.e. both physicians and doctors are encouraged/obliged to dispense generic products, the probability of observing swift generic entry seems even higher.

[41] This result needs a statistical explanation. In theory, the presence of a controlled entry would logically imply the positive realisation of entry in the dependent variable. If this is the case, the regressor should be dropped as predicting only successes and therefore being statistically irrelevant. This is indeed not the

controlled entry was recorded, the probability of observing generic entry increases significantly.

When deciding whether or not to enter a specific market, a generic producer may take into consideration the fact that the product in question has lost exclusivity also in other countries. In that case, entering in several countries might lead to economies of scale and enhance the attractiveness of entry in one particular country. The variable *n_countries_expired* takes into account this aspect. It reports the expected (positive) coefficient even though it is not always statistically significant.[42]

As explained, an INN that relates to different ATC4 categories is present in the data set in the form of multiple observations. It might be reasonable to consider that for these the decision to start selling products for one ATC4 class may be linked to the possibility of selling products based on the same INN in another class. At the same time, where the ATC4 classes are different there might be a selection by the generic company to enter the simpler and/or bigger ATC4 category. In the regressions presented, this is controlled for by the dummy variable *other_atc4*, which indicates whether or not there are multiple ATC4 categories linked to the INN. This control variable, even if always reporting a positive result, is never statistically significant.[43]

Also the level of promotional effort undertaken by the originator producer before the loss of exclusivity was considered. However, an endogeneity problem may occur when including this measure in the model specification. Being a potential instrument for the originator company to maintain brand recognition even after loss of exclusivity, promotional activity might be a response to the observed increased probability of having swift generic entry. In addition to this econometric problem, the data availability for promotional expenditure was limited to seven countries, significantly restricting the sample.

Results for the count data (number of generic companies entering) appear to go in the same direction as the probit analysis for what concerns the variables value sales and price. The number of formulations in which the originator drug was present in the market before expiry, significant at the 5% level only in the probit regressions one year after LoE, seems to have an effect on the number of generic producers entering, regardless of the time perspective considered.

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case since in many cases it was possible to identify the controlled entry in the data. For these entries, the probability of observing first independent generic entry after the controlled entry takes place was tested.

42 To check robustness, alternative approaches were considered. A simple alternative is the use of a dummy variable to account for the presence of at least one other country in which the INN in question lost exclusivity. Another alternative is to use, instead of the number of countries, the aggregate value sales of the INN in these countries before loss of exclusivity. Results for these two alternatives are consistent with the one presented.

43 Alternative specifications were also considered to check robustness. First, a specification using the number of ATC4 classes per INN was tested. Additionally, the probit specification was run with standard errors clustered at the INN/country level, to take into account the possible correlation between the choices of entering different ATC4 categories for the same INN. Finally, also a specification on the data set at country/INN level, i.e. ignoring therefore the possible ATC differentiation within INNs, was run. The results obtained with these three variations were consistent with the base line specification presented in Table 6 and 7.

A positive and statistically significant effect of compulsory generic substitution on the number of entrants is confirmed by the statistical significance in all regressions. The negative effect of price caps, affecting the probability of entry only in the short run, seems to have a consistent and long lasting effect on the number of generic entrants. The results for controlled entry are consistent with the probit model, while the other additional controls all report the expected sign.

The results are overall confirmed when observing the total number of generic producers present at the end of the period, presented in the final set of regressions in Table 7.[44]

3.2. Time to Entry

3.2.1. Introduction

The econometric analysis in this section aims at identifying the determinants of the delay of generic entry, i.e. the length of the time period between the loss of exclusivity (when generic producers can potentially enter) and the first actual entry of a generic producer.

Even if entry of generic producers eventually takes place, its delay vis-à-vis the date of loss of exclusivity is potentially costly to patients. Without the delay (or with shorter delay), competition between originator and generic producers is likely to drive prices down sooner and create savings for the patients. For this reason, it is interesting to search for determinants of the delay. For example, if a particular feature of regulatory regimes could be attributed to a short or no delay of generic entry, it could be used by regulators to speed up competition from generic producers in the pharmaceutical market.

3.2.2. Methodological framework

Time to entry (the time span between the loss of exclusivity and the entry of the first generic company) can be best analysed using methods to model time-to-event data. These methods have been developed to describe the time an individual spends in a state until the transition to another state and to study the relationship between the individual's characteristics and transition patterns.

The time spent in the state, in our case the time between the loss of exclusivity and the first generic firm's entry, is called a spell. The random variable to be studied is the length of the spell. Let T be a continuous random variable representing the length of a spell, with a cumulative distribution function $F(t)$ and a density function $f(t)$. The survivor function is $S(t) = 1-F(t)$, i.e. the probability of transition before t. The hazard rate is defined as $\bullet(t) = f(t)/S(t)$, which is the "instantaneous transition intensity" at moment t, provided that there was no transition until t.

[44] The sample has been restricted to those country/INNs for which observations are available for at least two years after loss of exclusivity. Estimation takes into account the difference in time period during which each INN is observed since the moment of loss of exclusivity ("exposure time").

The hazard rate is assumed to fulfil the proportional hazard assumption: $\lambda(t,X_{ijt}) = \lambda_0(t)\exp(\beta' X_{ijt})$. $\lambda_0(t)$ is called the baseline hazard function and depends only on the time since the loss of exclusivity, while vector X_{ijt} depends on other factors and can be time-dependent. The hazard rate for different molecules is therefore the baseline hazard multiplied by a factor related to the vector of the characteristics of the molecule.

The hazard rate can be specified in terms of discrete or continuous time. Entry of a generic firm can in principle take place at any point in time, so a continuous time approach seems appropriate. On the other hand, only monthly data are available and entries are grouped by month (so-called ties). When such cases are common, a discrete representation of a continuous time process would be preferable. Both approaches are used in the analysis.

3.2.3. Implementation

A panel data set was used for this purpose. One observation in the data set is related to a molecule in an ATC4 category, in a country in a month. Molecules from 17 countries were analysed and the time period covered is January 2000 – December 2007.[45] For each molecule per country, the first observation comes from one month before loss of exclusivity and the last observation is either in the month with the first generic firm entry or in December 2007 which is the last month in the data set. The data set is the right truncated spell data with varying censoring point. It means that for each country-INN-ATC4, at the end of a spell, we observe if entry of a generic firm took place or did not take place and the length of the spell is different for different country-INN-ATC4 combinations.

The dependent variable d_{ijt} is a dummy variable which is equal to one if there was first generic firm entry for molecule *i* in country *j* in month *t* since loss of exclusivity and zero otherwise. For different specifications of the hazard rate, different link functions are used.

Covariates from tables A – C are used: a set of regulatory variables, a set of INN characteristics and a country-specific variable *population*. In addition, to capture the time trend, bi-annual dummies were created (2000-2001 is the benchmark and therefore omitted) to indicate in which year the INN lost patent/data exclusivity. Discrete specifications include also the baseline hazard covariates.

The hazard proportionality assumption is checked by including into the regressions all variables interacted with functions of time since loss of exclusivity. If such interacted variables are not statistically significant, this indicates that their hazard is not likely to be time-dependent. This is done in a Cox regression with Breslow method for ties. Time functions considered are linear, quadratic and logarithmic functions of the number of months since the loss of exclusivity. The only variable that appears not to satisfy the hazard proportionality assumption is an INN characteristic *biosimilar*. For this reason, *biosimilar* was not used in the hazard models.

For several specifications the shape of the baseline hazard function needs to be selected. In continuous-time specifications, the Weibull function is used because it is flexible and can have an increasing, decreasing, as well as constant shape. In discrete-time specifications, the

[45] The number of molecules differs depending on the treatment of negative delays (see above). When an INN with a negative delay is included, it is assumed that a generic firm entry took place immediately after the loss of exclusivity.

quadratic function is used (selection based on descriptive statistics, see part 2.3). In addition, specifications with non-parametric baseline hazard (Cox) are considered.

To account for unobserved heterogeneity of INNs (so-called frailty), an INN-country-specific random intercept is included. Most of the regressions make distributional assumptions about the random effect (normal or inverse normal), but non-parametric frailty coming from a discrete distribution with up to two mass points is also considered.

Specifically, the following five specifications are analysed:

- Cox semi-parametric hazard model. The hazard rate in this model is specified as

$$\theta(t, char_{ijt}, reg_{ijt}, pop_{ijt} \mid v_{ij}) = v_{ij}\alpha t^{\alpha-1}\exp(\beta_1 char_{ijt} + \beta_2 reg_{ijt} + \beta_3 pop_{ijt})$$

The baseline hazard function $\bullet_0(t)$ remains unspecified and the partial likelihood estimation method is used. Time is assumed to be continuous. Ties are treated as if generated by discrete time.

- Weibull model with the hazard rate

$$\theta(t, char_{ijt}, reg_{ijt}, pop_{ijt}) = \alpha t^{\alpha-1}\exp(\beta_1 char_{ijt} + \beta_2 reg_{ijt} + \beta_3 pop_{ijt})$$

The baseline hazard has a shape of the Weibull function: $\bullet_0(t) = \bullet t^{\bullet-1}$ *where* $\bullet > 1$. The shape parameter $\bullet$ is estimated together with coefficients of regressors. When $\bullet$ is greater than 1, the hazard is increasing. When $\bullet$ is lower than 1, the hazard is decreasing. Finally, when $\bullet$ equals 1, the hazard is constant. Time is assumed to be continuous.

- Weibull model with frailty (INN-country-specific random effects). The hazard rate is

$$\theta(t, char_{ijt}, reg_{ijt}, pop_{ijt} \mid v_{ij}) = v_{ij}\alpha t^{\alpha-1}\exp(\beta_1 char_{ijt} + \beta_2 reg_{ijt} + \beta_3 pop_{ijt})$$

where $\bullet_{ij}$ is a random variable distributed independently of *t, X, Y* and *Z* and has an inverse normal distribution.

- Discrete-time specification for an underlying continuous-time process (cloglog) with parametric frailty

$$\theta(n, cahr_{ijn}, reg_{ijn}, pop_{ijn} \mid v_{ij}) = 1 - \exp(-\exp(\alpha_1 n^2 + \alpha_2 n + \beta_1 char_{ijn} + \beta_2 reg_{ijn} + \beta_3 pop_{ijn} + u_{ij}))$$

where n is the month, $u_{ij} = ln(v_{ij})$ is a random variable with the standard normal distribution and $\bullet_1 n^2 + \bullet_2 n$ is the baseline hazard function.

- Discrete-time specification for an underlying continuous-time process (cloglog) with non-parametric frailty from a discrete distribution with the support of two mass points:

$$\theta(n, char_{ijn}, reg_{ijn}, pop_{ijn} \mid \mu_r) = 1 - \exp(-\exp(\alpha_1 n^2 + \alpha_2 n + \beta_1 char_{ijn} + \beta_2 reg_{ijn} + \beta_3 pop_{ijn} + \mu_r))$$

For all specifications except Cox, maximum likelihood estimation is used to take care of censoring. Each observation in the data set contributes to the likelihood of the

information it carries: whether there was entry in period *t* or whether in period *t* the INN was still the realm of the originator company.

3.2.4. Non-Parametric Estimates of Time to Entry

First, the Kaplan-Meier estimator of the survivor function and the Nelson-Aalen estimator of the cumulative hazard are plotted. These two estimators do not use any parametric assumptions. Intuitively, the estimate of the survival at time t is the product of "survival rates" in each point in time until t, i.e. the product of the proportions of INNs which did not face the first generic entry at this time in the total number of INNs that before time t still had no generic competitors. Similarly, the cumulated hazard estimate is the sum of "exit ratios" for each month until t. Both are presented in Figure 24.

The estimated survivor function has a large drop of about 19% in the first month after loss of exclusivity, which means that about 19% of INN-country pairs experienced a generic firm entry right after the loss of exclusivity. Note that the full data set includes molecules with negative delays which for the purpose of this estimation are converted to zero delays.

The first few months after the loss of exclusivity, the survival probability is dropping at a decreasing pace. Later in time, the changes in the survivor function are smaller and relatively constant, resulting in the close-to-linear shape of the survival function.

The above observations are mirrored in the shape of the estimated cumulated hazard function. It starts at the level over 19%. Then it grows at a decreasing and then relatively constant pace.

The estimates suggest that the hazard rate of the first entry of a generic firm is decreasing, first at a diminishing rate and then at a relatively constant rate.

The non-parametric estimates were also calculated for the time elapsing between the first and the second entry of a generic competitor. These are presented in Figure 25. The survival function is convex and the cumulated hazard concave, indicating that the second generic firm entry (relative to the first entry) seems to take place more quickly than the first generic firm entry (relative to the loss of exclusivity). Already after three months, about 50% of INN-country pairs which have experienced the first generic firm entry face the entry of the second generic firm. Only about 10% of INN-country pairs which have experienced the first generic firm entry never note entry of the second generic firm.

3.2.5. Regression Results

The results for the full data set are presented in Table 8. Reported coefficients for dummy variables can be interpreted as a percentage change in the hazard rate due to a change in the covariate, holding everything else constant.

