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Generics in small markets or for low volume medicines

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List abbreviations

AT	Austria
ATC	Anatomical Therapeutic Chemical
BE	Belgium
BG	Bulgaria
CH	Switzerland
CY	Cyprus
CZ	Czech Republic
DE	Germany
DK	Denmark
EASP	Escuela Andaluza de Salud Pública (Andalusian School of Public Health)
EC	European Commission
EE	Estonia
EGA	European Generic Association
EL	Greece
EFPIA	European Federation of Pharmaceutical Industry and Associations
EMINet	European Medicine Information Network
ES	Spain
EU	European Union
FI	Finland
FR	France
GÖG	Gesundheit Österreich GmbH (Austrian Health Institute)
GNI	Gross National Income
HU	Hungary
IE	Ireland
INN	International Non-proprietary Name
IP	Intellectual property
IS	Iceland
IT	Italy
LT	Lithuania
LU	Luxembourg
LV	Latvia
MS	Member States
MT	Malta
NL	Netherlands
NO	Norway
PLI	Price level index for pharmaceuticals
PPI	Pharma Price Information
PPRI	Pharmaceutical Pricing and Reimbursement Information
PL	Poland
PT	Portugal
RO	Romania
SE	Sweden

SI	Slovenia
SK	Slovakia
UK	United Kingdom
WHO HFA	“Health for All” Database of the World Health Organisation

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1 Background and objectives

The ever rising prices of medicines and the consequent impact on pharmaceutical budgets is a growing concern for most countries in the EU and around the world. Generic competition is able to provide cheaper versions of medicines, offering an important pillar in cost-containment measures of national health policies. Hence, most Member States have implemented various supply-side (e.g. price control, price comparison, tendering, reimbursement, reference price system) and demand-side measures (e.g. INN prescribing, monitoring of prescription behaviour and generic substitution by pharmacists) to support and enhance the use of generics.

As stated in the Pharmaceutical Sector Inquiry 2009 *"... generic entry does not always take place as early as it potentially could".* Furthermore the report said that such eventual delays have significant cost / revenue impact. As stated on page 81 of the Sector Inquiry Report[1], it is estimated that the potential savings due to generic entry could have been 20 % higher than they actually were. Besides reasons due to competition, different stakeholders in the Member States made a significant number of comments on the regulatory framework, which they consider decisive for the pharmaceutical sector. The most important areas are patent law, marketing authorisation rules and pricing and reimbursement.

These difficulties of generic entry and the establishment of fair generic competition are especially relevant for smaller markets, for instance smaller countries in the European Union, but also for medicines, which only serve a smaller market segment leading to lower potential sales volumes.

The relevance to the current situation is also reflected in one of the questions recently discussed within the PPRI (Pharmaceutical Pricing and Reimbursement Information)[2] network on the availability of generics for specific products in Europe as this information was relevant for national decisions on reference pricing.

Problem definition

Patents and other intellectual property rights, such as test data protection, are important incentives that countries provide to potential innovators. Intellectual property rights allow the rights' holder to temporarily exclude others parties from producing, selling or importing the protected products or, at least, to build entry barriers that

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

2 http://ppri.goeg.at

limit competition and grant them a certain degree of monopolistic power. This system is assumed to provide a balance between the need of sufficient reward to the innovator in the form of temporary higher prices and profits, on one hand, and the interest of society, on the other: when exclusivity expires, society can benefit from the innovations at competitive prices.

Although any innovative product might face competition from other innovative intellectual property (IP) protected products, generic competition is usually expected to be one of the major drivers of price reductions and, hence, pharmaceutical expenditure containment and higher affordability when the market exclusivity of an originator product expires.

Yet this does not always happen, at least not to the extent that basic economic theory predicts and decision makers wish and expect. Sometimes generic entry does not occur immediately after exclusivity expiry or only one or a small number of generic producers enter the market, with the result that prices – either generics or originators prices – do not fall substantially. Even in cases where a substantial number of competitors enter the market, prices might not fall as much as competition theory predicts and as some interested parties – mainly the public authorities/payers – would like and expect. Countries react by taking specific policy measures, e.g. binding the price of generics to that of originators, or determining a fixed (percentage) discount from the price of the originator to include it in the national reimbursement systems.

Several factors might explain why competition does not operate as expected. If the causal factors can be identified, an appropriately designed policy might be designed and applied to remedy the problem.

In a first step, the research team synthesised the concerns and demands expressed by Member States (MS) and stakeholders who raised the awareness of the European Commission (EC) on the problem of non-accessibility of generics of low sales/in small indications and in smaller markets (which led to commissioning this study).

Definitions

Some of the key concepts used to refer to the problems addressed in the study are not precisely defined in literature and in the policy debate. It is therefore necessary to explicitly define the key terms used in this study.

