

ANNEXES

Annexes to Chapter A – Part I

Annex EC Competition Law

Introduction

- (1) In order to facilitate the understanding of the legal framework for this report, the EC competition rules are described in this annex.
- (2) The goal of the Community's competition rules is to foster and maintain effective competition in the common market for the benefit of European consumers. The main rules are contained in the EC Treaty (Articles 81 and 82 EC), but there is also secondary legislation. Guidance is furthermore provided through Commission guidelines and individual cases creating important precedents. The application of the EC competition rules by the Commission, national competition authorities and national courts is subject to the control of the European Court of Justice. A sound economic analysis is required when applying the competition rules.
- (3) It should be noted that the purpose of the report or this annex is not to carry out a competitive assessment of any of the agreements or company practices described. Such an assessment would require a case by case assessment taking into account all relevant facts.

Article 81 of the EC Treaty

- (4) Article 81(1) EC prohibits as incompatible with the common market all agreements between undertakings or concerted practices which may affect trade between Member States and which have as their object or effect the prevention, restriction or distortion of competition within the common market. The agreements covered by Article 81(1) can be horizontal (i.e. actual or potential competitors active at the same level of trade) or vertical in nature along the respective supply chain (e.g. production, wholesale, retail).
- (5) Article 81(1) EC prohibits in particular such agreements, decisions or practices which directly or indirectly fix purchase or selling prices or any other trading conditions, which limit or control production, markets, technical development, or investment, which share markets or sources of supply, which apply dissimilar conditions to equivalent transactions with other trading parties, and/or which make the conclusion of contracts subject to acceptance by the other parties of supplementary obligations which

have no connection with the subject of such contracts. The restriction of competition must be appreciable.¹

- (6) Article 81(3) EC provides that agreements and concerted practices which are covered by Article 81(1) EC can be compatible with EC competition law if four cumulative conditions are met: (1) the agreement or practice in question contributes to improving the production or distribution of goods or to promoting technical or economic progress, (2) it allows consumers a fair share of the resulting benefit, (3) it does not impose on the undertakings concerned restrictions which are not indispensable to the attainment of these objectives and (4) it does not afford the possibility of eliminating competition in respect of a substantial part of the products in question. The burden of proof that the conditions of Article 81(3) of the Treaty are fulfilled rests with the parties concerned.² Under Article 81(2) EC agreements and practices covered by Article 81(1) EC but not by Article 81(3) EC are prohibited and automatically void.

Article 82 of the EC Treaty

- (7) Article 82 EC provides that any abuse by one or more undertakings of a dominant position within the common market or in a substantial part of it is prohibited as incompatible with the common market in so far as it may affect trade between Member States.
- (8) Such abuse may consist of the following: a) directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions, b) limiting production, markets or technical development to the prejudice of consumers, c) applying dissimilar conditions to equivalent transactions with other trading parties, thereby placing them at a competitive disadvantage, d) making the conclusion of contracts subject to acceptance by the other parties of supplementary obligations which have no connection with the subject of such contracts. It goes without saying that abuse cannot be argued to exist if there is objective justification for the behaviour.

¹ Commission notice on agreements of minor importance which do not appreciably restrict competition under Article 81(1) of the Treaty (OJ C 368, 22.12.2001, p.13). Available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/deminimis.html>.

² Article 2 of Council Regulation No 1/2003 of 16 December 2002, on the implementation of the rules on competition laid down in Articles 81 and 82 of the Treaty (OJ L 4.1.2003, pp.1-25), available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/regulations.html>.

Council Regulation (EC) No 1/2003

- (9) This regulation sets out the rules for the Commission to enforce Articles 81 and 82 EC. It entered into force in 2004 and eliminated the possibility of notifying agreements to the Commission. It allows decentralised application of European competition law by national competition authorities and courts.
- (10) Article 17 of the regulation authorises the Commission to conduct an inquiry into a particular sector of the economy where prices or other circumstances suggest that competition may be restricted. The present inquiry is based on this provision. Within the context of a sector inquiry, the Commission disposes of most investigative powers, including information requests and inspections.

Commission Regulations concerning the Application of Article 81 EC ("block exemptions")

- (11) The Commission has adopted so-called block exemption regulations (BER) by which it declares Article 81(1) inapplicable to certain categories of agreements, decisions and concerted practices. The BER provide 'safe harbours': if an agreement falls within its scope and does not contain hard core infringements, companies can be confident that their agreement can be considered compatible with EC competition law. For the assessment of pharmaceutical companies' agreements and practices, in particular the Block Exemption Regulation on Technology Transfer (TTBER),³ the Block Exemption Regulation on research and development⁴ and the Block Exemption Regulation on vertical agreements,⁵ may be relevant.

³ Commission Regulation (EC) No 772/2004 of 27 April 2004 on the application of Article 81(3) of the Treaty to categories of technology transfer agreements, (OJ L 123, 27.4.2004, pp. 11-17), available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/transfer.html>.

⁴ Commission Regulation (EC) No 2659/2000 of 29 November 2000 on the application of Article 81(3) of the Treaty to categories of research and development agreements (OJ L 304, 5.12.2000, pp. 7-12) available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/horizontal.html>.

⁵ Commission Regulation (EC) No 2790/1999 of 22 December 1999 on the application of Article 81(3) of the Treaty to categories of vertical agreements and concerted practices (OJ L 336, 29.12.1999, pp. 21-25) available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/vertical.html>.

Commission Guidelines on the Application of Article 81 EC

- (12) The Commission has adopted guidelines on the applicability of Article 81 to horizontal cooperation agreements,⁶ to vertical agreements⁷ and to technology transfer agreements.⁸ Agreements whose purpose is to restrict competition are presumed to have negative effects. For other agreements an analysis of the effects is necessary. It is also recognised that horizontal cooperation can lead to substantial economic benefits.⁹ The guidelines are without prejudice to the possible parallel application of Article 82 of the Treaty. There are also general guidelines on market definitions, the application of Article 81(3) EC and the effect on trade between Member States.¹⁰

EC Competition Law and Intellectual Property Rights

- (13) EC competition rules do not call the existence of intellectual property rights into question. However, for example intellectual property rights are not exempted from the application of competition rules. The exercise by a company of its intellectual property rights can amount to an agreement restricting competition under Article 81 EC or an abuse of a dominant position under Article 82 EC. A relevant example of application of Article 82 in the pharmaceutical sector is the AstraZeneca case where the Commission concluded that the company was abusing its dominant position when it deliberately made misleading representations to national patent offices and national courts with a view to obtaining a longer protection period for its patented product than to which it was legally entitled.¹¹

⁶ Commission Notice - Guidelines on the applicability of Article 81 to horizontal co-operation agreements, (OJ C 3 of 06.01.2001, p. 2), available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/horizontal.html>.

⁷ Commission notice - Guidelines on Vertical Restraints, (OJ C 291, 13.10.2000, p.1), available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/vertical.html>.

⁸ Commission Notice- Guidelines on the application of Article 81 of the EC Treaty to technology transfer agreements, (OJ C 101 of 27.04.2004, p. 2), available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/transfer.html>.

⁹ Commission Notice - Guidelines on the applicability of Article 81 to horizontal co-operation agreements, (OJ C 3 of 06.01.2001, p. 2), available also at <http://ec.europa.eu/comm/competition/antitrust/legislation/horizontal.html>.

¹⁰ For further details see <http://ec.europa.eu/comm/competition/antitrust/legislation/legislation.html>.

¹¹ Commission Decision of 15 June 2005 in Case COMP/A.37.507/F3 – AstraZeneca. See also Commission Decision of 24.03.2004 in Case COMP/C-3/37.792 – Microsoft. Available also at <http://ec.europa.eu/comm/competition/antitrust/cases/index.html>, which in the meantime has been confirmed by the Court of First Instance.

Annexes to Chapter A – Part II

Annex: Methodology

Introduction

- (1) In order to understand certain aspects of this report, it is important to be aware of the main features of the methodology used in the sector inquiry. Therefore, an overview of these features is provided in this annex.
- (2) This first part of the Annex presents the general methodology applicable to the whole report. It describes how the information was collected. In this context, the focus lies on the methodological aspects relating to the surprise inspections and the requests for information which were used as investigative tools¹² in the sector inquiry. The annex then goes on to explain how the information was processed.
- (3) The second part of the annex provides more specific information on the methodology used in Chapter B.

General Methodology

Collection of Information

- (4) The information on which the report is based stems from surprise inspections, requests for information, submissions by stakeholders and specialised agencies and offices (e.g. EPO) and publicly available information. All the information was gathered with a view to assessing *"the introduction of innovative and generic medicines for human consumption onto the market"*.¹³

Inspections

- (5) The Commission's services carried out surprise inspections in January 2008 at the premises of a number of carefully selected originator and generic companies.
- (6) In the context of inspections, the Commission's services gather information which may be available in paper or electronic form at the inspected company. It may also conduct interviews where company representatives provide the information orally on the spot.

¹² Information on the methodological aspects of investigative tools are given to the extent possible, bearing in mind that the Commission does usually not reveal details of, for example, the concrete use of such a tool in any given case.