Control Variables

In all specifications, the *controlled entry* variable is statistically significant and greater than one. This implies that, holding everything else constant, INNs with entry controlled by originator companies face significantly earlier first entry (though not necessarily independent generic entry) than other INNs. This result is not surprising since the data counts the

controlled entry as the first generic firm entry. However, this result is not robust to the treatment of negative delays (see section 2.2.6).

The *pre-expiry number of formulations* has coefficients greater than one and statistically significant in four specifications. This implies that the larger the number of formulations, the faster first generic entry tends to be.

The coefficients of the *pre-expiry market value per capita* are greater than one and statistically significant, implying that the larger the value of the INN/ATC4/country market, the faster first entry of a generic competitor.

The coefficients of the *pre-expiry price* variable are slightly smaller than one and always statistically significant. Therefore, it appears that faster first generic firm entry can be associated with less expensive products.

Population variable helps to capture the effect of the size of the market. The estimated coefficients are always statistically significant, but equal or slightly larger than one.

Two dummies are included to capture the links between the same INN across countries and different ATC4 classes within one country. The coefficient of *already_expired_country* is always greater than one and significant in one specification. The coefficient of *other_atc4* also comes out greater than one and statistically significant in the second specification, suggesting that when an INN is present in several ATC4 classes, first generic entry may be faster than otherwise.

Regulatory Variables

Compulsory substitution: in all specifications the coefficient is greater than one and statistically significant. This implies that the hazard of the first generic entry for molecules in countries with compulsory generic substitution policy is higher than the hazard for molecules in countries without this policy. Therefore compulsory generic substitution policy appears to be correlated with faster generic entry. Figure 26 shows the predicted survivor and cumulated hazard functions estimated by the Cox regression from the first column of Table 8.

Physicians encouraged to prescribe INNs: the estimated coefficient is always larger than one and statistically significant in more general specifications with frailty. This suggests that, holding everything else constant, the INNs in countries where this policy is used have a higher hazard rate of the first generic company entering than other countries.

Frequent adjustment: in all specifications the coefficient appears greater than one but not statistically significant.

Differential copayment: the coefficient is always lower than one but statistically significant only in non-frailty regressions. Statistical significance also disappears in the robustness checks (see section 2.2.6). Therefore, the data do not appear to identify an effect of this variable.

Lowest_price_policy: in all specifications the coefficient is statistically insignificant. The data do not appear to identify an effect of this variable.

Price caps: the coefficient is statistically significant and lower than one, meaning that the hazard of first generic firm's entry for molecules in countries with price caps is lower than the hazard for molecules in countries without price caps. It would appear therefore that a policy of mandatory discounts/price caps for generic firms is correlated with slower generic entry (see also Figure 27 for illustration). This effect is however not very strong in that it disappears in the robustness checks (see part 2.5).

Time Trend

Bi-annual dummy variables are statistically significant and greater than one. Furthermore, when comparing their magnitude one can observe that the magnitude is the largest for the years 2006-2007 and it gets lower the earlier loss of exclusivity took place. That suggests that, holding everything else constant, the hazard rate of the first generic firm entry is larger, the later in the time period under analysis the loss of exclusivity occurs. (See Figure 28 for an illustration)

Baseline Hazard

The baseline hazard function shows the shape of the hazard rate of the first generic entry in time which is shared by all INN-country pairs. When not including frailty, this function is decreasing over time at a decreasing rate (the estimated Weibull parameter is lower than one), just as the descriptive Kaplan-Meier and Nelson-Aalen estimators suggested. When frailty is included, the hazard is almost constant over time (the estimated Weibull parameter almost equal to one). This suggests that frailty takes away the effect of very early first entries from the baseline hazard shared by all INNs.

Figure 29 presents the baseline cumulative hazard and the baseline survivor functions for an INN with the mean log of market value before loss of exclusivity (-5.04) estimated in the Cox regression reported in the first column of Table 8. Both functions have a close-to-linear shape.

3.2.6. Robustness

Table 8 presents five specifications of the hazard equation which allow for several robustness checks of the results. The results of continuous- and discrete-time models are to a large extent consistent. In models with frailty, the coefficient for *physicians_encourage_gen* becomes statistically significant. To the contrary, the coefficient of differential co-payment loses significance when frailty is included. The results are almost the same for all three frailty distributions.

Further robustness checks were done to test if the results are sensitive to the treatment of negative delays. The regressions were repeated on the data set with all negative delays dropped and on the data set with only substantial negative delays dropped. Substantial negative delays were defined as delays exceeding 3 months. Control variables are introduced to flag INN-country pairs with large and small negative delays. Table 9 presents the results. Cox and cloglog with non-parametric frailty models did not converge.

The coefficient of the *compulsory substitution* variable remains highly significant and greater than one in all specifications. The coefficient of the variable doctors prescribing generics comes out greater than one and statistically significant in all specifications. The coefficients

for the *differential copayment* and *price_cap* variables remain lower than one but never statistically significant.

3.3. Price Effects of Generic Entry and Generic Penetration

In order to assess the nature of the post generic entry market structure of the pharmaceutical markets, and in addition to the other evidence put forward by the report, an econometric analysis of the post-entry change in the average price level and generic producers' market share was carried out.

Two main model designs were set up. In the first design the long-run market structure was analysed, which amounts to modelling the change in average drug prices at the end of the sample relative to the price level prior to loss of exclusivity, and the end-of-sample shares of generic producers.

The second design is capturing four intermediate stages, or vintages, of the market. The first vintage model analyses price drops and generic shares one year after the first entry. Likewise, the second, third and fourth vintage models describe price drops and shares two, three and four years after the first entry, respectively.

Several robustness checks were also carried out by analysing different versions of the main models.

3.3.1. Data

The econometric analysis used a data set based on the combined company and IMS data set described in the Annex on methodology. The estimation used cross sectional data sets. In addition to the variables described in Tables A to C, the following variables were created.

- *Long-run price drop:* the percent drop of the average price level between the last data period (December 2007) and the level prior to loss of exclusivity for a given country/INN pair.

- *One-year, two-year, three-year and four-year price drops:* the percent drop of the average price level between the last quarter of the first (second, third, fourth) year after the first entry and the level prior to loss of exclusivity for a given country/INN pair.

- *Long-run generic shares:* volume shares of generic products in a given country, in a given INN, in the last quarter of the sample. This variable is a measure of the generic products' market penetration.

- *One-year, two-year, three-year and four-year generic shares:* volume shares of generic products in a given country, in a given INN, in the last quarter of the first (second, third, fourth) year after the first entry in the country/INN pair. This variable is also a measure of the generic products' market penetration.

3.3.2. Models

All models are linear regressions where the variation in the left hand side variable (explained variable) is explained by the right hand side variables (explanatory variables). The different models vary along their left hand side and right hand side variables.

Long-Run Price Drop Regressions

Long-run price drops were regressed against the following set of explanatory variables:[46]

- The final number of generic producers in the given country/INN pair;
- Characteristics of the INN;
- Regulatory variables at the country level;
- Population of the country;
- Indicator variables related to INNs which had negative delays during their history.

The estimation sample was restricted in each country to those INNs which already had at least two years of post-entry history.

The long-run price drop model attempts to shed light on the factors affecting the most complete price changes observable in the data and potentially related to the generic entry process. The models' coefficients can be interpreted as effects on the longer-term state of the market after the occurrence of entry.

Positive coefficients can be interpreted as factors inducing to tougher price competition, and the negative ones as those softening competition. Individual coefficients in the model represent partial effects. It means that each coefficient represents a complementary additional effect of a given explanatory variable holding the other variables constant.

In the cross section, some INNs are 'older' which means that more time passed since the first entry, while others are younger (but still are at least two years old). This variation across INNs is captured by the generic age variable which counts the number of periods since the first entry on the given INN.

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[46] Formally:

$$dprice_{ic} = \beta_0 + \beta_{ngenr} * ngenr_{ic} + char_{ic}'*\beta_{char} + reg_c'*\beta_{reg} + \beta_{pop} * pop_c + ndel_{ic}'*\beta_{ndek} + \varepsilon_{ic}$$

where *dprice* is the percent price drop, *ngenr* is the number of generic producers, *char* is the vector of INN characteristics, *reg* is the vector of regulatory variables, *pop* is the log of the country's populations, *ndel* is a dummy variable for negative delay cases and • is the error term. INNs are indexed by *i* and countries by *c*.

Vintage Price Drop Regressions

Four vintage price drop regressions were estimated. The corresponding one (two, three, four) year price drops were regressed against the same set of explanatory variables as in the long-run price drop regressions.

The series of vintage price drop models, relative to the long-run model, attempts to shed light both on the shorter and longer term effects after entry. Hence, the coefficients can still be interpreted as effects on the state of the market but this state is not necessarily the one where the market would eventually be stabilized, especially in the earlier vintages (the first and second years). Positive coefficients can be interpreted as factors conducive to tougher price competition, and the negative ones as those softening pricing.

Long-Run Generic Share Regressions

Long-run generic shares were regressed against the following set of explanatory variables:[47]

- The average price of generic products and the average price of originator products in the given country/INN pair;
- Characteristics of the INN;
- Regulatory variables at the country level;
- Population of the country;
- Indicator variables related to INNs which had negative delays during their history.

The estimation sample was again restricted in each country to those INNs which already had at least two years of post-entry history. The technical details of the long-run share regressions are similar to those of the long-run price drop regressions.

Positive coefficients can be interpreted as factors conducive to higher generic penetration. Individual coefficients in the model represent partial effects.

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[47] Formally:

$$gen\_share_{ic} = \beta_0 + \beta_{pg} * price\_gen_{ic} + \beta_{po} * price\_ori_{ic} + char_{ic}'*\beta_{char} + reg_c'*\beta_{reg} + \beta_{pop} * pop_c + ndel_{ic}'*\beta_{ndek} + \varepsilon_{ic}$$

where *gen_share* is the volume share of generic products, *price_gen* is the average price of generic products, *price_ori* is the average price of originator products, *char* is the vector of INN characteristics, *reg* is the vector of regulatory variables, *pop* is the log of the country's populations, *ndel* is a dummy variable for negative delay cases and • is the error term. INNs are indexed by *i* and countries by *c*.

Vintage Generic Share Regressions

Similarly to the price drop model, four vintage generic share regressions were estimated. The corresponding one (two, three, four) year generic shares were regressed against the same set of explanatory variables as in the long-run share regressions.

3.3.3. Main estimation results

Long-run price drop regressions

Table 10 summarizes the main results from the price drop regressions. The baseline long-run price drop model (Model VI.) shows that the coefficient of the *number of generic entrants* variable is positive and statistically significant even though its value is small.

In the long-run price drop regressions, regulatory variables are statistically significant. The signs, with the notable exception of the *price cap* regime indicator, are positive.

The *pre-expiry value per capita*, *generic* age and *biosimilar* variables have positive and statistically significant coefficients. The *pre-expiry number of formulations* estimate is negative and statistically significant. As it is explained in Section 1.3, this variable tends to have a positive effect on both the probability of entry and the number of entrants. The explanation of the different signs in the price drop and entry models could be that the number of formulations is a measure of product differentiation within a given INN. A market with more product differentiation attracts more entry and provides an opportunity to price relatively higher. The other variables do not seem to significantly contribute to the explanatory power of the regression.

Vintage Price Drop Regressions

The baseline vintage price drop models (Model I-V. in Table 10) show that the coefficient of the *number of generic entrants* variable has a small, statistically significant, positive estimate.

From the main regulatory variables, the *price caps* and *lowest price policy* variables are always statistically significant, the former having a negative, the latter a positive estimated coefficient. The *frequent adjustment*, *physicians encouraging* and *compulsory substitution* are significant and have a positive effect in most vintage regressions. Differential copayment is statistically significant only in the first two vintages with positive estimates.

The *pre-expiry value* of the INN per capita is also positive and statistically significant. The *population* variable has a statistically significant and negative estimate in most vintages. Possibly it picks up some of the country effects. The other variables do not seem to significantly contribute to the explanatory power of most of the regressions.

Long-Run Generic Share Regressions

Table 11 summarizes the main results from the generic share regressions. The baseline long-run generic share model (Model VI.) shows that both *generic* and *originator prices* have a

statistically significant estimate with the expected signs (negative and positive, respectively).[48]

Among the regulatory variables price cap, *frequent adjustment, physicians encouraging,* and *compulsory substitution* are statistically significant. The signs, with the exception of price cap, are positive.

The *pre-expiry value per capita, generic age, biosimilar* and *population* variables have positive and statistically significant coefficients.

The *controlled entry* estimate appears negative and significant.

The other variables do not seem to significantly contribute in a stable way to the explanatory power of the regression.

Vintage Generic Share Regressions

The baseline vintage generic share models (Model I-V. in Table 11) show that both *generic* and *originator prices* have a statistically significant estimate with the expected signs (negative and positive, respectively).

From the main regulatory variables, the *price caps* and *compulsory substitution* variables are always statistically significant, the former having a negative, the latter a positive estimated coefficient. *Frequent adjustment, lowest price policy* and *physicians encourage* are only significant (with positive coefficients) in two and three vintages, respectively. The differential copayment variable is not significant statistically in any of the main generic share regressions.