The expression "low volume medicines" refers to medicines which, for whatever reason, have relatively low (potential) global sales, e.g. due to a limited number of patients because of the rarity of disease. This will usually be reflected by a relatively

low consumption in terms of prescribed units accompanied by high unit prices. Typically these products are complex biological products for which production and launch of followers is difficult. For followers of normal molecules usually a sufficient return on investment is the critical factor e.g. for pharmacovigilance requirements, or licence cost together with the marketing expenses needed to gain market share.

When medicines are on-patent, a low sales level in terms of units can be compensated by high, profitable prices; but in the case of off-patent medicines the problem of lack of commercial attractiveness is usually aggravated by actual or potential competition that brings prices close to production costs.

The expression "small markets" refers to national/country markets with a relatively low aggregate sales value for both, single products and/or the whole market. The value of a market is mainly determined by the size of the population, the level of income per capita and the existence and level of coverage of health insurance. There are various speculations on potential thresholds of sales values to enter small markets (numbers given range between below 100,000 EUR annual sales in a ten million inhabitant market to 10 Mio. GBP (~ 11.8 Mio. EUR) annual turnover as quoted in the 2002 PPRS report of the UK Department of Health)[3] but no further concrete figures could be verified in published documents.

Another key phrase is "complex pharmaceutical form" which is defined as medicines requiring medical devices such as sprays, patches, inhalers for dispensing or take the form of an implant. If these "linked" medical devices are still under patent protection it is difficult for generic companies to re-produce these devices thus making it difficult to penetrate the market.

The term "availability" refers in this study to the inclusion of a medicine in any of a country's out-patient reimbursement lists – irrespective of the applicable reimbursement rate and rules, i.e. if it was basically reimbursable. The main reason for focussing on the out-patient market is the lack of data for hospital (only) medicines. The selection of products for analysis took this into consideration, i.e. also focussed on out-patient medicines. It must nevertheless be acknowledged that this fact might lead to an incomplete picture of availability.

"Genericisation" refers to the various aspects of market entry/penetration and generic competition linked to the appearance of followers to off-patent medicines, whether it be generics or biosimilars on the market. In this context it is important to point out that the biosimilars are more complex than generics.

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[3] www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009600, p. 124

The term "follower" is used as synonym term for generics as well as biosimilars in the report.

General objectives

To gain a better understanding on the availability of generics with low sales, generics in small markets in the EU and generics with complex pharmaceutical forms. In doing so, this paper determines factors and policies that may or may not lead to generic market entry and competition.

Specific objectives

1. To assess the present situation of availability and generic competition by means of a descriptive analysis of a sample of off-patent medicines in the EU markets

2. To explore to what extent availability and market competition in off-patent medicine markets of Europe is associated with global sales volume, market size and a set of economic, demographic and regulatory characteristics.

3. To assess which policies options might promote or limit genericisation of low sales medicines and in small markets.

2 Methods and data

The methodological approaches used in the study were:

1. Interviews with key stakeholders, mainly pricing and reimbursement officials of small markets and representatives of the generic industry a/o generic industry associations like the European Generic Association (EGA). This activity provided crucial inputs for the formulation of the problem, as well as for some of the factors affecting genericisation and for the identification of potential policy options to promote it.
2. A literature review that provided limited but valuable results of previous academic and institutional analysis on the topics addressed in the present study, as well as on the positions of the main stakeholders.
3. Quantitative analyses of the situation based on a sample of eleven off-patent medicines in European countries, cf. 2.3.1 for product selection.

In order to facilitate the reading, the next paragraphs contain a brief description of the methods and the overall results of the three approaches. Comprehensive reports are included as annexes of this study.

2.1 Interviews and contacts with stakeholders

Country representatives

In a first step the awareness of the problem of non-accessibility of generics in smaller markets was assessed by qualitative interviews with representatives of the PPRI[4] network (Pharmaceutical Pricing and Reimbursement Information). This process was carried out in form of an expert session with representatives of the PPRI network from Iceland, Estonia, Latvia and Norway in June 2010 in Oslo. Additional clarifications and information were received via mail from Malta and Belgium. These countries were especially addressed by the EMINet team as they have raised concerns with respect to availability of generics.

[4] http://ppri.goeg.at

Industry representatives

In addition, several generic companies and national generic manufacturers associations suggested by EGA were contacted. They received a presentation letter with a brief description of the study objectives, a list of the eleven substances selected for the analysis and a questionnaire. They were offered to respond to the questionnaire in writing or via a telephone conference. Two companies, (Sandoz and Actavis) and two industry associations, (Federation of Belgium Generic Manufacturers and Latvian Generics Manufacturers Association) replied and their answers are included in the annex. In addition, a personal interview took place in June 2010 in Vienna with a spokesperson of the Austrian generic manufacturer association.

Finally, members of the project team attended the conference "How sustainable generic medicines industry provides long-term healthcare solutions" organised by EGA in March 2010, which gave an additional possibility to collect information on the availability of generics.