¹³ For further details see Commission decision of 15 January 2008, available at: http://ec.europa.eu/comm/competition/sectors/pharmaceuticals/inquiry/decision_en.pdf

PHARMA SECTOR INQUIRY – ANNEXES

Requests for Information

- (7) Following the opening of the sector inquiry and the inspections, stakeholders (e.g. associations of originator and generic companies) were informed of the sector inquiry and were given the opportunity to submit their comments and observations. Subsequent to this, requests for information pursuant to Article 18 of Regulation (EC) 1/2003 were sent to the stakeholders. The bulk of these requests for information were dispatched in the period from March to May 2008. The requests were general in the sense that they were designed to collect information very broadly from a wide variety of stakeholders.
- (8) The following categories of stakeholders were addressed: originator companies, generic companies, wholesalers, parallel traders and a number of associations (representing patients, consumers, wholesalers, parallel traders, medical doctors, public hospitals, private hospitals, hospital pharmacists, private pharmacists), IMS Health (a provider of pharmaceutical data services), national competition authorities and national ministries of health, plus marketing authorisation authorities at European and national level. Contributions were also received from EFPIA and EGA, representing the originator and generics industry respectively.
- (9) Within each category of stakeholders, the addressees receiving the requests for information were selected on the basis of criteria such as the scope of their activity enabling them to refer to the pharmaceutical sector at national and European level.
- (10) In the light of the above, the Commission also obtained data and other information from IMS Health, which is cited or used in this report (including in empirical analyses performed by the Commission's services). IMS Health has not acted as an advisor, expert or consultant in connection with this report or, more generally, in connection with the sector inquiry.
- (11) In total, approximately 200 requests for information were sent.¹⁴ In particular, 46 originator companies and 39 generic companies received requests for information. Over the course of the sector inquiry, a number of companies were excluded from the sample of addressees. This was necessary, for example, when a company could credibly explain that it had minimum involvement or that its activity did not focus on medicines for human use (e.g. three originator companies and twelve generic companies were excluded). The overall return by stakeholders in terms of responses received by the Commission's services was high, despite the challenging deadlines that the stakeholders had to meet.
- (12) The general questionnaires asked for very detailed information on a variety of relevant issues, including, for example, general market conditions, economic data, products, patents, litigation, patent-related disputes and contacts, agreements and arrangements in the sector, stakeholders' experience with the legal and regulatory frameworks.

¹⁴ This number includes cases where more than one request for information was sent to the same addressees.

PHARMA SECTOR INQUIRY – ANNEXES

- (13) The addressees were asked to provide the information in electronic tables relating to the questionnaires. In instances where the information could not be inserted into tables, they were asked to provide textual responses. Some of the questions also required the submission of documents (e.g. originator companies' key documents on patent strategies), in order to further substantiate the responses.
- (14) For certain questions, the information requested concerned all INNs¹⁵ in which, for example, a stakeholder is "active"¹⁶, and for others, only 219 selected INNs (e.g. all litigation relating to any of these 219 INNs was requested). A full list of the 219 INNs can be found at the end of this annex.
- (15) The 219 INNs for which certain information was requested were selected as follows:
- (16) A first group of INNs was selected by considering, in three Member States (France, Germany and the United Kingdom), the 75 top-selling INNs that faced the loss of exclusivity (e.g. patent/IP expiry, data exclusivity) in the period 2000 – 2007. In each Member State, this list of 75 INNs represented, in value terms, well over 90% of sales of all INNs that faced loss of exclusivity in the period 2000 – 2007. The combination of the top 75 molecules in each of these Member States provided a final list of 128 INNs. This list is referred to as "E75".
- (17) A 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 already part of the E75 list). It is referred to as "T50".
- (18) A third group of other INNs was selected considering the 50 top-selling INNs having faced (possible) first generic entry in each of the selected countries, obtaining a total 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.
- (19) The combination of these three subgroups, with a view to obtaining a robust sample of INNs likely to be representative for the EU as a whole, makes up the final list of 219 INNs.

¹⁵ Pharmaceutically active molecules can be accorded an international non-proprietary name (INN), administered by the World Health Organisation (WHO), which is considered as the standard general name. For further information, see: <http://www.who.int/en/>

¹⁶ "Active" must be understood as a stakeholder, such as an originator or generic company, holding a marketing authorisation with which it sold products in any of the EU Member States in the relevant period under investigation.

PHARMA SECTOR INQUIRY – ANNEXES

- (20) The time period considered for the general requests for information was 2000 – 2007. In geographical terms, the information requested related to the whole of the EU, i.e. to each of the 27 Member States.¹⁷
- (21) In order to complete the information needed for the sector inquiry, a number of categories of stakeholders received a further, second request for information (e.g. originator and generic companies). All originator and generic companies that had been subject to surprise inspections also received requests for information relating to the inspection material. Companies were not obliged to provide non-confidential versions for their replies. In order to ensure the adequate protection of confidential information and business secrets, the names of the companies, as well as any information allowing their identification, were removed from this report.

Processing the Information Material

- (22) Once collected, the information described above was processed and the results of this are presented in the various chapters of the report.
- (23) Regarding stakeholder responses to the requests for information, a significant number of issues arose which required further clarification by the respondent stakeholders.¹⁸ These concerned, for example, matters detected where information received from originator companies did not sufficiently match supposedly equivalent information submitted by generic companies.
- (24) It was found during the processing of the information received that the number of responses eventually available for the various questions varied. This was due to the fact, for example, that the information requested was available with certain stakeholders but not with others. In other words, within a category of stakeholder, not every stakeholder may have been concerned by every question (to the same degree). As a consequence, the statistical analyses presented in the figures (e.g. graphs, charts) and tables are not always based on the same number of responses. Accordingly, the sample used in the statistical analysis may not always be the same size. Precise information on sample size is usually given in the graphs and tables or in the adjacent text.
- (25) Where results have greater significance on their own, the statistical analysis is based on the sample sizes emerging from the data. However, where inferences are drawn by direct comparison of separate figures and tables, the analysis is based upon comparable sample sizes.

¹⁷ For the years prior to the accession of any of the Member States, information was requested from those Member States that were already members of the EU.

¹⁸ Such clarification was requested of stakeholders by means of a procedure previously agreed with stakeholder associations in order to alleviate the burden imposed on stakeholders, e.g. by making provision for regular weekly dispatch of requests for clarification to stakeholders on the same day of the week).

- (26) Regarding the absolute sample size, the analysis undertaken in the sector inquiry attempted to use the largest possible number of observations. Where only fairly small sample sizes were available, the results have been checked for statistical robustness/significance.
- (27) As mentioned above, the 219 INNs to which certain questions in the requests for information related consist of various subgroups of INNs, which makes the 219 INNs an “artificial” universe. In more technical terms, the universe of the 219 INNs is not random.¹⁹ Therefore, the analyses in the report refer to one or both of the INN subgroups (the T50 list and/or the E75 list) in order to provide the most relevant universes of measurement. However, in order to illustrate the list of 219 INNs and its characteristics, the report may here and there also use all INNs as a universe of measurement.

Methodology Applied to Chapter B. ("Impact of Generic Entry and Regulatory Factors Affecting Generic Competition")

- (28) The subsequent section describes the data sources used for the statistical analysis conducted in Section B. as well as the methodology applied to prepare the datasets.

Data Sources

- (29) The statistical analysis made in Sections B. is based on two main sources of data.
- (30) First, the analysis used data collected 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, where the set of countries in which the companies were requested to provide data was limited to ten: Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Spain and the United Kingdom.
- (31) Second, the Commission has used data requested from IMS Health, a provider of pharmaceutical data services. 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 dates concerning loss of exclusivity, launch dates. For some Member States, IMS data were also available as regards the level of promotional activity (on a quarterly basis) at the brand level. Most emphasis has been given at 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 in the previous paragraph, IMS data were also obtained for all INNs belonging to ATC4 classes, within which loss of exclusivity took place at some point in the period 2000 – 2007.

¹⁹ The universe of the 219 INNs would have been random if, say, each INN of all possible INNs (population) had had an equal probability of being picked and included.

PHARMA SECTOR INQUIRY – ANNEXES

- (32) Progressively, the IMS dataset and the datasets from the companies were integrated into one dataset. The IMS dataset served as the "central" dataset into which the corresponding data items of the companies were combined (except where company data were not available or in individual cases where these data appeared inaccurate or incomplete).
- (33) The two datasets must be seen as complementary. The combined use of the IMS dataset and the company datasets made it possible to use company data to the largest extent possible, while being able to fill in "gaps" in one dataset with information available in the other dataset.
- (34) For instance, in order to keep the informational burden on companies limited, information on prices was asked for 10 Member States only (see above). All analyses of price developments in the other 17 Member States (Austria, Belgium, Bulgaria, the Czech Republic, Cyprus, Estonia, Finland, Ireland, Lithuania, Latvia, Luxemburg, Malta, Portugal, Romania, Slovakia, Slovenia, Sweden) therefore rely on IMS data. Likewise, the calculation of EU averages involved the use of IMS data for the price component relating to the 17 countries mentioned. Furthermore, the sample of firms to which the Commission sent questionnaires did not comprise the entire universe of firms active in the production and supply of medicines for human use. The sample contained 43 originator companies and 27 generic companies. The IMS dataset aims at tracking the sales of all actors in the field. For that reason, for those companies not part of the inquiry the analysis relied on information provided by the IMS dataset.
- (35) On the other hand, some types of data were only available from the companies themselves, not from IMS. For instance, the IMS dataset only contained expiry dates for Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden and the United Kingdom: in other words, for most of the EU 15 Member States plus the Czech Republic. In addition, IMS expiry dates were sometimes only available for some of the relevant products within the countries, not for all products.
- (36) Similarly, information on actual average transaction prices and discounts granted by the companies was not available in the IMS dataset, as this is information to which IMS has no access. IMS bases itself mainly on public sources, such as list prices and regulated prices. It then applies a conversion factor to take into account what it understands to be normal discount applicable to that industry level. Prices in the IMS dataset are therefore, normally speaking, not actual transaction prices. In the sector inquiry, by contrast, companies were specifically asked to provide actual average transaction prices.
- (37) For each INN, the date of loss of exclusivity in the country concerned was defined as either the date at which the first product based on the INN lost patent protection (including SPC protection) or the date at which the INN ceased to be protected by data exclusivity, whichever was the more recent in time.²⁰ This applied to all INNs for

²⁰ During the public consultation 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

which this information was 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.²¹ 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.

- (38) 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 dataset, combined with information provided by the companies.
- (39) After the publication of the Preliminary Report, additional data cleaning took place. In particular, the Commission services received data corrections from a number of companies as well as additional information on the presence of SPCs and data protection. Further, in a number of cases, the Commission corrected entry dates, where they did not appear to 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).
- (40) 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 dataset 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.
- (41) Information on the regulatory framework in the various Member States was compiled on the basis of the Öbig report of 2006²², 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.²³

be compared with the loss of data 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, as explained in Section B., 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.