The *controlled entry* variable has a statistically significant negative effect in two vintages.

The *biosimilar* indicator appears statistically significant with a positive coefficient in three vintages. The other variables do not seem to significantly contribute in a stable way to the explanatory power of the regression.

3.3.4. Robustness Checks

In order to assess the stability of the results, various robustness checks were implemented.

First, the models were re-estimated by (i) dropping observations related to negative time to entry larger than 3 months, and (ii) dropping all negative time to entry related observations.

The summary tables of all these robustness checks are presented in Table 12, Table 13 and Table 14. In these tables the signs of the statistically significant explanatory variables are displayed along with the specification tests.

[48] It should be noted that the price variables used in the generic share regressions are the *current* prices as opposed to the *pre-expiry price* variable in the entry models of Sections 1 and 2. The coefficients on the price variables in the share regressions measure own and cross-price effects (with respect to originator products of the same INN) on the generic shares.

Second, the models has also been estimated using (i) robust regressions, controlling for potential outliers, and (ii) instrumental variables estimations controlling for potential endogeneity of the *number of generic producers*, *the price of originator* and *price of generic products variables*. Endogeneity of these variables might arise as prices, quantities and the number firms is determined simultaneously in an industry equilibrium. The implemented two-step efficient GMM estimation used Hausman-Taylor-type instruments: the average number of generic producers, average prices of originator and generic products in other countries. These instruments can be motivated using the assumption that different countries represent separate markets with country specific demand shocks.[49]

The main results and qualitative conclusions from robust regressions and instrumental variables estimation, as shown in Table 15 and Table 16, are unchanged.

3.3.5. Conclusions

The main patterns emerging from the regression analysis of price drops and generic shares are the following.

- The *price cap* policies seem to have a negative effect both on the extent of price competition and on the penetration of generic drugs. A possible explanation could be that in the longer run the price cap becomes a focal point for the generic companies, i.e. the producers align their pricing to this focal point and even though they could potentially undercut this price they stick to it instead. This might result in higher average prices than without a price cap.

- The *frequent adjustment, physicians encourage* and *compulsory substitution, lowest reimbursed price* and, in a somewhat less pronounced way, the *differential copayment* policies tend to have a positive effect on the extent of price competition.

- The magnitudes of the coefficients on the regulatory variables (with the exception of *differential copayment*) in the price drop regressions tend to increase from the earlier vintages to the older ones. This pattern implies that the full effect of the different regulatory regimes on the extent of price competition is built up gradually after the first entry.

- The *compulsory substitution* and, in a somewhat less pronounced way, the *frequent adjustment*, physicians encouraging and *lowest reimbursed price* policies tend to have a positive effect on generic drug penetration.

- The results also provide some evidence that in the case of INNs in which controlled entry was observed overall generic market share penetration (controlled and independent) tends to be lower.

- Consistent with standard demand theory, the average price of generic products has a negative, while the average price of originator products a positive effect on the shares of generic drugs.

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[49] On instrumental variables estimation see, e.g., J.M. Wooldridge: *Econometric Analysis of Cross Section and Panel Data*, MIT Press, Cambridge, Massachusetts, 2002, Chapter 5.

- The *number of generic producers* of the same INN tends to positively affect price competition.

3.4. Potential Effects of Generic Entry on other INNs in the ATC4 Class

When a generic company enters with a generic version of a given INN, in the sense that it starts selling (some of the) formulations of the INN that have lost their exclusivity, this may have an impact not only on sales of the INN concerned (in particular, the total level of sales and the sales of the originator company), but also on the sales of other products based on different INNs.

In particular, generic entry in a given INN that lost its exclusivity and the subsequent reduction in the average price of this INN may attract consumption away from other INNs. ATC 4 classes contain INNs that share, to a greater or lesser extent, some therapeutic characteristics. Therefore, for the purpose of the sector inquiry, they constitute a reasonable starting point for the group of INNs within which to analyse patterns of potential substitution across INNs.

To identify such potential switching effects, the analysis looks at the evolution of volumes of other INNs that were active in the same ATC4 class when the loss of exclusivity took place. Most of the analysis focuses on the extent of correlation between, on the one hand, the volume of INNs sold in the same ATC4 class after LoE and, on the other hand, the prices of the INN of reference losing exclusivity. It should be emphasized, however, that this subsection does not necessarily pretend to reflect causal relations, but rather correlations. The coefficients studied in this section are merely an indicator of potential effects of generic entry on other INNs. Further, no position is taken on the economic significance of the estimated coefficients, e.g. whether they are large or small in the context of the ATC class. With respect to the previous subsections, the analysis presented below is characterised by having mainly an exploratory purpose.

For the purpose of the analysis, the principal data set (based on company data and IMS data for the INNs in the E75 list) was combined with monthly data on sales, volumes and prices obtained from IMS for all the INNs in any ATC4 class to which at least one INN in the E75 list belongs. The analysis was based on 9 Member States (Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Spain and UK).[50]

Consumption volumes of the various formulations relating to given INNs were converted into DDD in order to compare volume measures across different INNs within the same ATC4 class. The conversion was made using a data set obtained from the World Health Organisation. For those formulations for which this information was not available, the whole ATC4 class to which they belong was excluded from the analysis.

In a number of ATC4 classes, more than one INN lost exclusivity during the period 2000 – 2007. Loss of exclusivity by multiple INNs within the same ATC4 class in a short time span substantially complicates the identification of potential effects of generic entry on other INNs in the ATC4 class. In the analysis, attention was therefore focused on those ATC4 classes where only one loss of exclusivity occurred during the period of interest. Additionally, the sample is restricted to those ATC4 classes in which the INN losing exclusivity faces generic

[50] See Annex on methodology

entry, only in these instances potential effects of generic entry on other INNs could be expected.

Volumes of other INNs were analysed over a period covering 24 months before and 24 months after the date of generic entry. Given that a key factor in the analysis is the variation of volumes over time, only INNs with observations over at least two years, containing the month of loss of exclusivity, were considered.

The final sample used in the analysis included 190 INNs belonging to 29 different ATC4 classes in nine different countries. The set of INNs (and of ATC4 classes) observed is different from one country to another. In total, 57 country-ATC4 pairs were studied.

Descriptive statistics provide some indication of potential volume effects of generic entry on other INNs following loss of exclusivity. Figure 20 indicates that, on average, volumes consumed of an INN increased steadily after its loss of exclusivity. This may be partly related to the fact that the lower prices for the INNs losing exclusivity may stimulate demand for the production as such (e.g. lower copayments) but it might also draw demand away from other products based on other INNs.

Regression analysis was used to study patterns of potential switching at the more disaggregated level of individual INNs. The rationale for such switching is that generic entry in a given INN after loss of exclusivity may drive its prices down and attract consumption away from other INNs in the same ATC4 class. Therefore, one might expect to observe a positive correlation between the average price of the INN loosing exclusivity and the volumes consumed of other INNs in the same ATC4 class.

For each INN in the sample that did not lose exclusivity during the period 2000-2007, volumes consumed every month were regressed against the following set of explanatory variables:[51]

- The average price of the INN itself (the own price)
- the average price of the INN that has lost exclusivity in the same ATC4 class (the cross price)
- a linear time trend.

The inclusion of a time trend is motivated by possible changes in the market environment after LoE related to factors other than entry by generics. A linear time trend for time passed

[51] A similar approach to the one proposed by Engström, Jacob and Lundin (LFN 2006), *Sharp drop in prices after the introduction of generic substitution,* was followed to estimate this correlation using regression analysis. They estimate a single coefficient for the difference between the own price and the cross price. This is equivalent to imposing a restriction on the coefficients of these two variables. The null hypothesis that this restriction holds was tested and rejected for a substantial number of INNs in the sample analysed. Therefore, the less restrictive specification was chosen and both coefficients were estimated separately for each INN. They also include lags of the dependent variable in the specification to control for autocorrelation. After performing the Durbin Watson alternative test, the null hypothesis of no serial correlation was not rejected in most of the cases for the specification without the lagged dependent variable. Therefore, the specification without lags was chosen. It should be noted that the sample used in the study by Engström, Jacob and Lundin (2006) was related to the Swedish market only and therefore differs from the sample analysed here.

since LoE was therefore included in the specification to account at least to some extent for such other factors, which otherwise might introduce a bias in the correlations between volume and cross-price.

For each INN in each country, one regression was estimated.[52] For a substantial number of them, estimated coefficients (correlations) for the own price variable were positive. One should perhaps expect these coefficients to be negative, as the demand for normal goods should react negatively to price increases. The results of these regressions were considered as not being reliable (based on an inadequate model specification) and were therefore disregarded. It is recognised, however, that maintaining the cases where the own price coefficient was negative may introduce a sample bias. The results of the disaggregated analysis should therefore be considered with sufficient caution.

For the remaining 170 regressions, attention focused on the estimates for the coefficients of the cross price. Positive coefficients indicate a positive correlation between the volumes consumed of a given INN and the average price of another INN that lost exclusivity. This positive correlation can be interpreted as an indication of potential volume effects of generic entry between these two INNs. Negative coefficients indicate a negative correlation between volumes consumed and cross prices. This type of correlation may be due to some misspecification of the regression equation for the INN concerned. For instance, a linear time trend may not capture all the effects related to changes in the market environment after LoE, other than generic entry. A more flexible way of controlling for time, like the inclusion of time dummies, is not available in this disaggregated analysis given the limited amount of observations available for each regression. Alternatively, negative correlations might potentially also be related to idiosyncratic characteristics of some markets. For instance, it may denote some degree of complementarity between INNs, which would be compatible with therapies that combine more than a single INN (e.g. cocktails of medicines). This presumption has not been further explored as it is out of the scope of this analysis.

Figure plots the 170 coefficient estimates for the cross price against their t-value, a measure of the level of statistical significance of the estimate, obtained from the specification with a linear time trend. These coefficients reflect the correlation between price variation and the variation in consumption volumes of the INN considered. Note however that these coefficients cannot be interpreted as cross-price elasticities. This is because the regression equations contain additional controls such as the time trend and do not amount to an exercise of demand estimation. Out of 170 cross-price coefficients, 31 are positive and statistically significant, which constitutes an indication of potential switching between the pairs of INNs to which those estimates refer. Nine estimates are negative and statistically significant, which may be the result of some market specific characteristics as commented above.

A large number of cross-price effects do not seem to be significantly different from zero. This may imply that effectively there was no switching between the INN concerned and the INN losing exclusivity in that ATC4 class. At the same time, the insignificance of the coefficient for the cross price should not necessarily be interpreted as an indication of absence of cross-

[52] Formally:

$$volume\_sales_t = \beta_0 + \beta_{own} * price_t + \beta_{cross} * price\_ref_t + \beta_{time} * time\_exc_t + \varepsilon_t$$

where *volume_sales* is the sales of the INN in number of ddd, *price* is the average price of the INN, *price_ref* is the average price of the INN losing exclusivity within the ATC4 and *country, time_exc* is the time passed since LoE and • is the error term.

price effects. The ability to identify correlation depends on the effective variation of cross prices over time. Where prices are rigid, e.g. when even the prices of products sold under the INN losing exclusivity do not drop by much, one cannot expect to be able to identify a correlation with the consumption volumes of other INNs in a statistically significant way.

Table 17 shows the share of INNs in the sample for which the correlation coefficient was established. In the model specification with linear time trend, the share of INNs showing a positive and statistically significant cross price coefficient is only about 18%. At the same time, a substantial number of INNs appeared to show an insignificant cross price coefficient (about 77%). It has to be borne in mind, however, that these shares cannot necessarily be extrapolated to the wider sample of INNs, given that these INNs may substantially differ in character from the INNs maintained in the analysis.

It is noteworthy that in the model specification with time trend, the share of INNs with a negative and statistically significant cross price coefficient is lower than in the specification not using a time trend (5% vs. 20%). This might suggest that the model with time trend brings about more intuitive results and better captures the possibility that, over time, volume shifts occur which are not due to price movements but rather to time related factors.

The results of the analysis at the disaggregated level provide a first indication of the potential volume effects of generic entry on other INNs in the ATC 4 class, but should however be interpreted with caution. In this type of model, prices are potentially endogenous as they are an outcome of a market process where prices and quantities are simultaneously determined. The ordinary least squares estimator used in these series of regressions may produce biased estimates of the parameters in the model if the regressors are endogenous. In order to correct to some extent the potential endogeneity, panel data analysis on the pooled data for all INNs was performed.

The analysis at the disaggregated level was hence improved by regression analysis using the pooled data for all the INNs in the sample to make more (efficient) use of all the information contained in the full data set and to filter to some degree the potential endogeneity of prices.[53] Volumes consumed every month were regressed against the following set of explanatory variables:[54]

- the average price of the INN itself (the own price)
- the average price of the INN that has lost exclusivity in the same ATC4 class (the cross price)

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[53] In previous subsections, pooled-data analysis made use of a larger set of regressors than are used in this subsection. Here the analysis exploits the time dimension of the panel data, while most regressors used in previous subsections do not provide enough time variability to allow their use here.