2.2 Literature review

The problems of generics of low volume medicines and generics in small markets have been rarely addressed in literature so far. Nevertheless, a literature search was carried out in PubMed using the expressions "generic medicine" (descriptor according to MeSH[5]) and "small area" (no descriptor) and yielded 14 hits. Additional searches were done combining the term "drug" with the following expressions: generic entry, generic competition, barrier(s), obstacle(s), low sales, low volume and small country/ies. This second set of searches gave 309 additional hits. Most of the references initially selected neither dealt with small volume generics nor with small markets and were therefore not directly relevant to the present study.

Moreover, reports and surveys known by the authors were included in the review:

» PPRS: The Study into the extent of competition in the supply of branded medicines to the NHS. UK Department of Health and Association of the British Pharmaceutical Industry, 2002
» EMINet Generic Matrix, 2009

[5] http://www.nlm.nih.gov/mesh/meshhome.html MeSH is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts

» OFT market study: The Pharmaceutical Price Regulation Scheme. Office of Fair Trading, February 2007
» Pharmaceutical Sector Inquiry. European Commission, DG Competition, July 2009
» Bongers F. /Carradinha H.: How to Increase Patient access to Generic Medicines in European Healthcare Systems. European Generic Medicines Association (EGA), June 2009
» IMS report: Generic medicines: essential contributors to the long-term health of society. IMS Health, 2010

Additional information was obtained in the IMS Health Pharma Pricing and Reimbursement journal as well as in the SCRIP magazine.

2.3 Quantitative analyses

Several quantitative analyses were carried out on a sample of 11 active substances in the EU countries. They included a mapping and descriptive analysis of the situation as well as bivariate and multivariate analyses to identify potential associations between the variables selected as indicators of genericisation (i.e. generic availability and competition) and a set of independent variables that previous studies as well as experts and stakeholders point to as determinants of genericisation.

2.3.1 Data sources

The selection of the 11 active substances was based on an IMS Health list of around 100 substances including information on the brand name, the originator company, ATC code, patent, expiration date, sales (in value and volume) twelve months prior to expiration, costs per unit, date of first generic entry, number of generic competitors, price per sold unit of originator and generics post expiration and generic volume share substance sales. The IMS Health list refers to data as of 2008 and includes all EU-15 countries (excl. Luxembourg) plus Norway and Switzerland.

The data source for the mapping of availability as well as of current prices of the selected 11 active substances – originator brands and all followers – was derived from the PPI (Pharmaceutical Price Information) service of the Gesundheit Österreich GmbH / Austrian Health Institute[6] in summer 2010. All EU-Member States plus Iceland, Norway and Switzerland were included.

[6] http://www.goeg.at/en/PPI

For the purpose of mapping of availability and price development parallel imports were excluded and the analysis was centred on the out-patient reimbursement market.

2.3.2 Selection criteria for the 11 active substances

As mentioned under section 2.3.1, the basis for the selection of the 11 active substances was a list by IMS Health as of 2008. Besides the availability in the pharmacy market all substances had to be off-patent in the last three years (incl. biologicals). In addition, the following specific criteria were taken into account for the selection:

- Category 1: products with very high prices (price per unit > 70 EUR) and huge sales (total sales of the 16 countries around 125 Mio EUR per product)
- Category 2: products with moderate prices (price per unit between 5- 50 EUR) and large sales (total sales of the 16 countries per product varies between 1.5 – 10 Mio EUR per product)
- Category 3: products with low prices (price per unit < 5 EUR) but high sales (total sales in the 16 countries ~ 1.5 Mio EUR)
- Category 4: active substances for the treatment of rare disease and consequently leading to small sales (in terms of prescribed packs) but high sales value
- Category 5: complex pharmaceutical dosage forms i.e. medicines sold in combination with a medical device like patches or sprays.

An initial draft list of active substances was compiled by early March 2010 and presented to the EMINet Evaluation Committee at the meeting on 24 March 2010. The feedback of the EMINet Evaluation Committee was taken into account when the final list was drafted.

Feedback on the selected products was also received by the European Generic Medicines Association (EGA), listing not only potential reasons for late and limited competition, but also providing contact details to national generic manufacturers for specific clarifications (cf. Annex 9.1). The final list of active substances is displayed in Table 2.1.

Table 2.1:
List of eleven active substances included in the study

ATC code	INN	Originator name	Originator company	Research category
H01AC01	Somatropin	Genotropin	Pfizer	Cat. 1 (↑ price and ↑ sales)
H01CB02	Octreotide	Sandostatin	Novartis	Cat. 1 (↑ price and ↑ sales) Cat. 4 (biosimilar)
J01DF01	Aztreonam	Azactam	BMS	Cat. 2 (~ price and ↑ sales)
J01DH51	Cilastatin + Imipenem	Tienam	Merck & Co	Cat. 2 (~ price and ↑ sales)
J01XA02	Teicoplanin	Targocid	Sanofi-Aventis	Cat. 2 (~ price and ↑ sales)
J04AB04	Rifabutin	Mycobutin	Pfizer	Cat. 3 (↓ price and ↑ sales)
L02AE02	Leuprorelin	Eligrad	Abbott	Cat. 1 (↑ price and ↑ sales)
L02AE03	Goserelin	Zoladex	Astra Zeneca	Cat. 4 (complex ph. form)
N01AH01	Fentanyl patch	Durogesic	Johnson & Johnson	Cat. 4 (complex ph. form)
S01EA03	Apraclonidine	Iopidine	Nestle / Alcon	Cat. 3 (↓ price and ↑ sales)
V03AB25	Flumazenil	Anexate	Roche	Cat. 2 (~ price and ↑ sales)