²¹ 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.

²² Öbig - Österreichisches Bundesinstitut Für Gesundheitswesen, *Surveying, Assessing and Analysing the Pharmaceutical Sector in the 25 EU Member States*, 2006.

²³ Information was coded for each year between 2000 and 2007, taking into account possible evolutions in the different regulatory systems. Nevertheless, a large majority of the variables listed is time invariant.

PHARMA SECTOR INQUIRY – ANNEXES

INNs Considered

- (42) For the main part, the analysis in Section B. was performed on the basis of the "E75" list of INNs for which the Commission requested information from the companies.
- (43) The analysis in Chapter B. at Member State level was conducted each time on the basis of a national subset of the E75 list, namely of those INNs in the E75 list that were relevant for the Member State in question, i.e. on the basis of those INNs that (i) were effectively sold in that Member State and (ii) that faced loss of exclusivity in the period 2000 – 2007.
- (44) As a result, based on the IMS dataset, the national subsets of INNs in the various Member States contained the following numbers of INNs.²⁴

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

- (45) As is clear from the above table, there are major disparities between the subsets of molecules that were subject to analysis. In part, this is a natural consequence of significant disparities between the national markets for pharmaceutical products in the EU.^{25,26} The differences are explained in part by the fact that the set of INNs sold in each country differs. Further, differences also relate to the period considered. Some INNs had lost exclusivity before the year 2000 in some Member States, but not in

²⁴ The dashes (-) in the table relate to the fact that, as indicated above under "Data sources", the IMS dataset 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.

²⁵ 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.

²⁶ 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.

PHARMA SECTOR INQUIRY – ANNEXES

others. Other INNs will only lose exclusivity in some Member States after the year 2007. Consequently, the requirements (i) and (ii) mentioned in the previous paragraph resulted in subsets of molecules that were rather different (in size and composition) among the various Member States.²⁷

- (46) The dataset with company information changed, to a mild extent, the number of INNs that could be used for the analysis in a number of countries.²⁸ The merged dataset 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)

- (47) Also with company information included, few observations (INNs) appeared to be 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 also appeared unable to provide comprehensive information on the patent expiry date in these countries (many entries contained "N/A"). Further, the merge process of the company data with the IMS data turned out – from a technical matching perspective – less successful than for the other Member States. For this reason, section B. does not contain descriptive statistics for these countries.
- (48) The number of available observations (INNs) for Romania and Bulgaria, who became Member States in 2007, is also small. Further, there appear to be a substantial number

²⁷ 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).

²⁸ 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.

PHARMA SECTOR INQUIRY – ANNEXES

of data issues in the information provided for these countries. For this reason, Section B. does not contain descriptive statistics for these two countries.

- (49) Correspondingly, all graphs setting out developments over time and the regression 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 (for the reasons set out above).
- (50) 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 various types of qualitative information (product characteristics, characteristics of the regulatory environment). Not all types of data were available for the INNs and countries analysed in further detail or could be successfully merged. A number of dates relating to loss of exclusivity and entry required further cleaning (see below on the treatment of early entries). Accordingly, this led to six INNs not being used for the regression analysis.
- (51) Ultimately, the principal dataset used for the regression analyses was based on 1085 observations in total (cross-sectional, by country-INN-ATC4), relating to the 17 countries, 122 INNs and 924 country-INN pairs.
- (52) The analysis of substitution within ATC4 classes 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

- (53) All EU statistics (entry rates, market shares, price indices, etc.) in the section 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).
- (54) The rate used for the conversion of exchange rates is the average exchange rate in the year 2007.²⁹
- (55) Descriptive statistics on the impact of generic entry are mostly presented both as a “head count” measure (where within each country each INN is counted as equal) and as a weighted measure (where within each country each INN receives a weight to account for its relative importance).³⁰ Two types of weights are used for the latter

²⁹ For consistency, prices and values in the dataset 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.

³⁰ 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

purpose, depending on the context. For the purposes of establishing shares of generic entry, average time to entry and generic penetration, weights are used in relation to the sales value of each INN in the year before loss of exclusivity. By contrast, for the indices that track the development of prices over longer time periods, weights are used in relation to the value share of each INN sold in the month concerned (contemporary weights). 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.

- (56) 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.
- (57) 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.
- (58) The same approach is used for the volume indices.

Treatment of Early Entries

- (59) The measurement of time to entry was somewhat complicated by the fact that in the IMS dataset 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 probably just be assigned to a small measurement error. Those INNs with a longer time gap are more difficult to interpret. These instances may relate to cases where the companies made a mistake in the determination or production of the date of loss of exclusivity, to INNs for which the company or product status may not have been fully established or recorded in the IMS dataset³¹, but also to some possible "early" entries by generic firms, i.e. entries before the reported date of loss of

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).

³¹ The IMS reference information on company and product status refers to the situation in the spring of 2008, when the database was created. Hypothesis: certain companies entered on a licence when the product was still on-patent, and were thus recorded as making sales as of that time. However, after the loss of exclusivity, a licence is no longer necessary and the company continues to produce what has then become a generic product. This might be a possible explanation for certain companies selling "generic" products (according to the product status) before loss of exclusivity.

PHARMA SECTOR INQUIRY – ANNEXES

exclusivity. In the Preliminary Report these instances were regarded as entry at the date of loss of exclusivity, pending further analysis.

- (60) For the purpose of the Final Report, the Commission services sought to improve the accuracy of the entry dates 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 date was used as the date of first independent generic entry.
- (61) Where the dates continued to point to early entry, these observations were further compared with a dataset prepared by CRA and IMS in the course of the sector inquiry.³² Where this dataset gave a more plausible date of loss of exclusivity and/or entry date, the latter were 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.
- (62) 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).
- (63) Where the negative time to entry was more than three months ("substantial negatives"), the time to entry was also put to zero (as was the case in the Preliminary Report). This related to 39 cases (country-INN pairs). In view of the limited number of cases, the treatment of these observations in this way is not per se problematic to 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 loss of exclusivity (because no longer restricted by e.g. 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 loss of exclusivity).
- (64) In the regression analysis, the cases involving "substantial negative" time to entry were flagged (using dummies) and analysed further. Robustness checking pointed out that the results are rather insensitive to the method used (see below).
- (65) Information on company agreements further shed light on some of the remaining substantial negatives. Information was available on a number of supply/distribution and settlement agreements whereby originator companies allowed early entry to a generic company. These cases, 20 in total, were interpreted as a form of controlled

³² Dataset 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.

PHARMA SECTOR INQUIRY – ANNEXES

entry. In the subsequent regression analyses, they have been specifically flagged with a dummy variable.

- (66) 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 a 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.
- (67) These tests confirmed the robustness of the results towards the applied procedures.

PHARMA SECTOR INQUIRY – ANNEXES

Annexes to Chapter A – Part III

List of 219 INNs

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 *
CEFTRIAZONE *	CEFUROXIME AXETIL *	CELECOXIB #
CELIPROLOL *	CETIRIZINE *	CICLETANINE *
CICLOSPORIN *	CIPROFIBRATE *	CIPROFLOXACIN *
CISAPRIDE *	CITALOPRAM # *	CLARITHROMYCIN *
CLODRONIC ACID	CLOPIDOGREL #	CROMOGLICIC ACID + REPROTEROL *
CYPROTERONE + ETHINYLESTRADIOL	DALTEPARIN SODIUM *	DARBEPOETIN ALFA #
DESGESTREL + 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 + LISINAPRIL *	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 *

PHARMA SECTOR INQUIRY – ANNEXES

IRBESARTAN #	ISOTRETINOIN	ITRACONAZOLE *
LACIDIPINE *	LAMOTRIGINE # *	LANSOPRAZOLE # *
LETROZOLE	LEUPRORELIN # *	LISINAPRIL # *
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, ACCEL.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 *

Note: "*" – E75; "#" – T50

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

Annexes to Chapter B – Part I

Annex to Chapter B.1.2.: Further Product Life Cycle Management Strategies during Patent protection

Pricing

- (68) As patent expiry approaches, originator companies must consider their future pricing strategies, which will depend on product-specific price sensitivity (relating to Member State-specific demand-side characteristics). One strategy is simply to maintain the price following loss of exclusivity. The rationale behind such a strategy is the expectation that a significant share of market demand is inelastic. Possible reasons for the lack of price sensitivity are manifold but could include the deployment of measures aimed at achieving product loyalty.
- (69) The more common strategy is to initiate price competition with incoming generic companies. Price decreases can be implemented through cutting the list price or through selective price reductions or rebates for wholesalers, pharmacies or insurers. A large originator company might also attempt to use its economies of scale in order to drive small generic companies out of business. This strategy of price reductions in anticipation of generic entry was described by one company as being a means of creating an “unattractive generic market”.

Launch of an Own Generic

- (70) Originator companies might decide to launch a “generic version” of their own products as patent expiry approaches. Similarly they may decide to license the product to a third party. Most respondent originator companies stressed that the option of launching their own or an in-licensed generic product is only considered once generic competitors have entered the market or at least when generic competition has received approval. Several companies also stressed that “the presence of a high number of independent generics on the market may have a major role in deciding whether to launch a generic product”. Despite the existence of conditions encouraging originator companies to launch a generic version of their original product, respondent companies emphasised the fact that they review the option of launching or licensing generic versions of their products on a product-by-product and market-by-market basis.
- (71) Originator companies are divided over the question of whether to launch their own or in-licensed generics. Approximately 45% of originator companies indicated that between 2000 and 2007 they launched or seriously considered launching their own or an in-licensed generic. Companies not adopting the strategy of selling generic medicines (directly or indirectly) discarded this option due to inconsistencies with the focus on innovation of their overall business model.