[54] More formally, the following set of specifications have been estimated:

$$volume\_sales_{it} = \beta_0 + \beta_{own} * price_{it} + \beta_{cross} * price\_ref_{it} + time\_exc_{it}' * \beta_{time} + fix_i' * \beta_{fix} + \varepsilon_{it}$$

Where *volume_sales* are the sales of the INN in number of ddd, *price* is the average price of the INN, *price_ref* is the average price of the INN losing exclusivity within the ATC4 and country, *time_exc* is the control for time since LoE (missing in some specifications, an either as a linear trend or time dummies in the others), *fix* is the vector of fixed effects (INN and country effects separately in some specifications, INN/ATC4/country effects in the others) and • is the error term.

- a time trend

Given that the data was pooled for all the markets in the sample, fixed effects were introduced in the regression to control for specificities in each market that may explain differences in levels of consumption across markets. Fixed effects partially solve the problem of endogeneity by filtering any time-invariant endogeneity of prices. The potential time-variant endogeneity left may advise to interpret results as conservative estimates of the actual price effects. All regressions include a dummy for each INN in each ATC4 and country. With respect to the intercept, the same INN in different countries or ATC4 is treated independently. Only the coefficients for the prices are shown. In all regressions, the coefficient for the own price is negative and significant.

Regression 1 in Table 18 reports the results when no control for time is included in the specification. In this case, the coefficient for the cross price is positive but non significant. Regression 2 includes a linear time trend while regression 3 includes dummies for the time passed since the date of LoE. As stated above, one reason to think that time may matter is that a series of events happen after the LoE that may affect the environment in the market. Including a control for time passed since LoE may to some extent account for this fact, which otherwise may induce a biased estimation of the correlation between volume and cross-price. The linear time trend implies a linear relation between consumption and time, which may not be appropriate. The time dummies allow for a more flexible relationship between consumption and time. The coefficient for the cross price is positive and significant in regressions 2 and 3. As expected, in all regressions own-price coefficients are higher in absolute value terms than cross-price coefficients.

Results in Table 18 provide additional indication about the existence, on average, of correlation between the price of the INN losing exclusivity and the level of consumption in other INNs in the same ATC4 class.

To allow for different cross-price coefficients across settings, a similar model was estimated where dummies for each INN in each ATC4 and country were interacted with the cross-price. This exercise, by allowing coefficients for the cross-price to differ across markets, gets closer to the disaggregated analysis presented above, while using a distinct approach. Table 19 reports the share of positive and negative estimated cross-price effects from the model in differences. As above, three specifications were estimated, without time control, with a linear time trend and with time dummies. The latter provides a higher share of positive cross-price effects, which may be due to better controlling for changes in the market after loss of exclusivity. In comparison with Table 17, the low shares of non-significant effects may be a consequence of the more efficient use of the information contained in the data by estimating a single pooled-data regression (in contrast with the series of 170 regressions estimated in the disaggregated analysis).

Shares in Table 19, which are the result from the pooled-data analysis, are broadly consistent with those reported in Table 17, obtained from the disaggregated analysis presented above. Overall, the analysis shows that in a significant number of cases, generic entry after LoE appears to have had an impact not only on the sales of the INN concerned, but also on the sales of a number of other products based on different INN. At the same time, there is considerable heterogeneity across INNs with respect to the estimated cross-price effects seem to vary considerably from one INN to another.

Table A: INN characteristics used in the regression analysis (control variables)

Name	Description
preexp_value per capita	Value sales per capita (EUR) of the INN six months before patent expiry (per country)
lnpreexp_value	(idem – natural log)
preexp_price	Average price (EUR) per DDD of the INN six months before patent expiry (per country)
expiry_year	Year of loss of exclusivity (per country)
exp_02_03	Loss of exclusivity in 2002 or 2003 (dummy variable, per country)
exp_04_05	Loss of exclusivity in 2004 or 2005 (dummy variable, per country)
exp_06_07	Loss of exclusivity in 2006 or 2007 (dummy variable, per country)
pre_exp_numform	Number of formulations available at the moment of patent expiry in the country
main_chron	Indicates whether INN is used mainly for chronic indications (dummy variable)
biosimilar	Indicates if INN is a biosimilar (dummy variable)
ngenr	Number of generic companies
ngenr2	(idem - squared)
gen_age	Number of months that generic companies were present in the INN (up to 12.2007)
gen_age2	(idem - squared)

Table B: Regulatory Variables Used in the Regression Analysis

Name	Description
price_caps	Indicates existence of a price cap/ mandatory discounts for generic products (dummy variable, by year). The variable equals 1 if generic companies, when they enter have to respect a maximum price level or have to price a certain percentage or amount lower than e.g. the price charged by the originator at the time of entry.
freq_adjust	Indicates whether there is frequent adjustment (e.g. once every 6 months) of maximum reimbursement prices.
physicians_encourage_gen	Indicates whether physicians are required/encouraged to prescribe an INN, rather than a specific brand (by budget restrictions or budget incentives).
compulsory_substit	Indicates whether pharmacies are obliged to dispense generic products when these are available and less expensive (compulsory substitution).
diff_copay	Indicates whether patients need to pay the difference between the price of the product purchased and the reference price.
lowest_price_policy	Indicates whether the reimbursement level, at whatever point it is fixed, is set at the price level of the cheapest generic available on the market.

Table C: Other Control Variables Used in the Regression Analysis

Name	Description
controlled_entry	Indicates whether there has been controlled generic entry (e.g. through a an early distribution agreement, license agreement or settlement agreement; see Annex on methodology)
neg_delay	Indicates whether the implied time to entry is negative (see Annex on methodology)
neg_delay3 /	
large _neg3	Indicates whether the implied time to entry is negative by more than 3 months (see Annex on methodology)
small_neg3	Indicates whether the implied time to entry is negative, but less than 3 months (see Annex on methodology)
population	Population of the country
n_countries_expired	Number of other countries in which the INN had already lost exclusivity at the time of loss of exclusivity.

Table D: List of the 219 INN's included in the data set.

ACARBOSE	ADALIMUMAB	ADRAFINIL
ALENDRONIC ACID	ALFUZOSIN	AMISULPRIDE
AMITRIPTYLINE	AMLODIPINE	AMOROLFINE
AMOXICILLIN CLAVULANIC ACID	AMOXICILLIN LANSOPRAZOLE CLARITHROMYCIN	ANASTROZOLE
ATENOLOL	ATORVASTATIN	AZITHROMYCIN
BALSALAZIDE	BECLOMETASONE	BENAZEPRIL
BISOPROLOL	BRIMONIDINE	BRIVUDINE
BUDESONIDE	BUDESONIDE FORMOTEROL	BUFLOMEDIL
BUPRENORPHINE	BUSERELIN	CABERGOLINE
CALCIPOTRIOL	CALCIPOTRIOL BETAMETHASONE	CANDESARTAN CILEXETIL
CANDESARTAN CILEXETIL HYDROCHLOROTHIAZIDE	CAPSAICIN	CAPTOPRIL HYDROCHLOROTHIAZIDE
CARTEOLOL	CARVEDILOL	CEFATRIZINE
CEFIXIME	CEFPODOXIME PROXETIL	CEFTIBUTEN
CEFTRIAXONE	CEFUROXIME AXETIL	CELECOXIB
CELIPROLOL	CETIRIZINE	CICLETANINE
CICLOSPORIN	CIPROFIBRATE	CIPROFLOXACIN
CISAPRIDE	CITALOPRAM	CLARITHROMYCIN
CLODRONIC ACID	CLOPIDOGREL	CROMOGLICIC ACID REPROTEROL
CYPROTERONE ETHINYLESTRADIOL	DALTEPARIN SODIUM	DARBEPOETIN ALFA
DESOGESTREL ETHINYLESTRADIOL	DIACEREIN	DICLOFENAC
DIENOGEST ETHINYLESTRADIOL	DOMPERIDONE	DONEPEZIL
DOXAZOSIN	EBASTINE	ENALAPRIL
ENOXAPARIN SODIUM	EPOETIN ALFA	EPOETIN BETA
ESOMEPRAZOLE	ESTRADIOL	ESTRADIOL NORETHISTERONE
ETANERCEPT	ETHINYLESTRADIOL GESTODENE	ETIDRONIC ACID
ETODOLAC	EZETIMIBE	FELODIPINE
FENOFIBRATE	FENTANYL	FEXOFENADINE
FINASTERIDE	FLECAINIDE	FLUCONAZOLE
FLUOXETINE	FLUPIRTINE	FLUTICASONE
FORMOTEROL	FOSFOMYCIN TROMETAMOL	FOSINOPRIL
GABAPENTIN	GALANTAMINE	GLATIRAMER ACETATE
GLIMEPIRIDE	GOSERELIN	HYDROCHLOROTHIAZIDE BENAZEPRIL
HYDROCHLOROTHIAZIDE BISOPROLOL	HYDROCHLOROTHIAZIDE ENALAPRIL	HYDROCHLOROTHIAZIDE IRBESARTAN
HYDROCHLOROTHIAZIDE LISINOPRIL	HYDROCHLOROTHIAZIDE RAMIPRIL	HYDROMORPHONE
IBANDRONIC ACID	ILOPROST	IMATINIB
INFLIXIMAB	INSULIN ASPART	INSULIN GLARGINE
INSULIN HUMAN BASE	INSULIN HUMAN BASE INSULIN HUMAN ISOPHANE	INSULIN HUMAN ISOPHANE
INTERFERON BETA-1A	INTERFERON BETA-1B	IPRATROPIUM BROMIDE SALBUTAMOL
IRBESARTAN	ISOTRETINOIN	ITRACONAZOLE
LACIDIPINE	LAMOTRIGINE	LANSOPRAZOLE
LETROZOLE	LEUPRORELIN	LISINOPRIL
LORATADINE	LOSARTAN	LOSARTAN HYDROCHLOROTHIAZIDE
LOVASTATIN	MELOXICAM	METHYLPHENIDATE

METOCLOPRAMIDE ACETYLSALICYLIC ACID	METOPROLOL	METRONIDAZOLE
MIRTAZAPINE	MODAFINIL	MOMETASONE
MONTELUKAST	MOXIFLOXACIN	MOXONIDINE
NADOXOLOL	NADROPARIN CALCIUM	NEDOCROMIL
NICARDIPINE	NICORANDIL	NIFEDIPINE
NIZATIDINE	NOMEGESTROL	NORFLOXACIN
NORGESTIMATE ETHINYLESTRADIOL	OCTREOTIDE	OFLOXACIN
OLANZAPINE	OMEPRAZOLE	ONDANSETRON
OXALIPLATIN	PACLITAXEL	PANTOPRAZOLE
PAROXETINE	PEGFILGRASTIM	PERGOLIDE
PERINDOPRIL	PERINDOPRIL INDAPAMIDE	PIOGLITAZONE
PIROXICAM BETADEX	PRAMIPEXOLE	PRAVASTATIN
PRAVASTATIN ACETYLSALICYLIC ACID	PREGABALIN	QUETIAPINE
QUINAPRIL	QUINAPRIL HYDROCHLOROTHIAZIDE	RABEPRAZOLE
RAMIPRIL	RANITIDINE	RIBAVIRIN
RILMENIDINE	RISEDRONIC ACID	RISPERIDONE
ROFECOXIB	ROSIGLITAZONE	ROSUVASTATIN
ROXITHROMYCIN	SALBUTAMOL	SALMETEROL
SALMETEROL FLUTICASONE	SERTRALINE	SILDENAFIL
SIMVASTATIN	SIMVASTATIN EZETIMIBE	SOMATROPIN
SUMATRIPTAN	TAMSULOSIN	TELMISARTAN
TERBINAFINE	TESTOSTERONE	TIAGABINE
TIBOLONE	TILIDINE NALOXONE	TINZAPARIN
TIOTROPIUM BROMIDE	TIZANIDINE	TORASEMIDE
TRAMADOL	TRAMADOL PARACETAMOL	TRAZODONE
TRIPTORELIN	VACCINE, HEPATITIS B	VACCINE, HEPATITIS B VACCINE, ACEL.PERT.DIP.TET. POLIO & HIB
VACCINE, HEPATITIS B VACCINE, DIP.TET.PERT.POLIO & HIB.	VACCINE, INFLUENZA	VACCINE, PNEUMOCOCCAL
VACCINE, PNEUMOCOCCAL CONJUGATE	VACCINE, TICK BORNE ENCEPHALITIS	VALACICLOVIR
VALPROATE SEMISODIUM	VALSARTAN	VALSARTAN HYDROCHLOROTHIAZIDE
VENLAFAXINE	VIGABATRIN	ZOLPIDEM

Source: Pharmaceutical Sector Inquiry (selection based on IMS data)