Source: EMINet 2010

2.3.3 Statistical analysis

Based on 2010 PPI data (11 active substances in the 30 countries, EU-27 countries plus Iceland, Norway and Switzerland) a cross-sectional, univariate, bivariate and multivariate regression analyses was carried out at market level (a country/product pair) as well as at aggregated country and medicine level. The following indicators and independent variables were defined for the analyses:

Indicators of availability and generic competition

Based on the mapping of availability, which refers to data from the PPI survey, several potential market situations, which reflect various possible combinations of originator and generics of a medicine in a given national market, were defined:

1) Originator and more than one generic
2) Originator and one generic
3) Originator and no generic
4) No originator and more than one generic
5) No originator and one generic
6) No originator and no generic

Based on this typology, the following indicators were constructed:

Availability: Availability at market level is defined as existing (value 1) when either the originator, at least one generic, or both conditions have been found on that market, i.e. when the market is in states 1 to 5. Otherwise (state 6) the variable takes the value zero.

At aggregate country level availability is defined as the proportion of the 11 medicines which are available in each country. Similarly, at aggregated medicine level availability is defined as the proportion of countries where the medicine is available. These variables take a value between 0 and 1.

Generic competition: Three competition indicators are considered: Comp ind 1 and 2 are dichotomous variables that take the values 0 or 1, while comp ind 3 is a continuous variable.

» Comp ind 1:
  An individual market (country/product pair) is defined as competitive (value = 1) when there is more than one follower of an originator on the market. Otherwise the value of the variable is zero. Comp ind 1 for a given medicine or country is the quotient between the number of markets with more than one follower and the number of markets where the product is available.
» Comp ind 2:
  Comp ind 2 is less strict than Comp ind 1 in defining competition, i.e. Comp ind 2 will always be equal or larger than Comp ind 1. In fact, comp ind 2 actually reflects the availability of a follower.
» Comp ind 3:
  For a given market (country/medicine pair) the variable simply is the number of generics in that market. Markets with no generic availability were excluded from the analysis. At aggregate medicine/country level, Comp ind 3 is defined as the quotient between the total number of generic products on all markets of a given medicine/country where it is available and the number of markets where the medicine is available, respectively.

Other possible indicators of competition were also considered as dependent variables, namely, generic penetration, relative price of the medicine and relative generic price. Still, the data available were not comprehensive enough to allow a meaningful statistical analysis of the said indicators.

Demographic and economic variables:

» Total number of inhabitants (population)
» Price level index for pharmaceutical products (PLI) regarding EU-25 average[7]
» Gross national income (GNI)
» Total expenditure on health as a percentage of gross domestic product (GDP) 2008
» Per capita expenditure on health 2008
» Per capita general government expenditure on health
» Pharmaceutical market value (country) 2007
» Sales 2009 market value of the medicines in the sample.

Variables referred to generic policies:

» Generic Price Control (at manufacturer level)
» International price comparison for generics in place
» Pricing a/o reimbursement decision linked to originator
» Tendering-like practices applied in the outpatient sector
» Reference Price System (internal) in place
» Accelerated/specific procedure in place applied to generics for pricing a/o reimbursement decisions
» Reimbursement status of the medicine
» International non-proprietary name (INN) prescribing
» Generic substitution allowed

The sources for the demographic and economic variables are EUROSTAT, WHO and EFPIA (see chapter 9.3 in the Annex). All raw data can be obtained from EASP. All variables related to generics pricing and reimbursement policies are based on the EMINet Generic Matrix 2009.

[7] A PLI expresses the price level relation of a country to another one or a group of countries (e.g. EU) by dividing the purchasing power parities by the appropriate exchange rate.

3 Generics in small markets or low volume medicines

3.1 Mapping of availability

As mentioned in section 2.3.1 the data source for the mapping of availability was the PPI service of the Austria Health Institute. The mapping exercise showed that the overall availability – either originator or follower (generic resp. biosimilar) – of the eleven active substances was high for six active substances; but very low for the remaining five substances (Aztreonam, Cilastatin + Imipenem, Teicoplanin, Rifabutin and Apraclonidine) both with regard to originators and especially for followers.