Switch to OTC

- (72) Towards the end of the life cycle of an originator product, switching the medicine to an over-the-counter (OTC) pharmaceutical product which does not require a prescription by doctors may be considered.³³ Switching to OTC is sometimes considered by companies, but it is apparently not frequently used.
- (73) One reason that this strategy is seldom used could be that a pre-condition for such a switch to OTC products is that it must be authorised by a marketing authorisation agency upon request of the originator company. For a switch to OTC of prescription medicines to be authorised, there has to be proof that the therapeutic area it addresses allows self-diagnosis and monitoring by the patient. Therefore, the dosing regime and instructions should be understandable for patients and no exposure to significant risks should result from the product.
- (74) If these requirements are met, the attractiveness of a switch to OTC products lies primarily in the marketing opportunities that ensue. This further requires an increased marketing budget and an effective consumer healthcare division. Otherwise, the OTC medicine must be licensed to another company.
- (75) Contrary to prescription medicines, direct advertising of OTC medicines to the consumer is allowed. In general, OTC medicines do not compete with generic products,³⁴ which makes the timing of the switch less crucial than for other life cycle management strategies. Nevertheless, a switch to OTC products late in the life cycle and before patent expiry is generally preferable because at this point it becomes an

³³ To be more precise, the switch tends to be to behind-the-counter (BTC) products that do not require a prescription but can only be sold through pharmacies.

³⁴ As submitted during the public consultation, it is acknowledged that sometimes competition between generics and originators on the one hand and OTC's on the other takes place.

PHARMA SECTOR INQUIRY – ANNEXES

option to strengthen the product image and brand loyalty of the patient. Moreover, the switch to OTC products can extend the data protection period.³⁵

³⁵ Article 74(a) of Directive 2001/83/EC of 28.11.2004 on the Community code relating to medicinal products for human use as amended by Directive 2004/27/EC of the European Council and the Parliament of 31 March 2004 (OJ L311/67 p.67).

Annexes to Chapter B – Part II

Annex to Chapter B.1.3.: Econometric Analysis

- (1) This section provides the main results of the regression analyses undertaken by the Commission services. Part 1 describes the analysis of some of the main determinants of the pattern of generic entry in terms of both occurrence and number of entrants. Part 2 explores the main drivers of the time to entry. Part 3 describes the analysis of the main determinants of the effect of generic entry in terms of prices and shares of sales. Finally, Part 4 analyses the effects of generic entry on other INNs in the ATC4 class.
- (2) Tables and figures can be found at the end of this annex. The set of characteristics and potential determinants considered is presented in tables A – C. 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.

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

1.1. Introduction

- (3) The Preliminary Report contained several descriptive statistics on the pattern of generic entry at the aggregate level, per country and per size class, based on the information provided to the Commission by the companies and IMS. Using the same information, the econometric analysis presented below 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.
- (4) 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.
- (5) Each INN in the dataset 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.³⁶ At 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.

- (6) 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.³⁷

1.2. Methodological Framework

- (7) 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 interest³⁸, 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.³⁹
- (8) The second model presented focuses on the number of generic entrants observed one and two years after loss of exclusivity (count data model).⁴⁰ The model is estimated assuming a negative binomial distribution of the dependent variable⁴¹ and computing the marginal effect of each of the determinants on the dependent variable.

³⁶ 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").

³⁷ 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.

³⁸ 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.

³⁹ Formally, let π_i denote the probability of observing entry of a generic company and x_i the vector of regressors to be tested on their impact on this probability. The model estimates the conditional probability as $\pi_i = \text{Prob}[y_i = 1 | x_i] = F(x_i' \beta)$, where β 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).

⁴⁰ 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 completeness, this model was also tested. The results are fully consistent with those presented for probit and count data (see 1.3).

⁴¹ The Poisson distribution is the most commonly used distributional form for the count data model. In the Poisson distribution, the probability mass function of y_i , the number of generic entrants observed, conditional on x_i , the regressors, is given by $\pi_i = \text{Pr}[y_i = y | x_i] = [(\exp(-\lambda_i) * \lambda_i^y) / y!]$ where $\lambda_i \equiv$

- (9) As a natural consequence of the models chosen (involving a specification of the distribution function), the maximum likelihood estimation method was used.
- (10) 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 1.1 this modification has been applied to all the specifications presented.⁴²
- (11) 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 subsample of INN/countries.⁴³ 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.

$\exp(x_i' * \beta)$. 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.

⁴² 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 has been done in the present case for table 1.1. 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 by taking the exponential of the coefficient, in order to give a measure of the marginal effect of each of the regressors. The measure obtained in this way is called the *incidence rate ratio*. The basis for this conversion is as follows: For a dummy variable x_{ik} , the conditional mean of y_i , the number of generic entrants, can be compared in the case that $x_{ik}=1$ and in the alternative case that $x_{ik}=0$, respectively when the policy k is in place and it is not, keeping the other variables in x_i constant. With a Poisson distribution, it holds that

$$\frac{E[y_i | x_{ik} = 1, x_i^*]}{E[y_i | x_{ik} = 0, x_i^*]} = \exp[\beta_k],$$

where x_i^* is the vector of regressors excluding the variable of interest x_{ik} . This modification was not applied to the coefficients presented in table 1.2.

⁴³ The variables referring to the ATC4 category of each INN were available only for certain countries. The same applies to the variable promotional expenditure.

- (12) 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.
- (13) 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).

1.3. Regression Results

- (14) Table 1.1 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).
- (15) 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.
- (16) 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 tend to enter in those medicines which might be the less complicated to produce.⁴⁴
- (17) 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.⁴⁵

⁴⁴ 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.

⁴⁵ 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.

PHARMA SECTOR INQUIRY – ANNEXES

- (18) For what concerns the regulatory variables (Table B) the full set of variables was tested.
- (19) Policies involving compulsory substitution of generic products by pharmacists seem to positively affect the probability of entry. The coefficient found is positive and statistically significant in all the specifications. On average, Member States in which a compulsory substitution policy is in place appear to have a higher probability of seeing generic entry within one or two years of about 10-15%⁴⁶.
- (20) The presence of price caps appears to negatively affect the probability of entry, at least in the short run. The size of this negative effect is in the range of 10 to 15%, keeping other factors constant. The other regulatory variables included do not seem to show coefficients that are statistically significant in a stable manner.
- (21) 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.⁴⁷
- (22) 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.⁴⁸
- (23) 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

⁴⁶ 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 to increase further.

⁴⁷ In cases in which a controlled entry was recorded, the probability of observing independent generic entry would accordingly appear to increase. This finding may be partly explained by the fact that in a number of cases involving controlled entry, it was not possible to distinguish the date of first generic entry and first independent entry. As a result, the estimated coefficient may pick up some cases of controlled entry rather than independent entry. It is also important to bear in mind that the number of cases identified as controlled entry is rather low. See Annex on Methodology for further details.

⁴⁸ 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 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.

- 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.⁴⁹
- (24) 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.
 - (25) 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.
 - (26) A positive and statistically significant effect of compulsory generic substitution on the number of entrants is confirmed by the statistical significance in all regressions. Keeping other factors constant, the number of entrants in Member States which require generic substitution by pharmacists appears in the order of 50% higher one year after loss of exclusivity than in Member States in which this policy is not in place.⁵⁰
 - (27) 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 incidence rate ratio for this variable ranges between around 0.60, after one year, and 0.70, after two years. This means that in the presence of a price cap, the number of generic entrants after one or two years appears to be about 30-40% lower than in the case without such a policy. The results for controlled entry are consistent with the probit model, while the other additional controls all report the expected sign.

⁴⁹ 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 1.1 and 1.2.

⁵⁰ With reference to table 1.2, the estimated coefficients for compulsory_substit in the full sample regressions are 0.44 (after one year) and 0.51 (after two years). Taking the exponential, $\exp(0.44)=1.55$ and $\exp(0.51)=1.61$. See also footnote 42.

- (28) 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 1.2.⁵¹

2. Time to Entry

2.1. Methodological framework

- (29) 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.
- (30) 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 $\theta(t) = f(t)/S(t)$, which is the "instantaneous transition intensity" at moment t , provided that there was no transition until t .
- (31) The hazard rate is assumed to fulfil the proportional hazard assumption: $\theta(t, X_{ijt}) = \theta_0(t) \exp(\beta' X_{ijt})$. $\theta_0(t)$ 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.
- (32) 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.

⁵¹ 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").

2.2. Implementation⁵²

- (33) A panel dataset was used for this purpose. One observation in the data set is related to a molecule in a country in a month. Molecules from 17 countries were analysed and the time period covered is January 2000 – December 2007.⁵³ 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.
- (34) 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 or before month t since loss of exclusivity and zero otherwise. For different specifications of the hazard rate, different link functions are used.
- (35) 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.
- (36) 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 *biosimilar*. For this reason, *biosimilar* as a characteristic of an INN was not used in the hazard models.
- (37) 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 quadratic function is used (selection based on descriptive statistics, see part 2.3). Also specifications with non-parametric baseline hazard (Cox) are considered.
- (38) To account for unobserved heterogeneity of INNs (so-called frailty), an INN-country-specific random intercept is included. Most of the regressions make distributional

⁵² This subsection, which is of a more technical nature, can be skipped without losing understanding of the results presented in the next subsections.

⁵³ 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.

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.

(39) Specifically, the following five specifications are analysed:

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

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

The baseline hazard function $\theta_0(t)$ 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. Variable *char* is a vector of INN characteristics, *reg* is a vector of regulatory variables and *Pop* is country's population size.

- 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: $\theta_0(t) = \alpha t^{\alpha-1}$ where $\alpha > 1$. The shape parameter α is estimated together with coefficients of regressors. When α is greater than 1, the hazard is increasing. When α is lower than 1, the hazard is decreasing. Finally, when α 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

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

where v_{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

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

where n is the month, $u_{ij} = \ln(v_{ij})$ is a random variable with the standard normal distribution and $\alpha_1 n^2 + \alpha_2 n$ 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:

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

- (40) 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 or before period t or whether in period t the INN was still the realm of the originator company.

2.3. Non-Parametric Estimates of Time to Entry

- (41) 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 2.1.
- (42) 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.
- (43) 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.
- (44) 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.
- (45) 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.
- (46) 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 2.2. 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.