Table 6: Results regression analysis occurrence of entry

	First entry within 1 year		First entry within 2 years	
COEFFICIENT	1	2	1	2
price_caps	-0.14***	-0.10**	-0.07	-0.04
	[0.04]	[0.04]	[0.05]	[0.05]
compulsory_substit	0.11*	0.14**	0.13**	0.16***
	[0.06]	[0.06]	[0.06]	[0.06]
physicians_encourage_gen	0.07	0.11**	0.09	0.13**
	[0.05]	[0.05]	[0.06]	[0.06]
freq_adjust	0.05	0.07	0.03	0.05
	[0.05]	[0.05]	[0.05]	[0.05]
diff_copay	-0.02	-0.02	-0.01	-0.02
	[0.07]	[0.07]	[0.07]	[0.07]
lowest_price_policy	-0.06	-0.07	0.01	-0.01
	[0.05]	[0.05]	[0.05]	[0.06]
ln_preexp_value_per_capita	0.11***	0.10***	0.11***	0.11***
	[0.02]	[0.02]	[0.02]	[0.02]
ln_population	0.05**	0.04*	0.05**	0.04*
	[0.02]	[0.02]	[0.02]	[0.02]
ln_preexp_price	-0.07***	-0.07***	-0.07***	-0.07***
	[0.02]	[0.01]	[0.02]	[0.02]
pre_exp_numform	0.03**	0.03**	0.02	0.02
	[0.01]	[0.01]	[0.01]	[0.01]
Biosimilar	0.11***	0.12***	0.22***	0.24***
	[0.04]	[0.04]	[0.04]	[0.04]
other_atc4	0.05	0.05	0.04	0.04
	[0.06]	[0.06]	[0.06]	[0.06]
n_countries_expired	0.02**	0.01*	0.01	0.01
	[0.01]	[0.01]	[0.01]	[0.01]
controlled_entry	0.41***	0.42***	0.35***	0.37***
	[0.12]	[0.13]	[0.12]	[0.13]
expiry_year	0.05***	0.05***	0.06***	0.06***
	[0.01]	[0.01]	[0.02]	[0.02]
Observations	765	735	675	649
Pseudo R-squared	0.2243	0.2266	0.2424	0.2475

Robust standard errors in brackets
*** p<0.01, ** p<0.05, * p<0.1
Constant included

Table 7: Results regression analysis number of generic entrants

	Number of entrants 1 year		Number of entrants 2 years		Number of entrants, long run	
COEFFICIENT	1	2	1	2	1	2
price_caps	-0.56***	-0.43***	-0.37***	-0.25**	-0.28***	-0.23**
	[0.13]	[0.14]	[0.12]	[0.13]	[0.09]	[0.10]
compulsory_substit	0.44**	0.57***	0.51***	0.59***	0.45***	0.47***
	[0.17]	[0.18]	[0.16]	[0.17]	[0.12]	[0.13]
physicians_encourage_gen	0.45***	0.61***	0.23	0.34**	0.17	0.22*
	[0.15]	[0.16]	[0.15]	[0.16]	[0.11]	[0.12]
freq_adjust	-0.12	-0.05	-0.11	-0.06	-0.18	-0.16
	[0.14]	[0.16]	[0.13]	[0.15]	[0.11]	[0.12]
diff_copay	0.03	0.05	0.05	0.08	0.2	0.2
	[0.20]	[0.20]	[0.19]	[0.20]	[0.16]	[0.17]
lowest_price_policy	0.11	0.01	-0.02	-0.11	-0.04	-0.07
	[0.14]	[0.15]	[0.13]	[0.14]	[0.10]	[0.10]
ln_preexp_value_per_capita	0.42***	0.42***	0.41***	0.41***	0.36***	0.35***
	[0.06]	[0.06]	[0.05]	[0.05]	[0.04]	[0.04]
ln_population	0.33***	0.32***	0.36***	0.36***	0.37***	0.38***
	[0.06]	[0.06]	[0.05]	[0.06]	[0.04]	[0.04]
ln_preexp_price	-0.27***	-0.29***	-0.23***	-0.25***	-0.18***	-0.18***
	[0.05]	[0.06]	[0.05]	[0.05]	[0.04]	[0.04]
pre_exp_numform	0.08***	0.09***	0.08***	0.09***	0.06**	0.06**
	[0.03]	[0.03]	[0.03]	[0.03]	[0.02]	[0.02]
biosimilar	0.21*	0.29**	0.28**	0.36***	0.56***	0.62***
	[0.12]	[0.12]	[0.11]	[0.12]	[0.09]	[0.09]
other_atc4	0.27	0.29	0.21	0.22	0	-0.03
	[0.17]	[0.19]	[0.15]	[0.17]	[0.11]	[0.12]
n_countries_expired	0.01	0	0.02	0.01	-0.02	-0.02
	[0.02]	[0.02]	[0.02]	[0.02]	[0.02]	[0.02]
controlled2	1.17***	1.40***	1.20**	1.44**	0.63*	0.76**
	[0.44]	[0.51]	[0.50]	[0.57]	[0.33]	[0.38]
expiry_year	0.14***	0.13***	0.16***	0.15***	0.12***	0.11***
	[0.04]	[0.04]	[0.04]	[0.04]	[0.03]	[0.03]
Observations	765	735	675	649	675	649
AIC	2445.714	2239.998	2558.199	2374.446	3194.79	3017.648
BIC	2524.592	2318.196	2634.949	2450.528	3271.54	3093.731

Robust standard errors in brackets
*** p<0.01, ** p<0.05, * p<0.1
Constant included

Table 8: Results analysis time to entry

	Cox	Weibull	Weibull with inverse normal frailty	Discrete with normal frailty	Discrete with non-parametric frailty
price_caps	0.752***	0.737***	0.576***	0.619***	0.604***
	(0.007)	(0.002)	(0.001)	(0.000)	(0.000)
Compulsory_substit	1.614***	1.603***	1.946***	1.568***	1.600***
	(0.001)	(0.001)	(0.002)	(0.005)	(0.003)
physicians_encourage_gen	1.233	1.213	1.448*	1.450***	1.507***
	(0.104)	(0.110)	(0.050)	(0.010)	(0.003)
freq_adjust	1.103	1.106	1.158	1.055	1.131
	(0.367)	(0.315)	(0.368)	(0.657)	(0.304)
diff_copay	0.766*	0.757**	0.722	0.951	0.894
	(0.064)	(0.040)	(0.128)	(0.767)	(0.498)
lowest_price_policy	0.940	0.950	0.939	0.894	0.913
	(0.608)	(0.652)	(0.725)	(0.405)	(0.481)
lnpreexp_value_per_capita	1.494***	1.488***	1.788***	1.567***	1.555***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
populationa	1.000**	1.000**	1.000***	1.229***	1.153***
	(0.012)	(0.011)	(0.004)	(0.000)	(0.002)
preexp_price	0.977***	0.975***	0.967***	0.974***	0.973***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
pre_exp_numform	1.035*	1.031*	1.057**	1.033	1.030
	(0.065)	(0.065)	(0.042)	(0.111)	(0.147)
other_atc4	1.213	1.231*	1.279	1.228	1.221
	(0.138)	(0.089)	(0.204)	(0.159)	(0.173)
already_expired_country	1.123	1.133	1.236	1.192	1.178
	(0.258)	(0.194)	(0.171)	(0.132)	(0.155)
controlled_entry	2.261***	1.854***	3.270***	2.278***	2.814***
	(0.000)	(0.002)	(0.000)	(0.001)	(0.000)
exp_02_03	1.668***	1.603***	1.988***	1.844***	1.681***
	(0.000)	(0.000)	(0.001)	(0.000)	(0.001)
exp_04_05	2.108***	1.983***	2.678***	2.252***	2.188***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
exp_06_07	2.363***	2.548***	3.596***	2.541***	2.374***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
surtime				0.949***	0.944***
				(0.000)	(0.000)
surtimesq				1.001***	1.001***
Observations	22326	22326	22326	23196	23196
Frailty theta=0 test, p-value			0.000	0.000	
Weibull parameter p		0.711	1.104		

p values in parentheses, * significant at 10%; ** significant at 5%; *** significant at 1%

a: for computational reasons, the variable population is included in levels in the first three regressions presented, while its logarithm is used in the last two.

Table 9: Results analysis time to entry

	Full data set			**No large (>3months) negative delays**			**Data set without any negative delay**		
	Weibull	**Weibull with inverse normal frailty**	**Discrete with normal frailty**	**Weibull**	**Weibull with inverse normal frailty**	**Discrete with normal frailty**	**Weibull**	**Weibull with inverse normal frailty**	**Discrete with normal frailty**
price_caps	0.898	0.796	0.867	0.917	0.825	0.883	0.912	0.810	0.837
	(0.286)	(0.217)	(0.155)	(0.414)	(0.305)	(0.235)	(0.405)	(0.259)	(0.185)
compulsory_substit	1.507***	2.063***	1.455***	1.539***	2.100***	1.491***	1.586***	2.238***	1.662***
	(0.003)	(0.004)	(0.006)	(0.002)	(0.003)	(0.004)	(0.003)	(0.002)	(0.005)
physicians_encourage_gen	1.218*	1.498*	1.297**	1.287**	1.652**	1.350**	1.261*	1.663**	1.495**
	(0.098)	(0.060)	(0.029)	(0.039)	(0.018)	(0.014)	(0.068)	(0.016)	(0.011)
frequent_adjust	0.998	1.014	0.976	1.044	1.110	1.009	1.120	1.224	1.118
	(0.983)	(0.939)	(0.810)	(0.684)	(0.579)	(0.933)	(0.328)	(0.301)	(0.417)
diff_copay	0.872	0.790	0.984	0.860	0.779	0.958	0.785	0.701	0.888
	(0.310)	(0.335)	(0.912)	(0.273)	(0.300)	(0.769)	(0.101)	(0.151)	(0.521)
lowest_price_policy	1.110	1.197	1.057	1.079	1.132	1.033	1.056	1.066	1.007
	(0.357)	(0.379)	(0.627)	(0.514)	(0.546)	(0.784)	(0.660)	(0.753)	(0.962)
lnpreexp_value_per_capita	1.479***	1.966***	1.456***	1.497***	1.952***	1.481***	1.610***	2.094***	1.711***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
populationb	1.000	1.000	1.102**	1.000	1.000*	1.103**	1.000	1.000	1.126**
	(0.145)	(0.114)	(0.018)	(0.119)	(0.094)	(0.018)	(0.290)	(0.177)	(0.028)
preexp_price	0.980***	0.971***	0.982***	0.978***	0.967***	0.979***	0.977***	0.967***	0.975***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
pre_exp_numform	1.006	1.024	1.004	1.010	1.034	1.008	1.016	1.045	1.025
other_atc4	1.258*	1.409	1.243*	1.293**	1.455*	1.283**	1.356**	1.519*	1.366**
	(0.057)	(0.118)	(0.072)	(0.041)	(0.092)	(0.048)	(0.021)	(0.063)	(0.049)
already_expired_country	1.070	1.159	1.079	1.082	1.177	1.092	1.113	1.248	1.176
controlled_entry	0.982	1.098	1.018	1.045	1.260	1.091	1.053	1.182	1.114
	(0.929)	(0.802)	(0.930)	(0.839)	(0.557)	(0.689)	(0.866)	(0.755)	(0.784)
exp_02_03	1.590***	2.164***	1.614***	1.551***	2.020***	1.630***	1.547***	1.933***	1.806***
	(0.000)	(0.001)	(0.000)	(0.001)	(0.003)	(0.000)	(0.001)	(0.005)	(0.001)
exp_04_05	1.939***	2.991***	1.817***	1.910***	2.763***	1.877***	1.897***	2.565***	2.221***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
exp_06_07	2.771***	5.266***	2.281***	2.720***	4.639***	2.382***	2.669***	3.982***	2.768***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
large_neg3	12.657***	84.026***	9.235***						
	(0.000)	(0.000)	(0.000)						
small_neg3	12.320***	78.832***	8.830***	10.489***	49.391***	8.295***			
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)			
surtime			0.951***			0.951***			0.968***
			(0.000)			(0.000)			(0.003)
surtimesq			1.001***			1.001***			1.000***
			(0.000)			(0.000)			(0.000)
Observations	22326	22326	23196	22292	22292	23129	22237	22237	23019
Frailty theta=0 test, p-value		0.000	0.493		0.000	0.492		0.000	0.008
Weibull parameter p	.863	1.524		.832	1.413		.792	1.274	

p values in parentheses, * significant at 10%; ** significant at 5%; *** significant at 1%

b: the variable population was included in levels in the first two regressions of each set, while in logarithm in the third one.