The authors checked via GÖG's Pharmaceutical Price Information Service (PPI)[8] whether the active substance was included in any national public price catalogue, irrespective of the applicable reimbursement rate or rule. In case of non-listing, the product was also searched in the national authorised medicines list. If the product was authorised but not reimbursable[9], despite being a prescription medicine, it was considered as non-available. The same was the case if it was not authorised at all, cf. Table 3.1 for details. The research and the selection of medicines concentrated, due to lacking data availability in hospitals, on the out-patient market. We want to stress that minor distortions of our findings might therefore be possible. The mapping of active substances did not take parallel imports into account as this was not topic of this study.

Graph 3.1allows a European overview of the availability of the followers (generic or biosimilar) of the eleven active substances: In nine European countries followers were marketed at least for five out of the eleven surveyed molecules. Germany was the country with the highest number generic alternatives for the eleven active substances (n=7).

Nine countries featured three to four generics out of the eleven active substances whereas in the remaining eleven countries only for one or two of the molecules followers were available. These countries were especially the Baltic countries (EE, LV, LT) as well as European countries like Iceland, Slovenia, Czech Republic, Hungary, Bulgaria and Romania. A couple of molecules were only available in generic version(s)

[8] http://www.goeg.at/en/PPI

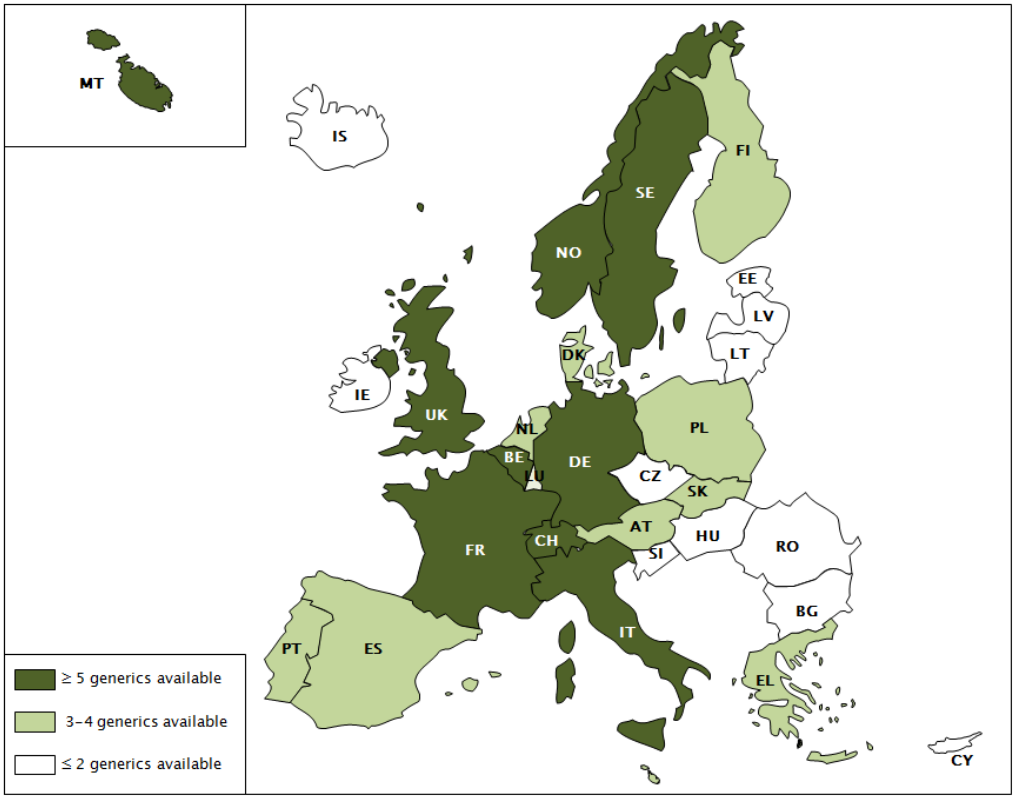
[9] Please note that a medicine that is basically reimbursable must not necessarily be automatically paid by the national third party payer.

in some countries, for example Flumazenil in Cyprus, Denmark and Estonia when looking at the out-patient reimbursement market.

For three substances, no follower could be found in any of the 30 surveyed countries.

EGA confirmed that only five of the selected products were marketed in Latvia, with only two generics. Latvia stated that in some case this could be due to already low prices of originators but also explained that they are faced with a general lack of medicines on the market, even if registered.[10]

Graph 3.1
Cumulated number of (generic) followers for the eleven selected substances in Europe, 2010



Source: EMINet 2010

[10] Only 3,152 out of 4,296 registered medicines are marketed.

These results were quite surprising as according to the obtained IMS list the patent for the active substances included in this study were already expired a couple of years ago.

A more detailed description of the availability of the 11 selected active substances – originator and generic follower – is provided in Table 3.1. This overview disregards the different strengths and package sizes. It only displays whether for any strength or presentation of the active substance a (generic) follower (including biosimilar) was available.