2.4. Regression Results

- (47) The results for the full data set are presented in table 2.1. 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.

2.4.1. Control Variables

- (48) 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 2.5).
- (49) 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.
- (50) 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/Member State market, the faster first entry of a generic competitor. Specifically, for a given *pre-expiry price* (among other variables), this coefficient shows that INNs with larger volumes attract first generic entry faster than INNs with lower volumes.
- (51) The coefficients of the *pre-expiry price* variable are slightly smaller than one and always statistically significant.⁵⁴
- (52) The *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.
- (53) 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.

2.4.2. Regulatory Variables

- (54) *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. Furthermore, the

⁵⁴ The price is, however, correlated with the *pre-expiry market value per capita*. A change of price will cause a change in value, therefore coefficients of both variables need to be considered when analysing the impact of price on time to entry. The overall effect depends on how value changes with price. When a marginal price increase is followed by a value increase, the overall effect on hazard is likely to be positive due to the fact that the positive effect of value is stronger than the negative effect of price. When a marginal price increase is followed by a value decrease, the overall effect on hazard is likely to be negative.

magnitude of this coefficient is large relative to the other significant coefficients. Figure 2.3 shows the predicted survivor and cumulated hazard functions estimated by the Cox regression from the first column of table 2.1.

- (55) *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.
- (56) *Frequent adjustment*: in all specifications the coefficient appears greater than one but not statistically significant.
- (57) *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 2.5). Therefore, the data do not appear to identify an effect of this variable.
- (58) *Lowest price policy*: in all specifications the coefficient is statistically insignificant. The data do not appear to identify an effect of this variable.
- (59) *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 2.4 for illustration). This effect is however not very strong in that it disappears in the robustness checks (see part 2.5).

2.4.3. Time Trend

- (60) 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 2.5 for an illustration)

2.4.4. Baseline Hazard

- (61) 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.
- (62) Figure 2.6 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 2.1. Both functions have a close-to-linear shape.

2.5. Robustness

- (63) Table 2.1 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.
- (64) 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 2.2 presents the results. Cox and cloglog with non-parametric frailty models did not converge.
- (65) 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 remains lower than one but not statistically significant.

3. Price Effects of Generic Entry and Generic Penetration

- (66) 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.
- (67) 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.
- (68) 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.
- (69) Several robustness checks were also carried out by analysing different versions of the main models.

3.1. Data

(70) The econometric analysis used a dataset based on the combined company and IMS dataset described in the Annex on methodology. The estimation used cross sectional datasets. 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.

3.2. Models

(71) 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.

3.2.1. Long-Run Price Drop Regressions

(72) Long-run price drops were regressed against the following set of explanatory variables:⁵⁵

- The final number of generic producers in the given country/INN pair;

⁵⁵ 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 ε is the error term. INNs are indexed by *i* and countries by *c*.

PHARMA SECTOR INQUIRY – ANNEXES

- 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.
- (73) The estimation sample was restricted in each country to those INNs which already had at least two years of post-entry history.
- (74) 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.
- (75) Positive coefficients can be interpreted as factors conducive 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.
- (76) 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.

3.2.2. Vintage Price Drop Regressions

- (77) 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.
- (78) 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.

3.2.3. Long-Run Generic Share Regressions

- (79) Long-run generic shares were regressed against the following set of explanatory variables.⁵⁶
- 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.
- (80) 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.
- (81) Positive coefficients can be interpreted as factors conducive to higher generic penetration. Individual coefficients in the model represent partial effects.

3.2.4. Vintage Generic Share Regressions

- (82) 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.

⁵⁶ Formally:

$$\begin{aligned} gen_share_{ic} = & \beta_0 + \beta_{pg} * price_gen_{ic} + \beta_{po} * price_ori_{ic} \\ & + char_{ic} * \beta_{char} + reg_c * \beta_{reg} + \beta_{pop} * pop_c + ndel_{ic} * \beta_{ndek} + \varepsilon_{ic} \end{aligned}$$

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 ε is the error term. INNs are indexed by *i* and countries by *c*.

3.3. Main estimation results

3.3.1. Long-run price drop regressions

- (83) Table 3.1 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.
- (84) 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.
- (85) 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.

3.3.2. Vintage Price Drop Regressions

- (86) The baseline vintage price drop models (Model I-V. in Table 3.1) show that the coefficient of the *number of generic entrants* variable has a small, statistically significant, positive estimate.
- (87) 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.
- (88) 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.
- (89) In terms of magnitude, the coefficients of the *price cap* and the *physicians encouraging* policies appear to have the largest magnitude among the regulatory variables. The existence of a *price cap* policy, all other things being equal, reduces the overall post-entry price drop in the order of 15 percentage points. A *physicians encouraging* policy adds to the overall price drop by a similar extent (all other things being equal). The other statistically significant regulatory variables tend to have an effect on price drops with a similar but slightly smaller magnitude.

3.3.3. Long-Run Generic Share Regressions

- (90) Table 3.2 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).⁵⁷
- (91) 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.
- (92) The *pre-expiry value per capita*, *generic age*, *biosimilar* and *population* variables have positive and statistically significant coefficients.
- (93) The *controlled entry* estimate appears negative and significant.
- (94) The other variables do not seem to significantly contribute in a stable way to the explanatory power of the regression.

3.3.4. Vintage Generic Share Regressions

- (95) The baseline vintage generic share models (Model I-V. in Table 3.2) show that both *generic* and *originator prices* have a statistically significant estimate with the expected signs (negative and positive, respectively).
- (96) 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.
- (97) The *controlled entry* variable has a statistically significant negative effect in two vintages.
- (98) 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.
- (99) In terms of magnitude, the *compulsory substitution* variable has the largest coefficient estimates among the regulatory variables. Having a compulsory substitution policy increases, all other things being equal, the share of generic drugs by 12-25 percentage

⁵⁷ 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.

points (the effect becomes gradually stronger towards older vintages). The second largest magnitudes among the regulatory variables' coefficients are those of the *price cap* variable. The presence of a price cap policy decreases, all things being equal, the share of generic drugs by about 15% (this magnitude is stable among vintages). The magnitude of the other statistically significant regulatory variables is about 6-10 percentage points.

3.4. Robustness Checks

- (100) In order to assess the stability of the results, various robustness checks were implemented.
- (101) 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.
- (102) The summary table of all these robustness checks is presented in Table 3.3. In this table the signs of the statistically significant explanatory variables are displayed along with the specification tests.
- (103) 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.⁵⁸
- (104) The main results and qualitative conclusions from robust regressions and instrumental variables estimation, as shown in Table 3.4 and Table 3.5, are unchanged.

3.5. Conclusions

- (105) 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

⁵⁸ 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.

PHARMA SECTOR INQUIRY – ANNEXES

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

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

- (106) 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.
- (107) 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.
- (108) 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.

- (109) For the purpose of the analysis, the principal dataset (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).⁵⁹
- (110) 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.
- (111) 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 entry, only in these instances potential effects of generic entry on other INNs could be expected.
- (112) 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.
- (113) 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.
- (114) Descriptive statistics provide some indication of potential volume effects of generic entry on other INNs following loss of exclusivity in Chapter B. 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.

⁵⁹ See Annex on methodology

- (115) 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 losing exclusivity and the volumes consumed of other INNs in the same ATC4 class.
- (116) 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:⁶⁰
- 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.
- (117) 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 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.
- (118) For each INN in each country, one regression was estimated.⁶¹ 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

⁶⁰ 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.

⁶¹ 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 ε is the error term.

sample bias. The results of the disaggregated analysis should therefore be considered with sufficient caution.

- (119) 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, (see above). 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.
- (120) Figure 4.1 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.
- (121) Out of 170 cross-price coefficients, 31 (or 18% of the total; visible in the top right area of Figure 4.1) are positive and statistically significant, which constitutes an indication of potential switching between the pairs of INNs to which those estimates refer.⁶² Nine estimates (5%; in the bottom left area of Figure 4.1.) are negative and statistically significant, which may be the result of some market specific characteristics as commented above.
- (122) A large number of cross-price effects (about 77%; middle area) 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-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

⁶² It has to be borne in mind that the shares given 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.

correlation with the consumption volumes of other INNs in a statistically significant way.

- (123) Table 4.1 shows the share of INNs in the sample for which the correlation coefficient was established, both in a model with time trend (the model used above) and without time trend. It is noteworthy that in the former model, the share of INNs with a negative and statistically significant cross price coefficient is lower than in the latter specification (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.
- (124) 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.
- (125) 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 dataset and to filter to some degree the potential endogeneity of prices.⁶³ Volumes consumed every month were regressed against the following set of explanatory variables:⁶⁴
- 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 time trend
- (126) 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

⁶³ 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.

⁶⁴ 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 ε is the error term.

problem of endogeneity by filtering any time-invariant endogeneity of prices.⁶⁵ Specifically, 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 accordingly treated independently. Only the coefficients for the prices are shown. In all regressions, the coefficient for the own price is negative and significant.

- (127) Regression 1 in Table 4.2 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 one might expect, the estimated own-price coefficients are higher in absolute value terms than the cross-price coefficients.⁶⁶
- (128) Results in Table 4.2 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.
- (129) 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 4.3 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 4.1, the somewhat lower 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).
- (130) Shares in Table 4.3, which are the result from the pooled-data analysis, are broadly consistent with those reported in Table 4.1, obtained from the disaggregated analysis presented above. Overall, the analysis shows that in a 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

⁶⁵ The remaining potential time-variant endogeneity may be a reason to interpret the results as conservative estimates of the actual price effects.

⁶⁶ This result is expected except when the volumes of the products investigated were to differ substantially.

PHARMA SECTOR INQUIRY – ANNEXES

same time, there is considerable heterogeneity across INNs with respect to the estimated as the 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 loss of exclusivity (per country)
lnpreexp_value per capita	(idem – natural log)
preexp_price	Average price (EUR) per DDD of the INN six months before loss of exclusivity (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.