Table 10: Regressions of price drops following entry

		Model I		Model II		Model III		Model IV		Model V	
		1 year price drops		2 year price drops		3 year price drops		4 year price drops		long_run (total) price drops	
Regulation	price_caps	**-0.103*** **	0.000	**-0.145*** **	0.000	**-0.137*** **	0.001	**-0.166*** **	0.000	**-0.201*** **	0.000
	compulsory_substit	**0.078** **	0.025	**0.087***	0.067	**0.144*** **	0.001	**0.144*** **	0.000	**0.168*** **	0.000
	physicians_encourage_gen	**0.138*** **	0.000	**0.153*** **	0.000	**0.170*** **	0.000	**0.176*** **	0.001	**0.230*** **	0.000
	freq_adjust	0.028	0.211	**0.123*** **	0.000	**0.110*** **	0.002	**0.122*** **	0.002	**0.126*** **	0.000
	diff_copay	**0.144*** **	0.001	**0.121*** **	0.000	0.050	0.202	0.017	0.589	**0.078*** **	0.006
	lowest_price_policy	**0.074*** **	0.002	**0.082*** **	0.002	**0.104*** **	0.002	**0.159*** **	0.000	**0.054***	0.056
Characteristics	preexp_value_per_capita	0.007	0.445	**0.016***	0.062	**0.032*** **	0.468	**0.039*** **	0.235	**0.034*** **	0.016
	population	**-0.028** **	0.010	**-0.040*** **	0.001	**-0.049*** **	0.406	**-0.046** **	0.123	-0.020	0.012
	pre_exp_numform	**-0.011** **	0.048	**-0.012** **	0.027	-0.007	0.002	-0.016	0.005	**-0.015** **	0.000
	biosimilar	0.025	0.215	**0.050** **	0.031	0.021	0.327	0.043	0.013	**0.062** **	0.829
	other_atc4	-0.027	0.515	0.042	0.236	0.039	0.862	**0.088** **	0.573	0.007	0.305
	already_expired_country	0.005	0.877	-0.004	0.914	0.008	0.449	-0.028	0.032	-0.035	0.146
	n_countries_expired	0.006	0.217	0.006	0.352	0.007	0.007	**0.021** **	0.037	0.009	0.096
	ngenr	**0.029*** **	0.000	**0.017*** **	0.000	**0.012*** **	0.419	**0.013** **	0.302	**0.010*** **	0.589
	gen_age						0.004		0.010	**0.018***	0.000
	gen_age2									0.000	0.096
	controlled_entry	-0.042	0.207	**-0.076***	0.070	-0.042		0.058		-0.022	0.589
Characteristics	neg_delay	-0.001	0.981	0.051	0.222	0.036	0.641	-0.007	0.936	-0.004	0.944
	neg_delay3	**-0.098***	0.099	**-0.143***	0.053	-0.128	0.157	-0.122	0.194	0.001	0.992
	_cons	**0.459** **	0.013	**0.761*** **	0.000	**1.007*** **	0.001	**1.030*** **	0.004	**0.440** **	0.049
Other	N	464		368		260		181		394	
	r2	0.336		0.413		0.389		0.498		0.380	
	F-test of joint significance, p-value:	0.000		0.000		0.000		0.000		0.000	
Descriptive stats,	Ramsey's RESET test, p-value:	0.829		0.486		0.086		0.268		0.302	
		one-year price drop		two-year price drop		three-year price drop		four-year price drop			
	Mean	0.22		0.32		0.38		0.41			
	Standard deviation	0.27		0.28		0.28		0.28			
	Min.	-2.17		-1.24		-0.88		-0.85			
	Max.	0.91		0.94		0.95		0.96			

OLS estimates

** significant at 10%; ** significant at 5%; *** significant at 1%; heteroscedasticity robust p-values are displayed next to the coefficient estimates*

Table 11: Regressions of Generic Market Shares

		Model I		Model II		Model III		Model IV		Model V	
		1 year shares		2 year shares		3 year shares		4 year shares		long_run (final) shares	
Regulation	price_caps	**-0.156*** **	0.000	**-0.151*** **	0.000	**-0.150*** **	0.000	-0.150	0.001	-0.138	0.000
	compulsory_substit	**0.124*** **	0.000	**0.151*** **	0.001	**0.192*** **	0.106	0.044	0.283	0.074	0.013
	physicians_encourage_gen	**0.080*** **	0.009	**0.065***	0.096	0.076	0.104	0.120	0.047	0.102	0.024
	freq_adjust	**0.078*** **	0.002	**0.091*** **	0.002	0.058	0.000	0.264	0.000	0.205	0.000
	diff_copay	-0.026	0.423	-0.010	0.781	-0.018	0.674	-0.043	0.392	0.005	0.894
	lowest_price_policy	**0.092*** **	0.001	**0.081** **	0.014	0.054	0.186	0.033	0.484	0.038	0.280
Characteristics	preexp_value_per_capita	-0.003	0.775	0.000	0.969	0.002	0.040	0.043	0.280	0.087	0.003
	population	0.010	0.318	**0.023***	0.067	0.014	0.622	-0.006	0.549	-0.006	0.320
	pre_exp_numform	-0.002	0.624	-0.009	0.147	-0.005	0.889	0.021	0.104	0.017	0.094
	biosimilar	**0.039***	0.082	**0.069** **	0.011	**0.070** **	0.582	0.079	0.109	-0.001	0.989
	other_atc4	0.011	0.696	0.015	0.690	0.026	0.427	0.013	0.780	0.004	0.921
	already_expired_country	**-0.058***	0.052	-0.031	0.384	-0.034	0.163	0.001	0.945	0.000	0.972
	n_countries_expired	**0.010***	0.093	0.010	0.138	0.011	0.382	0.019	0.357	0.049	0.000
	price_gen	**-0.002** **	0.048	**-0.005*** **	0.000	-0.005	0.033	-0.056	0.375	-0.107	0.026
	price_ori	**0.001** **	0.017	**0.004** **	0.018	0.008	0.337	-0.029	0.005	-0.006	0.002
	gen_age						0.136	0.033	0.001	0.004	0.081
	gen_age2									0.037	0.000
	controlled_entry	-0.052	0.191	**-0.101***	0.051	**-0.129** **				-0.001	0.026
Other	neg_delay	**0.194*** **	0.000	**0.159*** **	0.004	**0.130***	0.051	0.053	0.485	0.086	0.099
	neg_delay3	**-0.275*** **	0.000	**-0.178** **	0.018	**-0.164***	0.064	-0.068	0.478	-0.054	0.466
	_cons	0.063	0.725	-0.048	0.824	0.187	0.515	0.197	0.581	-0.783	0.000
	N	463		387		272		192		385	
	r2	0.322		0.295		0.278		0.332		0.367	
	F-test of joint significance, p-value:	0.000		0.000		0.000		0.000		0.000	
	Ramsey's RESET test, p-value:	0.009		0.182		0.971		0.013		0.672	

OLS estimates

** significant at 10%; ** significant at 5%; *** significant at 1%; heteroscedasticity robust p-values are displayed next to the coefficient estimates*

Table 12: Robustness Checks of Price Drop and Generic Share Regressions (full Sample)

	price drops					**generic shares**				
	vintage regressions				**long-run regressions**	**vintage regressions**				**long-run regressions**
	1 year	**2 year**	**3 year**	**4 year**		**1 year**	**2 year**	**3 year**	**4 year**	
Ramsey test	OK	OK	X	OK	OK	X	OK	OK	X	OK
price cap	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
compulsory substit.	POS	POS	POS	POS	POS	POS	POS	POS	POS	POS
physicians encour.	POS	POS	POS	POS	POS	POS	POS	X	POS	POS
frequent adjustment	X	POS	POS	POS	POS	POS	POS	X	X	POS
diff. copayement	POS	POS	X	X	POS	X	X	X	X	X
lowest price policy	POS	POS	POS	POS	POS	POS	POS	X	X	X
pre expiry value per capita	X	POS	POS	POS	POS	X	X	X	X	POS
population	NEG	NEG	NEG	NEG	NEG	X	POS	X	X	POS
pre expiry number of formats	NEG	NEG	X	X	NEG	X	X	X	X	X
biosimilar	X	POS	X	X	POS	POS	POS	POS	X	POS
other atc4	X	X	X	POS	X	X	X	X	X	X
already expired country	X	X	X	X	X	NEG	X	X	X	X
number of countries expired	X	X	X	POS	X	POS	X	X	X	X
number of generic entrants	POS	POS	POS	POS	POS					
price of generics products						NEG	NEG	X	NEG	NEG
price of originator produts						POS	POS	X	POS	POS
controlled entry	X	NEG	X	X	X	X	NEG	NEG	X	NEG

OLS regressions

Ramsey tests: OK means a p-value larger than 0.1.

Coefficients: POS - positive, statistically significant estimate; NEG - negative, statistically significant estimate; X - nonsignificant estimate.

Table 13: Robustness Checks of Price Drop and Generic Share Regressions (negative delay aboe -3 months dropped)

	price drops					generic shares				
	vintage regressions				long-run regressions	vintage regressions				long-run regressions
	1 year	2 year	3 year	4 year		1 year	2 year	3 year	4 year	
Ramsey test	OK	OK	OK	OK	OK	X	OK	OK	X	OK
price cap	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
compulsory substit.	POS	POS	POS	POS	POS	POS	POS	POS	POS	POS
physicians encour.	POS	POS	POS	POS	POS	POS	POS	POS	POS	POS
frequent adjustment	X	POS	POS	POS	POS	POS	POS	POS	X	POS
diff. copayement	POS	POS	X	X	POS	X	X	X	X	X
lowest price policy	POS	POS	POS	POS	X	POS	POS	X	X	X
pre expiry value per capita	X	POS	POS	POS	POS	X	X	X	X	X
population	NEG	NEG	NEG	NEG	X	X	POS	X	X	POS
pre expiry number of formats	NEG	NEG	X	X	NEG	X	X	X	X	X
biosimilar	X	POS	X	X	POS	X	POS	POS	X	POS
other atc4	X	X	X	X	X	X	X	X	X	X
already expired country	X	X	X	X	X	NEG	X	X	X	X
number of countries expired	X	X	X	POS	X	X	X	X	X	X
number of generic entrants	POS	POS	POS	POS	POS					
price of generics products						NEG	NEG	X	NEG	NEG
price of originator products						POS	POS	POS	POS	POS
controlled entry	X	X	X	X	X	X	X	NEG	X	NEG

OLS regressions
Ramsey tests: OK means a p-value larger than 0.1.
Coefficients: POS - positive, statistically significant estimate; NEG - negative, statistically significant estimate; X - nonsignificant estimate.

Table 14: Robustness Checks of Price Drop and Generic Share Regressions (all negative delays dropped)

	price drops					generic shares				
	vintage regressions				long-run regressions	vintage regressions				long-run regressions
	1 year	2 year	3 year	4 year		1 year	2 year	3 year	4 year	
Ramsey test	OK	OK	OK	OK	OK	X	OK	OK	X	OK
price cap	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
compulsory substit.	POS	POS	POS	POS	POS	POS	POS	POS	POS	POS
physicians encour.	POS	POS	POS	POS	POS	POS	POS	POS	POS	POS
frequent adjustment	X	POS	POS	POS	POS	POS	POS	POS	X	POS
diff. copayement	POS	POS	X	X	POS	X	X	X	X	X
lowest price policy	POS	POS	POS	POS	X	POS	POS	X	X	X
pre expiry value per capita	X	X	POS	POS	POS	X	X	X	X	X
population	NEG	NEG	NEG	NEG	X	X	POS	X	X	POS
pre expiry number of formats	X	X	X	X	NEG	X	X	X	X	X
biosimilar	X	POS	X	X	POS	X	POS	POS	X	POS
other atc4	X	X	X	X	X	X	X	X	X	X
already expired country	X	X	X	X	X	NEG	X	X	X	X
number of countries expired	X	X	X	POS	X	X	X	X	X	X
number of generic entrants	POS	POS	POS	POS	POS					
price of generics products						NEG	NEG	X	NEG	NEG
price of originator produts						POS	POS	POS	POS	POS
controlled entry	X	X	X	X	X	X	X	NEG	X	NEG

OLS regressions

Ramsey tests: OK means a p-value larger than 0.1.

Coefficients: POS - positive, statistically significant estimate; NEG - negative, statistically significant estimate; X - nonsignificant estimate.