Each of the eleven active substances is described in detail in factsheets (including information on manufacturers of originator and generics, pharmaceutical forms, sales and average unit costs) in the Annex 9.4.

Table 3.1
Overview of availability of the eleven active substances in EU-27 plus CH, NO and IS in the out-patient reimbursement market, September 2010

INN	Only generic	Only originator	Originator & generic	INN authorised not reimb.	INN not authorised
Octreotide	–	BG, CY, CZ, EL, HU, IE, LV, LU, PT, RO, SI, SK, CH, IS	AT, BE, DE, DK, ES, FI, FR, IT, NL, MT*, PL, SE, UK, NO	EE, LT	–
Somatropin	–	BG, CY, EE, HU, LV, SI	AT, BE, CZ, DE, DK, EL, ES, FI, FR, IE, IT, LT, LU, MT*, NL, PL, PT, RO, SE, SK, UK, NO, CH, IS	–	–
Leuprorelin	–	AT, BG, CZ, DK, EE, ES, FI, FR, HU, IE, IT, LV, LT, LU, NL, PL, PT, RO, SI, UK, IS	BE, DE, EL, NO, MT*, SE, SK, CH	–	CY
Flumazenil	CY, DK, EE	AT, BG, CZ, EL, HU, RO, SI, SK, IS	BE, DE, ES, FI, FR, IT, NL, MT*, PL, PT, SE, UK, NO, CH	IE, LV, LT, LU	–
Aztreonam	–	AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, IT, MT*, PT, RO, SE, SI, SK, UK, NO, CH	–	IE, LV, LU, NL	CY, HU, LT, PL, IS
Cilastatin + Imipenem	EL, HU	AT, BE, CY, CZ, EE, FI, SE, SI, UK, NO, IS, CH	DE, ES, FR, IT, NL, PL, RO	BG, IE, LU, LT, SK, PT	DK, LV, MT
Teicoplanin	–	AT, BE, BG, CZ, DE, DK, ES, EL, FI, FR, HU, IE, LU, NL, PL, RO, SE, SI, UK, NO	IT, MT*, CH	SK	CY, EE, LV, LT, PT, IS
Rifabutin	–	AT, BE, CZ, DE, DK, ES, FI, FR, IE, IT, LU, MT*, NL, RO, SE, UK, CH	–	EL	BG, CY, EE, HU, LV, LT, PL, PT, SI, SK, NO, IS
Apraclonidine	–	AT, BE, DE, DK, EL, ES, FI, FR, IE, IT, LU, MT*, NL, PT, SE, UK, NO, CH	–	BG	CY, CZ, EE, HU, LV, LT, PL, RO, SI, SK, IS
Fentanyl Patch	SI, SK	–	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU,IE, IT, LT, LU, LV, MT*, NL, PL, PT, RO, SE, UK, NO, CH, IS	–	–
Goserelin	–	AT, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HU, IE, IT, LV, LT, LU, MT*, NL, PL, PT, RO, SE, SI, SK, NO, IS	DE, UK, CH	–	–

* The Maltese reimbursement list does not indicate the product name or the company; therefore the products status could not always be determined.

Cyprus and Malta only public sector

Source: PPI 2010

3.2 Detailed descriptions including prices and volume of three selected substances

In the following section three of the eleven substances (Octreotide, Goserelin and Flumazenil) were selected for a detailed description and analysis. They were chosen because they reflect three claimed market hurdles with respect to genericisation:

» Biological product (perhaps with a limited number of potential patients due to the rareness of the disease).
» Complex pharmaceutical form i.e. patches, injectable implants, sprays and
» low sales volumes.

Octreotide

Octreotide – a hypthalamic hormone – is an example of a complex biological product which lowers many substances in the body such as insulin, growth hormone and glucagon. This medication is mainly used to treat acromegaly as well as to reduce flushing episodes and watery diarrhoea caused by cancerous tumours.

The originator company is Novartis and its brand name is in most countries Sandostatin. Novo Nordisk, Ratiopharm, Hospira and Hexal are just a few examples of companies, which further distribute Octreotide. Table 3.2 gives a detailed overview with respect to indication, pharmaceutical forms, patent expiry, average price per unit in 2010 and total sales as well as cost per unit 12 months prior to patent expiry.

Novartis also markets a modified released version of Octreotide, which is called Sandostatin "LAR". No generic followers could be found for the extended "LAR" version in Europe.

In summer 2010, availability of Octreotide was very high. Only in two countries (EE, LT) Octreotide was neither available as originator nor as biosimilar. In both markets Octreotide was authorised, but it is not clear if the market authorisation holder has applied for regular reimbursement. In the remaining 28 investigated countries Octreotide was marketed either only as originator (n=14) or as originator and as biosimilar (n=14), cf. Table 3.1.