PHARMA SECTOR INQUIRY – ANNEXES

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)
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.
other_atc4	Indicates, for an INN present in more than one ATC4 category, whether at the time the INN lost exclusivity in the ATC4 category under consideration, that INN had already lost exclusivity in some other ATC4 category.

PHARMA SECTOR INQUIRY – ANNEXES

Table 1.1: Results regression analysis occurrence of entry

COEFFICIENT	First entry within 1 year		First entry within 2 years	
	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

PHARMA SECTOR INQUIRY – ANNEXES

Table 1.2: 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

PHARMA SECTOR INQUIRY – ANNEXES

Table 2.1: 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*** (0.007)	0.737*** (0.002)	0.576*** (0.001)	0.619*** (0.000)	0.604*** (0.000)
Compulsory_substit	1.614*** (0.001)	1.603*** (0.001)	1.946*** (0.002)	1.568*** (0.005)	1.600*** (0.003)
physicians_encourage_gen	1.233 (0.104)	1.213 (0.110)	1.448* (0.050)	1.450*** (0.010)	1.507*** (0.003)
freq_adjust	1.103 (0.367)	1.106 (0.315)	1.158 (0.368)	1.055 (0.657)	1.131 (0.304)
diff_copay	0.766* (0.064)	0.757** (0.040)	0.722 (0.128)	0.951 (0.767)	0.894 (0.498)
lowest_price_policy	0.940 (0.608)	0.950 (0.652)	0.939 (0.725)	0.894 (0.405)	0.913 (0.481)
lnpreexp_value_per_capita	1.494*** (0.000)	1.488*** (0.000)	1.788*** (0.000)	1.567*** (0.000)	1.555*** (0.000)
populationa	1.000** (0.012)	1.000** (0.011)	1.000*** (0.004)	1.229*** (0.000)	1.153*** (0.002)
preexp_price	0.977*** (0.000)	0.975*** (0.000)	0.967*** (0.000)	0.974*** (0.000)	0.973*** (0.000)
pre_exp_numform	1.035* (0.065)	1.031* (0.065)	1.057** (0.042)	1.033 (0.111)	1.030 (0.147)
other_atc4	1.213 (0.138)	1.231* (0.089)	1.279 (0.204)	1.228 (0.159)	1.221 (0.173)
already_expired_country	1.123 (0.258)	1.133 (0.194)	1.236 (0.171)	1.192 (0.132)	1.178 (0.155)
controlled_entry	2.261*** (0.000)	1.854*** (0.002)	3.270*** (0.000)	2.278*** (0.001)	2.814*** (0.000)
exp_02_03	1.668*** (0.000)	1.603*** (0.000)	1.988*** (0.001)	1.844*** (0.000)	1.681*** (0.001)
exp_04_05	2.108*** (0.000)	1.983*** (0.000)	2.678*** (0.000)	2.252*** (0.000)	2.188*** (0.000)
exp_06_07	2.363*** (0.000)	2.548*** (0.000)	3.596*** (0.000)	2.541*** (0.000)	2.374*** (0.000)
surtime				0.949*** (0.000)	0.944*** (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.

PHARMA SECTOR INQUIRY – ANNEXES

Table 2.2: 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 (0.286)	0.796 (0.217)	0.867 (0.155)	0.917 (0.414)	0.825 (0.305)	0.883 (0.235)	0.912 (0.405)	0.810 (0.259)	0.837 (0.185)
compulsory_substit	1.507*** (0.003)	2.063*** (0.004)	1.455*** (0.006)	1.539*** (0.002)	2.100*** (0.003)	1.491*** (0.004)	1.586*** (0.003)	2.238*** (0.002)	1.662*** (0.005)
physicians_encourage_gen	1.218* (0.098)	1.498* (0.060)	1.297** (0.029)	1.287** (0.039)	1.652** (0.018)	1.350** (0.014)	1.261* (0.068)	1.663** (0.016)	1.495** (0.011)
frequent_adjust	0.998 (0.983)	1.014 (0.939)	0.976 (0.810)	1.044 (0.684)	1.110 (0.579)	1.009 (0.933)	1.120 (0.328)	1.224 (0.301)	1.118 (0.417)
diff_copay	0.872 (0.310)	0.790 (0.335)	0.984 (0.912)	0.860 (0.273)	0.779 (0.300)	0.958 (0.769)	0.785 (0.101)	0.701 (0.151)	0.888 (0.521)
lowest_price_policy	1.110 (0.357)	1.197 (0.379)	1.057 (0.627)	1.079 (0.514)	1.132 (0.546)	1.033 (0.784)	1.056 (0.660)	1.066 (0.753)	1.007 (0.962)
lnpreexp_value_per_capita	1.479*** (0.000)	1.966*** (0.000)	1.456*** (0.000)	1.497*** (0.000)	1.952*** (0.000)	1.481*** (0.000)	1.610*** (0.000)	2.094*** (0.000)	1.711*** (0.000)
populationb	1.000 (0.145)	1.000 (0.114)	1.102** (0.018)	1.000 (0.119)	1.000* (0.094)	1.103** (0.018)	1.000 (0.290)	1.000 (0.177)	1.126** (0.028)
preexp_price	0.980*** (0.000)	0.971*** (0.000)	0.982*** (0.000)	0.978*** (0.000)	0.967*** (0.000)	0.979*** (0.000)	0.977*** (0.000)	0.967*** (0.000)	0.975*** (0.000)
pre_exp_numform	1.006 (0.057)	1.024 (0.118)	1.004 (0.072)	1.010 (0.041)	1.034 (0.092)	1.008 (0.048)	1.016 (0.021)	1.045 (0.063)	1.025 (0.049)
other_atc4	1.258* (0.057)	1.409 (0.118)	1.243* (0.072)	1.293** (0.041)	1.455* (0.092)	1.283** (0.048)	1.356** (0.021)	1.519* (0.063)	1.366** (0.049)
already_expired_country	1.070 (0.929)	1.159 (0.802)	1.079 (0.930)	1.082 (0.839)	1.177 (0.557)	1.092 (0.689)	1.113 (0.866)	1.248 (0.755)	1.176 (0.784)
controlled_entry	0.982 (0.929)	1.098 (0.802)	1.018 (0.930)	1.045 (0.839)	1.260 (0.557)	1.091 (0.689)	1.053 (0.866)	1.182 (0.755)	1.114 (0.784)
exp_02_03	1.590*** (0.000)	2.164*** (0.001)	1.614*** (0.000)	1.551*** (0.001)	2.020*** (0.003)	1.630*** (0.000)	1.547*** (0.001)	1.933*** (0.005)	1.806*** (0.001)
exp_04_05	1.939*** (0.000)	2.991*** (0.000)	1.817*** (0.000)	1.910*** (0.000)	2.763*** (0.000)	1.877*** (0.000)	1.897*** (0.000)	2.565*** (0.000)	2.221*** (0.000)
exp_06_07	2.771*** (0.000)	5.266*** (0.000)	2.281*** (0.000)	2.720*** (0.000)	4.639*** (0.000)	2.382*** (0.000)	2.669*** (0.000)	3.982*** (0.000)	2.768*** (0.000)
large_neg3	12.657*** (0.000)	84.026*** (0.000)	9.235*** (0.000)						
small_neg3	12.320*** (0.000)	78.832*** (0.000)	8.830*** (0.000)	10.489*** (0.000)	49.391*** (0.000)	8.295*** (0.000)			
surtime			0.951*** (0.000)			0.951*** (0.000)			0.968*** (0.003)
surtimesq			1.001*** (0.000)			1.001*** (0.000)			1.000*** (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.

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.1: 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
Other	controlled_entry	-0.042	0.207	-0.076*	0.070	-0.042		0.058		-0.022	0.589
	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
	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*

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.2: 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*

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.3a: 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. copayment	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 products						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.

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.3b: 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. copayment	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.

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.3c: 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. copayment	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 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.

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.4: 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
Other	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
	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

PHARMA SECTOR INQUIRY – ANNEXES

Table 3.5: 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
	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
Other	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 products in other countries, same INN; average price of generic products in other countries, same atc4 category; average price of originator products in other countries, same INN; average price of originator products in other countries, same atc4 category.

PHARMA SECTOR INQUIRY – ANNEXES

Table 4.1: 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 4.2: 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 4.3: 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 2.1: First generic entry after the loss of exclusivity: Kaplan-Meier estimator of the survivor function and Nelson-Aalen estimator of the cumulative hazard for all INN-country pairs analysed

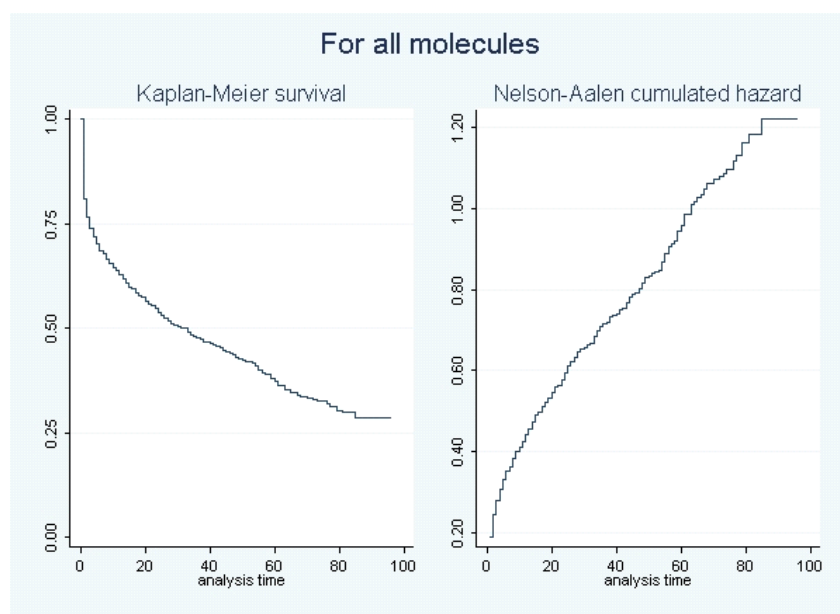


Figure 2.2: Second generic entry after the first generic entry: Kaplan-Meier estimator of the survivor function and Nelson-Aalen estimator of the cumulative hazard for all INN-country pairs analysed.