Table 15: GMM and robust regressions of price drops following entry

		GMM estimates				Robust regression estimates			
		endogenous variable: ngenr							
		Model I		Model II		Model III		Model IV	
		2 year price drops		long-run (total) price drops		2 year price drops		long-run (total) price drops	
Regulation	price_caps	**-0.134*** **	0.000	**-0.205*** **	0.000	**-0.140*** **	0.000	**-0.198*** **	0.000
	compulsory_substit	0.035	0.523	**0.158*** **	0.002	**0.129*** **	0.000	**0.176*** **	0.000
	physicians_encourage_gen	**0.194*** **	0.000	**0.294*** **	0.000	**0.183*** **	0.000	**0.215*** **	0.000
	freq_adjust	**0.164*** **	0.000	**0.170*** **	0.000	**0.114*** **	0.000	**0.145*** **	0.000
	diff_copay	**0.138*** **	0.000	**0.068** **	0.042	**0.113*** **	0.001	0.064	0.067
	lowest_price_policy	**0.077** **	0.018	0.044	0.162	**0.085*** **	0.003	**0.054***	0.050
Characteristics	preexp_value_per_capita	-0.019	0.261	0.011	0.421	**0.015***	0.082	**0.039*** **	0.000
	population	**-0.090*** **	0.001	**-0.060*** **	0.003	**-0.042*** **	0.001	-0.010	0.399
	pre_exp_numform	**-0.014** **	0.023	**-0.018*** **	0.004	**-0.013** **	0.030	**-0.011** **	0.044
	biosimilar	0.003	0.917	0.023	0.431	**0.048***	0.050	**0.043***	0.079
	other_atc4	**0.071***	0.065	0.038	0.244	0.029	0.347	0.027	0.370
	already_expired_country	0.059	0.218	0.010	0.796	-0.019	0.560	-0.030	0.337
	n_countries_expired	0.001	0.934	0.008	0.218	0.005	0.376	**0.009***	0.072
	ngenr	**0.055*** **	0.000	**0.031*** **	0.000	**0.016*** **	0.000	**0.008*** **	0.001
	gen_age			**0.007*** **	0.003			0.016	0.399
	gen_age2			0.000	0.970			0.000	0.463
	controlled_entry	-0.024	0.633	-0.001	0.970	-0.050	0.191	-0.027	0.463
Characteristics	neg_delay	-0.046	0.420	-0.070	0.279	0.040	0.322	0.033	0.393
	neg_delay3	-0.027	0.767	0.076	0.308	-0.084	0.122	-0.087	0.108
	_cons	**1.190*** **	0.000	**0.927*** **	0.001	**0.782*** **	0.000	0.328	0.142
Other	N	368		394		368		394	
	r2	0.194		0.267		0.412		0.422	
	F-test of joint significance, p-value:	0.000		0.000		0.000		0.000	
	Ramsey's RESET test, p-value:	0.018		0.004		0.012		0.367	
	Hansen test, p-value (H0: overidentification restrictions hold):	0.967		0.155					
	rank test, p-value (H0: rank condition does not hold):	0.000		0.000					
	endogeneity test of endogenous variable, p-value (H0: exogeneity):	0.002		0.002					

** significant at 10%; ** significant at 5%; *** significant at 1%; heteroscedasticity robust p-values are displayed next to the coefficient estimates*
instruments in GMM regressions: average number of generic producers in other countries in the same INN, average number of generic producers in other countries in the same atc4 category

Table 16: GMM and robust regressions of generic market shares

		GMM estimates				Robust regression estimates			
		endogenous variable: price_gen, price_ori							
		Model I		Model II		Model III		Model IV	
		2 year shares		long-run (final) shares		2 year shares		long-run (final) shares	
Regulation	price_caps	**-0.169*** **	0.000	**-0.155*** **	0.000	**-0.166*** **	0.000	**-0.173*** **	0.000
	compulsory_substit	**0.141*** **	0.004	**0.206*** **	0.000	**0.169*** **	0.000	**0.239*** **	0.000
	physicians_encourage_gen	**0.076***	0.064	**0.112** **	0.011	**0.081** **	0.039	**0.120*** **	0.005
	freq_adjust	**0.121*** **	0.000	**0.087*** **	0.003	**0.097*** **	0.002	**0.102*** **	0.001
	diff_copay	0.006	0.878	0.020	0.603	-0.012	0.772	-0.023	0.595
	lowest_price_policy	**0.086*** **	0.008	0.024	0.493	**0.080** **	0.020	0.027	0.414
Characteristics	preexp_value_per_capita	-0.004	0.704	0.019*	0.066	0.003	0.782	**0.025*** **	0.007
	population	**0.023***	0.082	**0.049*** **	0.000	**0.027***	0.061	**0.053*** **	0.000
	pre_exp_numform	**-0.011***	0.085	-0.010	0.113	-0.011	0.121	**-0.012***	0.080
	biosimilar	0.044	0.112	**0.081*** **	0.005	**0.080*** **	0.006	**0.093*** **	0.002
	other_atc4	0.025	0.538	0.005	0.892	0.017	0.657	0.000	0.991
	already_expired_country	-0.003	0.944	0.009	0.801	-0.034	0.384	0.009	0.809
	n_countries_expired	0.005	0.474	0.000	0.945	**0.012***	0.064	0.002	0.724
	price_gen	**-0.004*** **	0.000	**-0.005*** **	0.000	**-0.005** **	0.046	**-0.005** **	0.022
	price_ori	**0.002** **	0.036	**0.003*** **	0.006	0.004	0.148	0.004	0.113
	gen_age			**0.036*** **	0.000			**0.039*** **	0.000
	gen_age2			**-0.001** **	0.011			**-0.001***	0.061
Other	controlled_entry	**-0.144*** **	0.009	**-0.116** **	0.011	**-0.105** **	0.024	**-0.085***	0.061
	neg_delay	**0.179*** **	0.001	0.070	0.162	**0.174*** **	0.000	**0.105** **	0.026
	neg_delay3	**-0.198** **	0.013	-0.005	0.936	**-0.179*** **	0.008	-0.055	0.409
	_cons	-0.057	0.798	**-0.765*** **	0.000	-0.119	0.636	**-0.850*** **	0.002
	N	326		372		387		385	
	r2	0.336		0.377		0.306		0.411	
	F-test of joint significance, p-value:	0.000		0.000		0.000		0.000	
	Ramsey's RESET test, p-value:	0.631		0.815		0.056		0.175	
	Hansen test, p-value (H0: overidentification restrictions hold):	0.679		0.524					
	rank test, p-value (H0: rank condition does not hold):	0.075		0.000					
	endogeneity test of endogenous variable, p-value (H0: exogeneity):	0.103		0.135					

** significant at 10%; ** significant at 5%; *** significant at 1%; heteroscedasticity robust p-values are displayed next to the coefficient estimates*
instruments in GMM regressions: pre-expiry price level; average price of generic produts in other countries, same INN; average price of generic produts in other countries, same atc4 category; average price of originator produts in other countries, same INN; average price of originator produts in other countries, same atc4 category.

Table 17: Shares of cross-price coefficients from one-by-one regressions at INN/ATC4/country level

Cross-price coefficient	No time control			Linear time trend		
	Significant	Non significant		Significant	Non significant	
Positive	34%		57%	18%		61%
		23%			43%	
Negative	20%		43%	5%		39%
		23%			34%	
	54%	46%	100%	23%	77%	100%

Significance at 5%

Table 18: Estimates from fixed-effects model, pooled-data (uniform coefficients)

	Dependent variable: Level of consumption		
Variable	**1**	**2**	**3**
ln_own_price	-0.34***	-0.33***	-0.33***
	[0.03]	[0.03]	[0.03]
ln_cross_price	0.03	0.14***	0.17***
	[0.02]	[0.02]	[0.03]
INN/ATC4/country fixed effects	Yes	Yes	Yes
Time control	No	Linear trend	Time dummies
Observations	14478	14748	14478
Adjusted R-squared	0.9755	0.9757	0.9759

Standard errors in brackets
*** p<0.01, ** p<0.05, * p<0.1
Constant included

Table 19: Shares of cross-price coefficients from pooled-data regressions

Cross price coefficient	No time control			Linear time trend			Time dummies		
	Sig.	Non sig.		Sig.	Non sig.		Sig.	Non sig.	
Positive	20%		53%	25%		64%	27%		65%
		33%			39%			38%	
Negative	15%		47%	11%		36%	10%		35%
		32%			25%			25%	
	35%	65%	100%	36%	64%	100%	37%	63%	100%

Significance at 5%

Figure 24: First generic entry after loss of exclusivity: Kaplan-Meier estimator of the survivor function and Nelson-Aalen estimator of the cumulative hazard for all INN-country pairs analysed

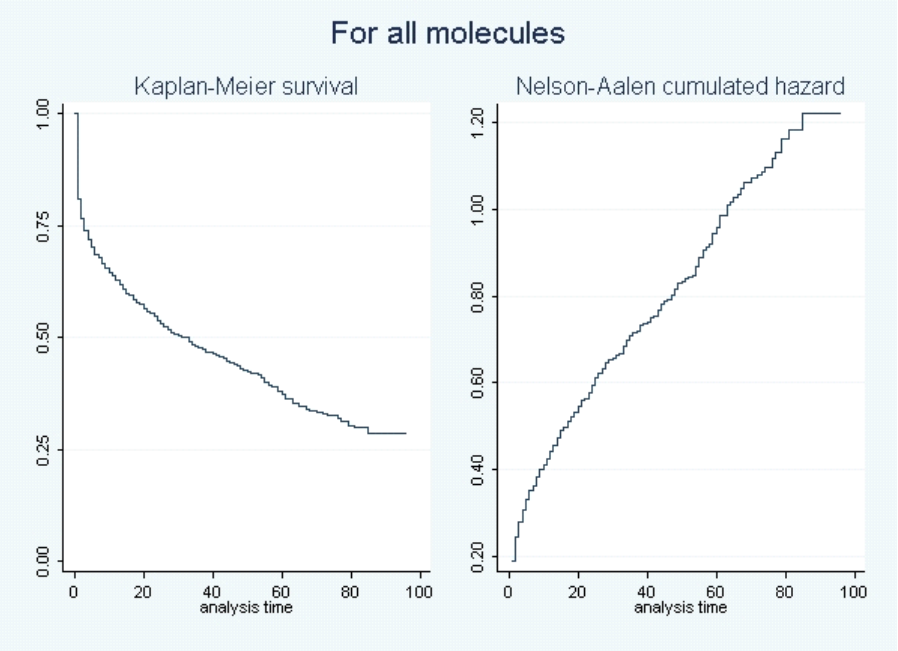


Figure 25: Second generic entry after loss of exclusivity: Kaplan-Meier estimator of the survivor function and Nelson-Aalen estimator of the cumulative hazard for all INN-country pairs analysed

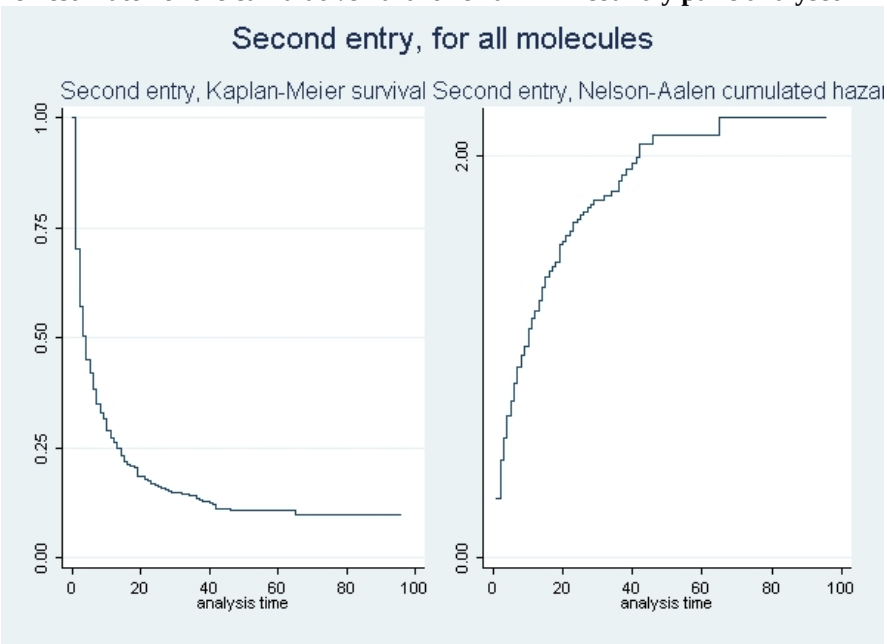


Figure 26: Survivor and cumulative hazard functions estimated by the Cox Regression, by compulsory substitution.