Table 3.2
Factsheet Octreotide September 2010

Active substance	Octreotide		
ATC code	H01CB02, Hypthalamic hormones	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	~ 90 EUR
Originator brand name	Sandostatin©	**Average price for 0.1 mg/ml ampoule in 2010 (PPI)**	8.5 EUR (ex-factory originator)
Patent expiry in Europe	Ranges from 2000/11 – 2006/03	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 125 Mio EUR
Pharmaceutical forms and strengths	Ampoule: 0.05mg/ml, 0.1mg/ml, 0.5mg/ml (Solution for injection or concentrate for solution for infusion) Vial: 1mg (0.2mg/ml), 5mg (1mg/ml) (Solution for injection or concentrate for solution for infusion)	**Originator company** **Further distributors**	Novartis Novo Nordisk, Ratiopharm, Hospira/Mayne, Bendalis, Hexal, GP Pharm EFG, Toscina, Italfarmaco, Chemi SpA, Lifepharma, Sandoz, AAH Pharmaceuticals, Sun Pharmaceuticals

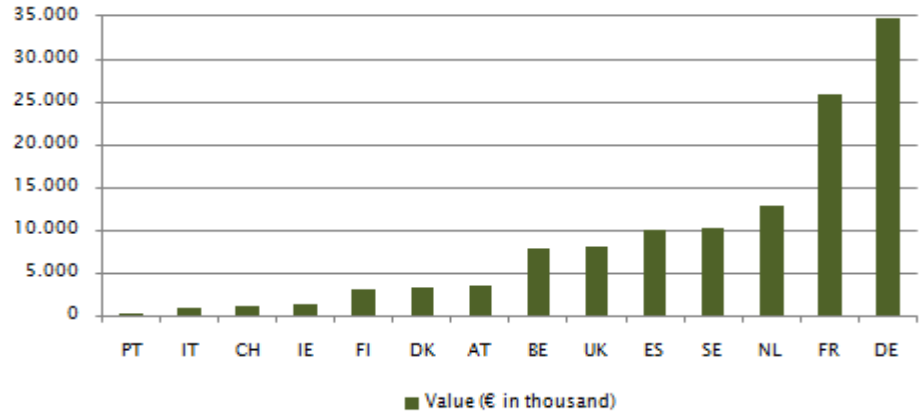
- IMS average cost per unit as well as total sales include Sandostatin and Sandostatin LAR

Source: EMINet 2010, IMS 2008

Based on the IMS list (EU-15 countries, excl. Luxembourg plus Norway and Switzerland) the standard cost per unit for Octreotide was on average 90 EUR 12 months prior to patent expiration; this includes the cost for Sandostatin as well as Sandostatin LAR. In general, the IMS standard unit cost takes all marketed strengths/ preparations of the given substance into account – single products, e.g. with a lower strength/ smaller pack size may be much cheaper.

Looking at the sales of Octreotide prior to patent expiry (hence only originators) – again including Sandostatin and Sandostatin LAR as based on IMS data – we see that five countries (ES, SE, NL, FR, and DE) each had above 10 Mio EUR sales and Belgium and the UK almost 10 Mio EUR sales value The sales value in the remaining countries (AT, DK, FI, IE, CH, IT, PT) was below 5 Mio. EUR (cf. Graph 3.2)

Graph 3.2
Sales (in EUR 1,000) of Octreotide in Europe 12 months prior to patent expiration



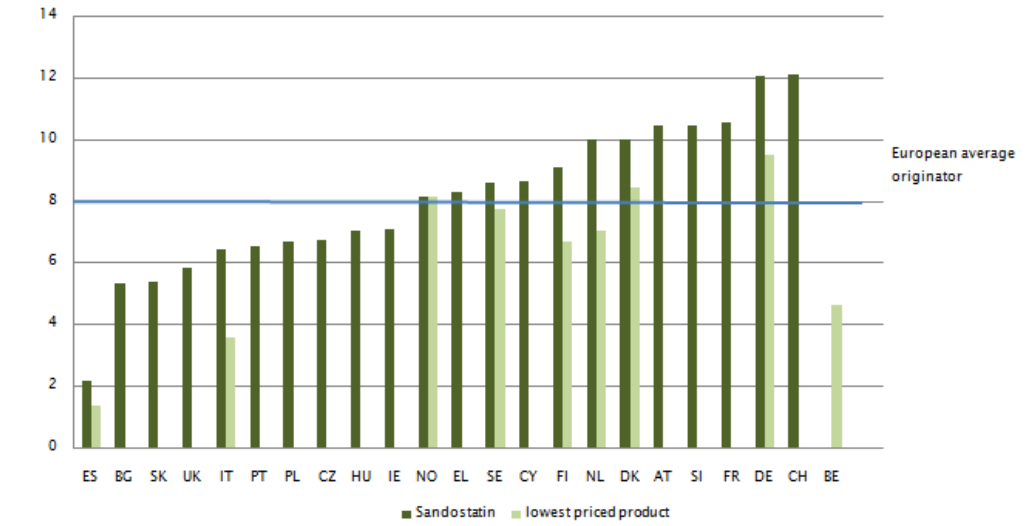
Source: IMS 2008

The picture looks quite different if only one form of Octreotide – leaving out the modified release version "LAR" – is considered. Based on 2010 PPI data the European average unit ex-factory price of 1 ml ampoule with 0.1 mg/ml Octreotide is 8.1 EUR, as shown in Graph 3.3. In 2010, biosimilars for Octreotide were marketed in 13 European countries; but pricing was not available for all of them. According to PPI data the average unit ex-factory price for biosimilars was 8.1 EUR in Europe.