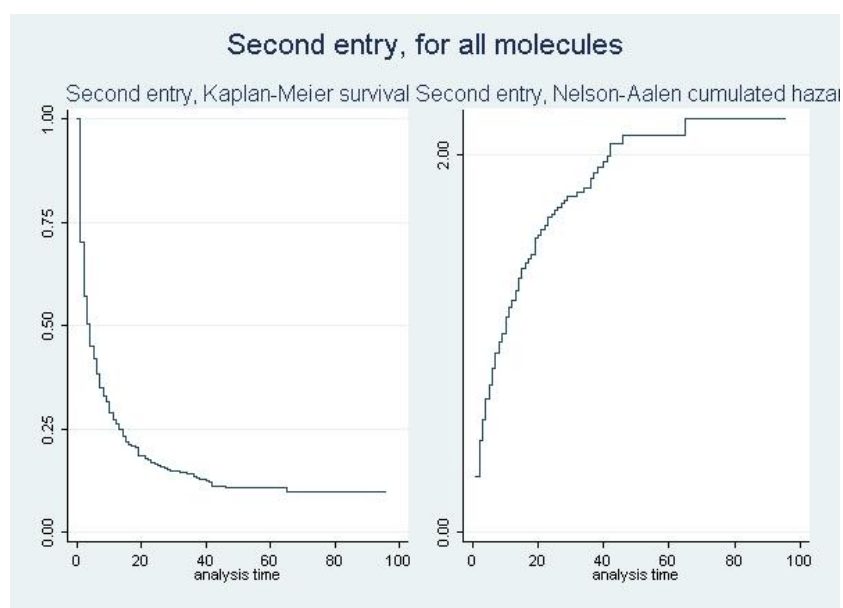


Figure 2.3: Survivor and cumulated hazard functions estimated by the Cox Regression, by compulsory substitution

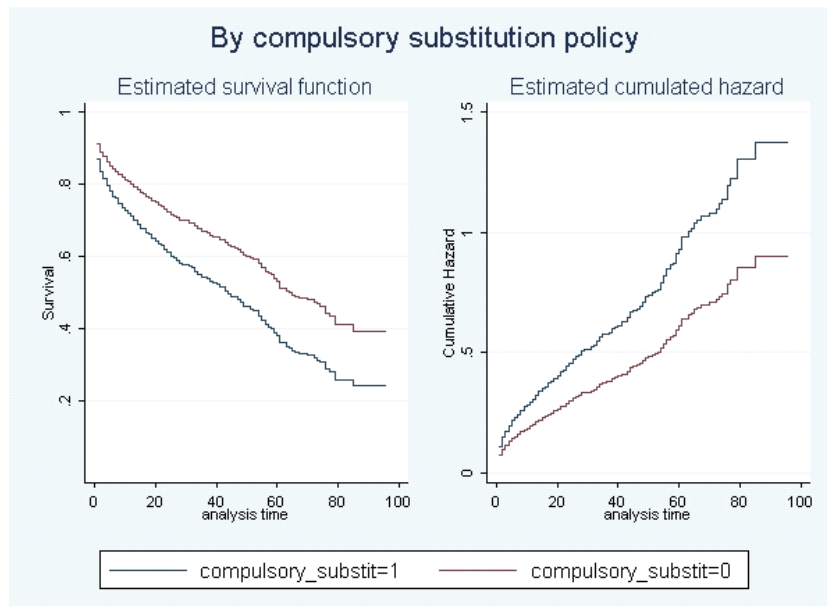
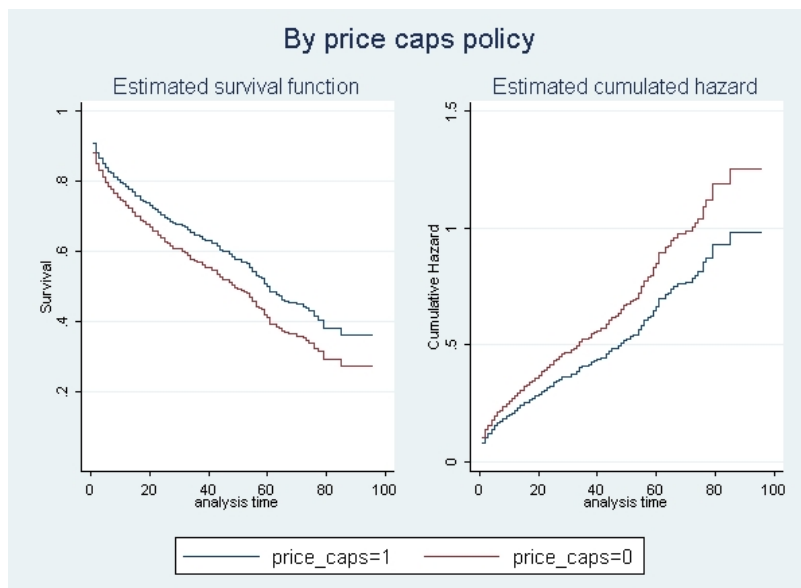


Figure 2.4: Survivor and cumulated hazard functions estimated by the Cox Regression, price caps policy



PHARMA SECTOR INQUIRY – ANNEXES

Figure 2.5: Survivor and cumulated hazard functions estimated by the Cox Regression, by bi-annual dummies

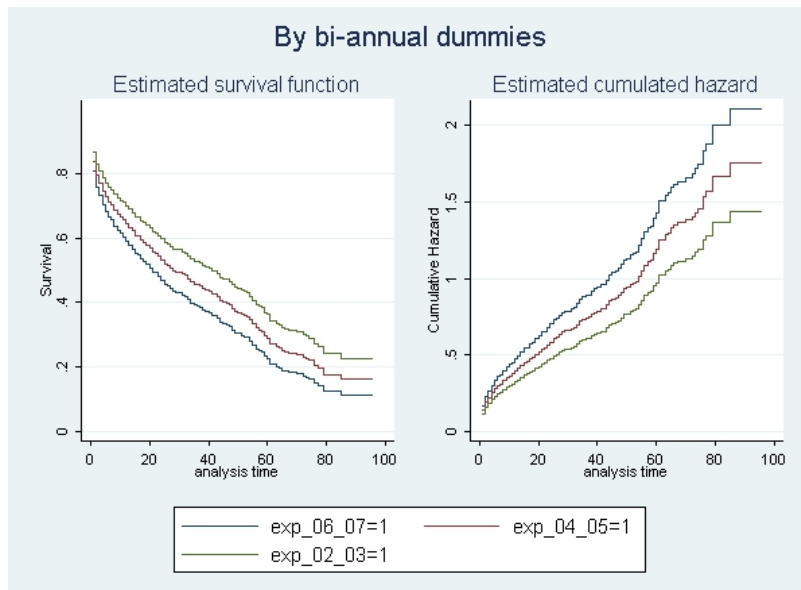


Figure 2.6: Baseline survivor and cumulated hazard functions estimated by the Cox Regression

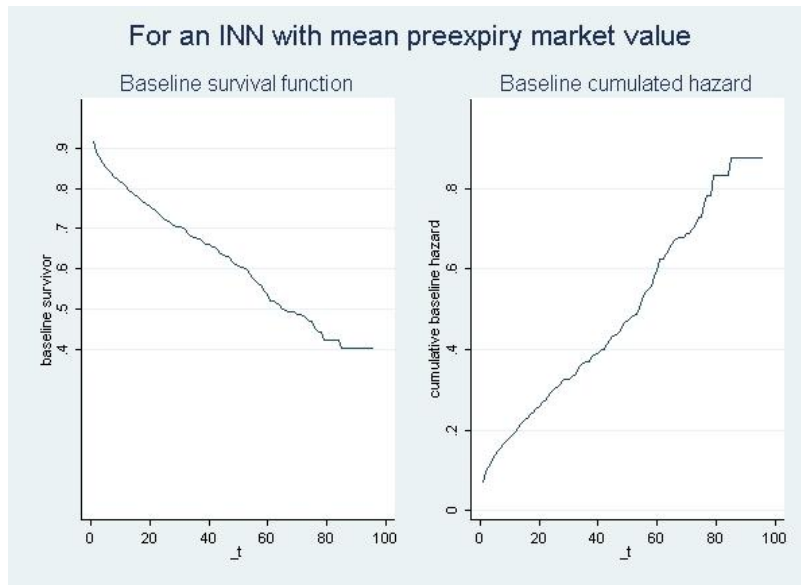
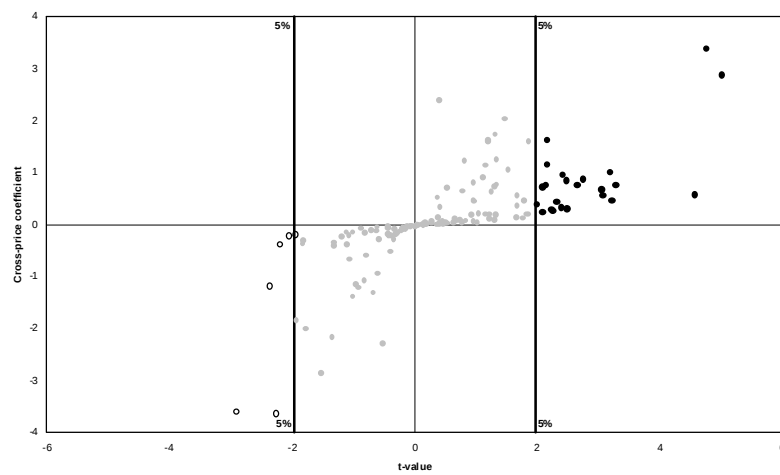


Figure 4.1: Estimated cross-price coefficients



Annexes to Chapter B – Part III

Annex to Chapter B.2.1.: Claim types

Overview of Claim Types Found in Pharmaceutical Patents

- (131) Fundamentally, two types of patent claim exist under EPC: a product claim and a process claim. A product claim relates to the characteristics of a physical entity (e.g. composition), while a process claim relates to the production process. However, medicines are never simply produced for market consumption as the pure active agent. Rather, they are sold in different physical forms, such as tablets or solutions for injection, and are also supplied at different dosage strengths. The same pharmaceutically active substance may furthermore be suitable for a number of therapeutic uses.⁶⁷
- (132) Patents in the pharmaceutical sector are therefore often referred to in terms of the type of products or processes that they claim. The following is a brief outline of the main ‘types’ of claims that are commonly found in pharmaceutical patents. Providing they meet the three requirements for patentability (novelty, inventive step and industrial applicability), all of them can be patented.