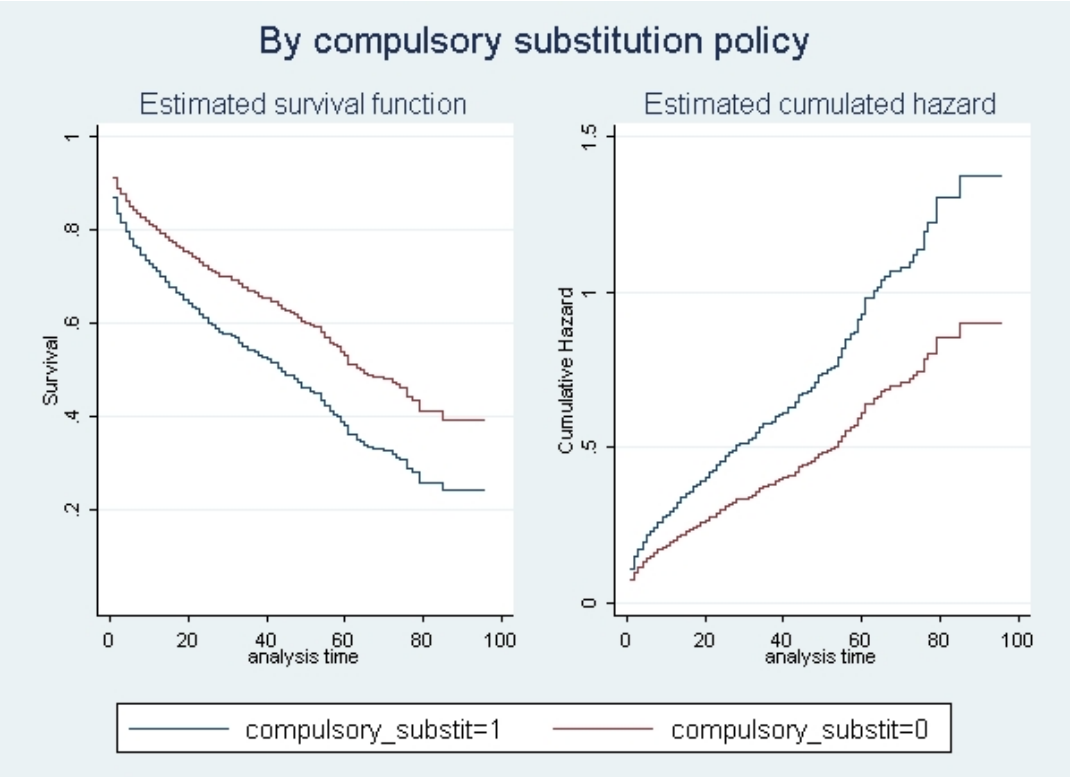


Figure 27: Survivor and cumulated hazard functions estimated by the Cox Regression, by free price policy

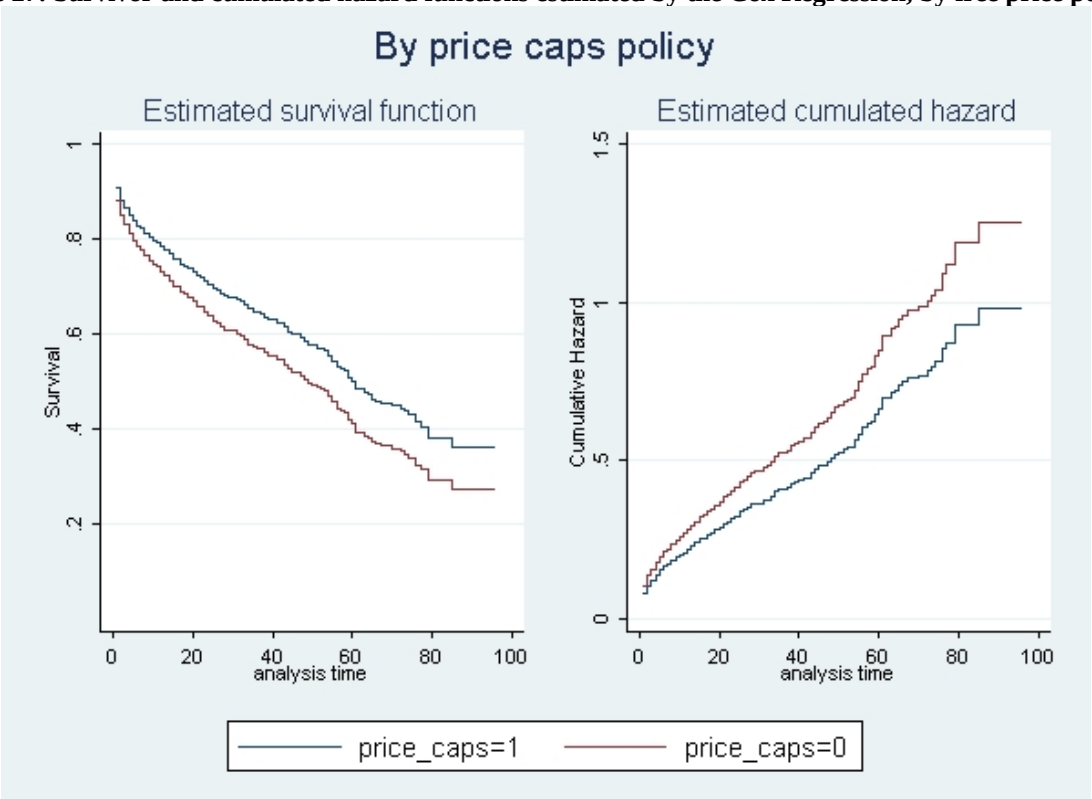


Figure 28: Survivor and cumulated hazard functions estimated by the Cox Regression, by bi-annual dummies

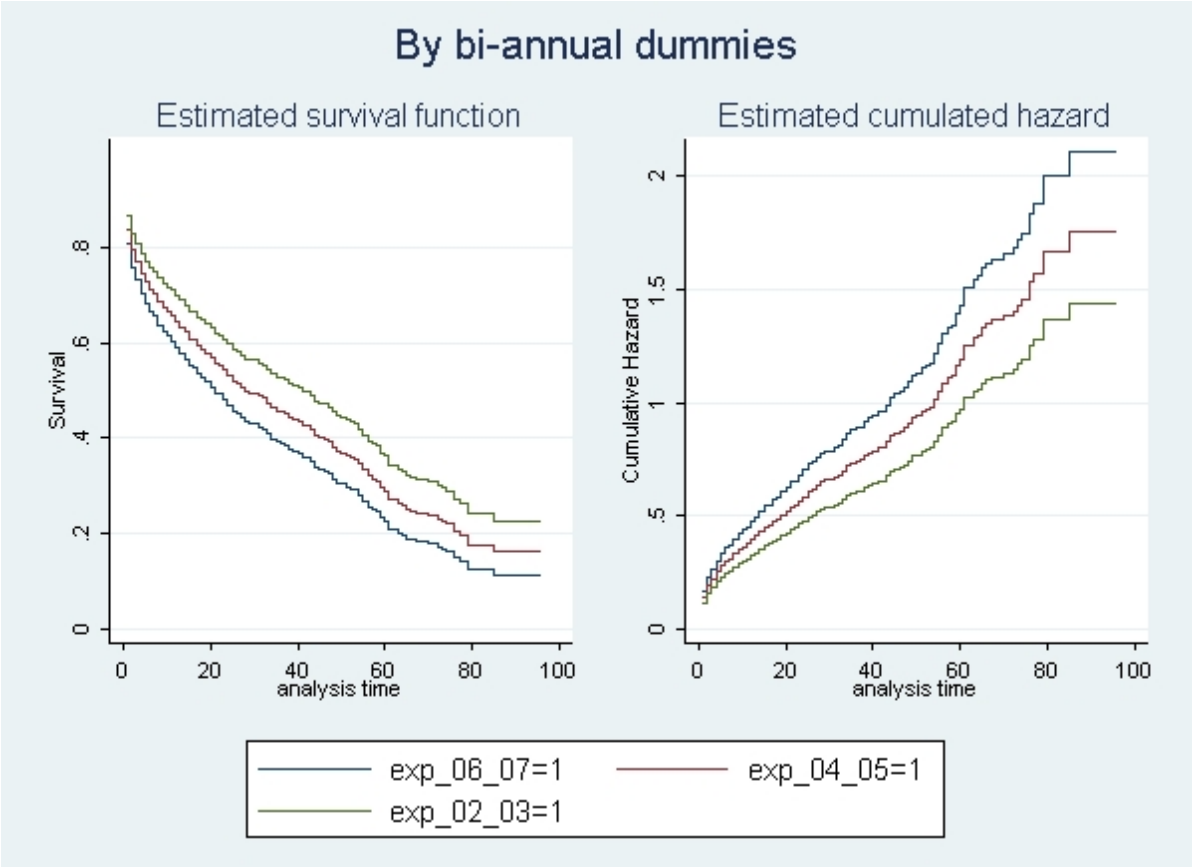


Figure 29: Baseline survivor and cumulated hazard functions estimated by the Cox Regression

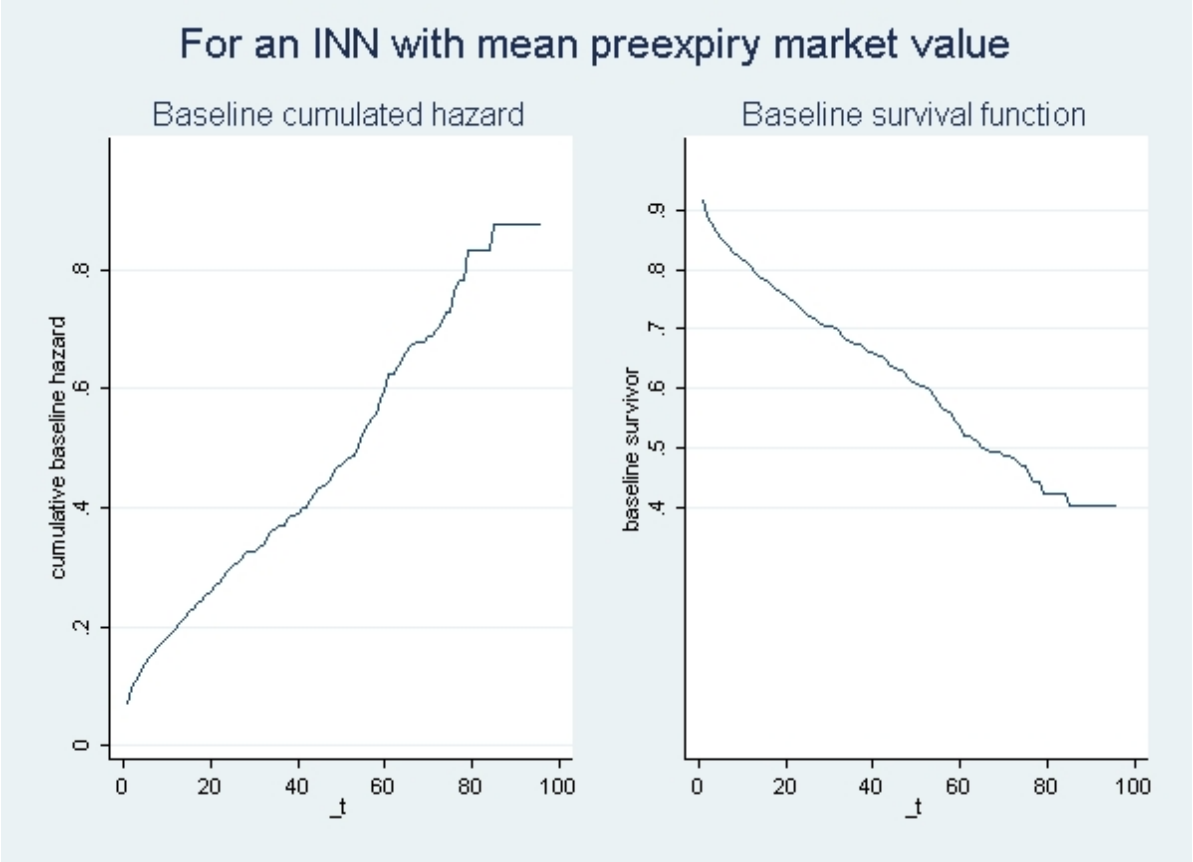
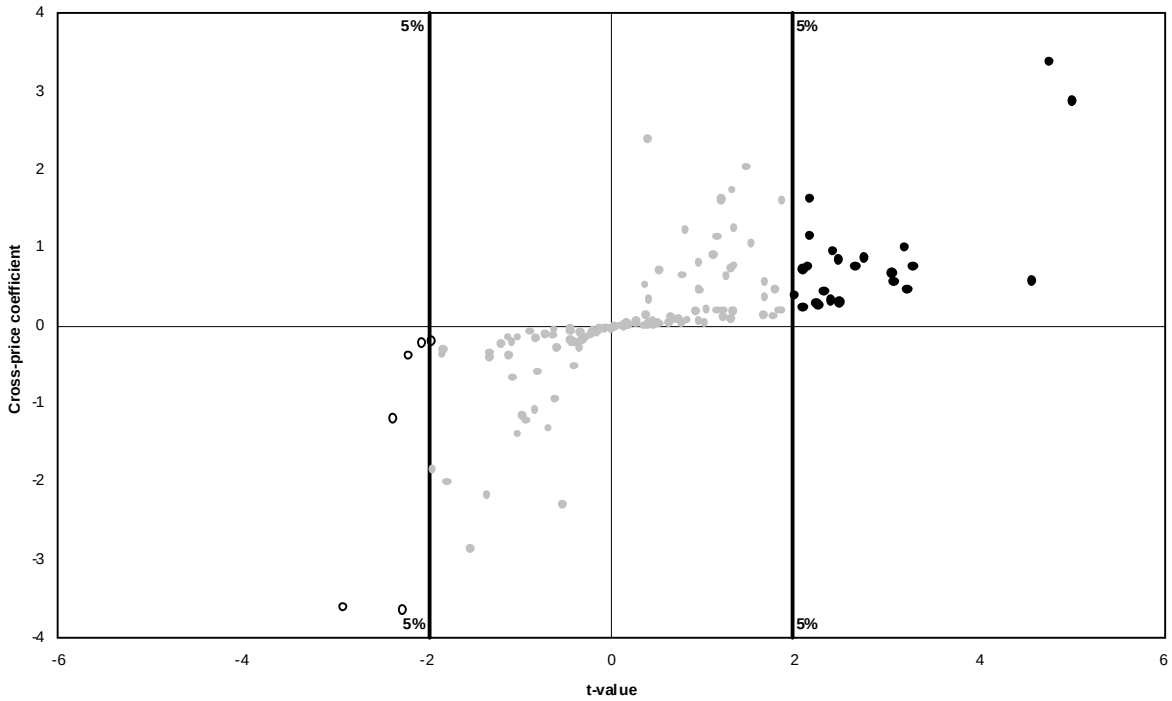


Figure 30: Estimated cross-price coefficients



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