Compound, Basic, NCE/NME or API patent

- (133) These terms cover patent claims for new molecules which have a therapeutic use. The molecules have never been disclosed previously and are therefore new in their own right.
- (134) An expression which has been coined for patents for such products is the term “primary patent”, the implication being that this is the first ever patent covering a particular pharmaceutically active agent. All other patents that build on these primary patents, by applying the active agent in a new way, are termed “secondary patents”. The following descriptions are of claims which could be found in these secondary patents. It should be noted, however, that many of the following claims can also be found in primary patents.

⁶⁷ For example, the pharmaceutically active agent sildenafil was first used as an anti-hypertensive drug and later as a treatment for impotence (Viagra®).

Intermediates

- (135) Intermediates are molecules which, in themselves, are not pharmaceutically active but can be used in further chemical processes to manufacture a pharmaceutically active agent. Claims for intermediates can form a central part of a company's protection strategy when applying for intellectual property rights because they might stop competitors from manufacturing the pharmaceutically active agent.

Salt forms

- (136) Many molecules can exist in one or more salt forms. Salts are formed from the chemical reaction between an acid and a base. The selection of the correct salt can be crucial to the success of a product because one salt form can have superior or advantageous properties over another. For example, one salt form may have a much better chance of being absorbed into the body than another. Alternatively, a particular salt form may be much more stable, allowing manufacturers to prepare or store formulations of the drug more economically.

Polymorphic Forms (polymorphs)

- (137) Many molecules can exist in different crystalline forms, that is to say, the shape of the crystals they form is different. Such molecules are said to be polymorphic. Examples exist where different polymorphic forms of a pharmaceutically active agent possess advantageously different properties.⁶⁸

Solvates and Hydrates

- (138) A pharmaceutically active agent can exist in different solvated forms. This means that when crystalline, each active molecule is associated with one or more solvent molecules – they effectively represent a mixture of solvent and active agent.⁶⁹ When the solvent is water, the solvates are termed hydrates. Solvates of pharmaceutically-active agents can also possess advantageous properties.

Metabolites

- (139) When substances are administered to a mammal, enzymes in the body can modify them chemically to produce new molecules known as metabolites. This is part of the natural metabolic processes of the body. In some cases, it has been discovered that a putative pharmaceutically active agent does not have any therapeutic effect in the body, but only has such effects after it has been metabolised. It is hence the metabolite which possesses the pharmaceutical activity. In some cases it is therefore desirable to obtain protection for metabolites.

⁶⁸ A high-profile example of this was GSK's "Form II Ranitidine" (Zantac®), a different crystalline form of the molecule ranitidine for which a patent was obtained after the expiry of the patent for the Form I polymorph.

⁶⁹ The presence of solvent molecules results from the chemical processes used to make the pharmaceutically active agent

PHARMA SECTOR INQUIRY – ANNEXES

Pro-drugs

- (140) Pro-drugs are inactive molecules formed by chemical modification of a pharmaceutically active agent. When administered to mammals, however, metabolic processes in the body remove the chemical modification to reveal the active agent. Pro-drugs are often made when the active agent has little or no ability to find its way into the blood stream when administered via a normal route, e.g. orally. The modification to form the pro-drug is aimed at producing a molecule which can find its way into blood plasma, where it is subsequently metabolised to release the pharmaceutically active agent.

Drug combinations

- (141) Combinations of two or more pharmaceutically active agents can often give rise to surprising or unexpected effects. For example, two drugs, when combined, may have a synergistic effect.

Formulations

- (142) Formulations – sometimes referred to as galenical forms or galenics – relate to pharmaceutical preparations of a pharmaceutically active agent. They may, for example, take the form of a tablet, an oral suspension or a solution for injection. Formulations comprise more than just the active ingredient, and typically contain other compounds, often referred to as pharmaceutical excipients. These excipients can have a profound effect on the behaviour of the active agent, often assisting in its delivery to the body. Protection for these products is therefore also of great concern to pharmaceutical companies since it is usually the formulations themselves which are marketed.

Particle Sizes

- (143) When pharmaceutically active agents are formulated for administration, they are very often manufactured as particles of active agent before being formed into tablets or other solid forms. These particles can have different sizes. Sometimes, the particle size and/or shape can give rise to advantageous properties, for example when a particular particle size can prove to be much more suitable for the tableting process.

Devices

- (144) The term 'devices' extends to products aimed at delivering a pharmaceutically active agent. Common examples might be a dry powder inhaler containing an anti-asthmatic or a transdermal patch comprising a cardiovascular agent. Device claims can also be of great commercial importance if a company finds a new and improved method of administering a medicine.

Dosage Regimes⁷⁰

- (145) The amount and frequency with which a medicine is administered, often referred to as the dosage regime, can sometimes alter the characteristics of the medicine or treatment and thus give rise to an advantageous effect. For example, a specific dosage regime can produce a reduction in side-effects while maintaining therapeutic efficacy of the medicine.

Process claims

- (146) Process claims in the pharmaceutical area are typically concerned with methods for the preparation of a pharmaceutically active agent or intermediates. Their protection via one or more patents can be of significant commercial importance to both originator and generics companies if industrial-scale processes can be found which are substantially more economical than others.

Medical Use Claims⁷¹

- (147) The exclusion in the European Patent Convention (EPC) of the patentability of methods for the treatment of the human or animal body by surgery or therapy provided a stumbling block to obtaining a patent for a new medical use for a known substance. Under the EPC, where products are defined as being for use as a medicament (a so-called 'first medical use claim'), the restriction 'for use as a medicament' is considered to render the product novel if that product has not been used previously in medicine.
- (148) Similarly, a process for the production of a medicament for a specific medical use (a so-called 'second or further medical use claim') was also considered to be novel if the medicament had never been used for the claimed therapeutic indication. This was essentially a process claim and is often referred to as a 'Swiss-type claim'. However, under the revised EPC 2000, product claims which are restricted to a specific medical use are now also considered novel over other medical use claims for the same product but for different therapeutic indications. Thus, if a company finds a new medical use

⁷⁰ The question of patentability of dosage regimes at the EPO is currently before the Enlarged Board of Appeal.

⁷¹ The question of whether there is a difference between Swiss-type claims and use-limited product claims at the EPO is currently before the Enlarged Board of Appeal.

PHARMA SECTOR INQUIRY – ANNEXES

for a known medicament, a patent for that new use may be obtained. This is sometimes termed the 'use-limited product protection for second and further medical uses'.

Annex to Chapter C.

Annex to Chapter C.2.4.: Overview of the USA Regulatory Environment on Patent Settlement Agreements

The Hatch Waxman Act: specific process for the approval of generic products

- (1) In the USA, innovative pharmaceutical products must primarily be approved by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act, via the "New Drug Application" (NDA) process.⁷² This process, which necessitates the demonstration of product safety and effectiveness by means of adequate investigations, may be long and risky for a company. The innovator must submit certain patent information to the FDA when filing an NDA. This information is published in the so-called "Orange Book".⁷³
- (2) Since 1984 and the enactment of the "Hatch-Waxman Act"⁷⁴ (which was later amended in 2003⁷⁵) alternative ways of achieving FDA approval for a generic product may be employed. The Act provides a streamlined process for submitting an "Abbreviated New Drug Application" (ANDA) to the FDA in order to obtain approval for a product that is shown to be a generic copy of a previously approved innovator medicine⁷⁶. The Hatch-Waxman Act makes the approval of ANDAs dependent on the status of patents for the originator medicine.
- (3) If a generic company wishes to market a generic product prior to the expiry of a patent, it must submit a so-called Paragraph IV certification, which is recognised as an act of infringement. Following notification by the generic company, the patent holder (the NDA holder) may file a suit within 45 days. In such a case, the generic company may receive approval for ANDA only after 30 months, upon expiry of the patent, or upon a favourable decision of the court. If the court decides that the patent is valid and has been infringed, the approval of the ANDA cannot be effective until the patent expires.⁷⁷

⁷² See 21 U.S.C. § 301.

⁷³ See 21 U.S.C. § 355(b)(1), (c)(2).

⁷⁴ Codified as amended at 21 U.S.C. § 355 and 35 U.S.C. §§ 156 and 271 (d)-(h).

⁷⁵ Amended as part of the Medicare Prescription Drug, Improvement, and Modernisation Act of 2003.

⁷⁶ See 21 U.S.C. § 355(b)(2).

⁷⁷ See 21 U.S.C. § 355.

PHARMA SECTOR INQUIRY – ANNEXES

- (4) In order to challenge pharmaceutical patents, the Hatch-Waxman Act provides prospective generic companies with an additional incentive: the grant of a 180-day exclusivity period. Exclusivity may be granted to the first ANDA applicant to file a paragraph IV certification. The FDA cannot issue marketing approval to a subsequent ANDA with the certification on the same product until the 180-day exclusivity period has been ended or forfeited. It is expected that the first ANDA applicant can obtain better profits than subsequent entrants.⁷⁸
- (5) Commentators have considered that the processes implemented through the Hatch-Waxman Act give specific incentives to generic companies to challenge originator companies' patents with less risk. This incentive might well influence the dynamics of litigation.

⁷⁸ See 21 U.S.C § 355(j)(5)(B)(iv).