As already mentioned, it is said that around 11.5 Mio. EUR sales in a mature market are a threshold for companies to invest in the production of a follower. In the case of the biological Octreotide this could be verified for six countries (DE, NL, SE, BE, FR, and ES) with sales prior to patent expiry being above 10 Mio. EUR and biosimilars consequently launched. However, this threshold did not seem to apply to Italy and Finland, which both showed less than 5 Mio. EUR sales before patent expiry but had biosimilars on the market in 2010. In terms of economic of scale it makes sense to launch generics, and especially biologicals, that are by definition resource intense to produce in as many countries as possible. This was confirmed by EGA and a number of interview partners.

Still the fact that, due to their specific properties, biologicals are not subject to mandatory generic substitution in a number of countries or are even explicitly excluded from substitution schemes like in Belgium could pose an important entry barrier for marketing of such medicines. Nonetheless, no explicit sales thresholds for biosimilars could be found in literature.

Graph 3.3
Ex-factory unit price comparison of originators and generics of Octreotide (1 ml ampoule) 0.1 mg/ml in EUR, September 2010



DK, FI, NL, SE, UK: ex-factory prices were calculated with average mark-ups as published in Austrian regulation on the calculation of the EU-average price[11]

Source: PPI 2010

Octreotide was chosen as an example of a complex biological product. EGA stated reasons why in their opinion generic companies are not capable of producing such products:

» Dedicated manufacturing facilities are needed for these special production requirements.
» The regulatory pathway is often not well defined for biological products.
» There is great uncertainty about the regular pathway and standards required for regulatory approval for these products.

However, these arguments should be taken with caution, as there is specific EU legislation in place since 2005. In addition, the example of Octreotide shows that a follower entered the market quickly around 2003 in a number of countries even if the expected sales were below the "potential" threshold in a number of Member States.

[11] http://www.bmg.gv.at/cms/site/standard.html?channel=CH0723&doc=CMS1078931881119

Goserelin

Goserelin is an active substance that is marketed in a complex pharmaceutical form – as injectable implant. It is a cytostaticum hormone, which is mainly used for the treatment of hormone-sensitive cancers of the prostate and breast and some benign gynaecological disorders.

The originator manufacturer of Goserelin (brand name: Zoladex) is Astra Zeneca. Three further companies (Cell Pharma, Genus Pharmaceuticals and Acino Pharma) could be identified of providing Goserelin implantable "sticks" in Europe in summer 2010.[12] Table 3.3 gives details on Goserelin with regard to its pharmaceutical form, patent expiry, average price per unit in September 2010 and total sales as well as cost per 12 months prior to patent expiry.

Table 3.3
Factsheet Goserelin September 2010

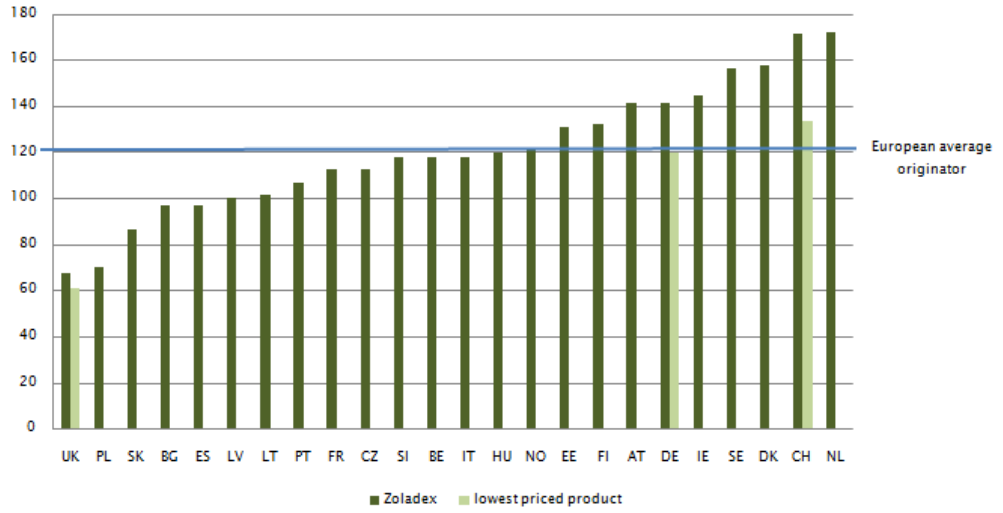
Active substance	Goserelin		
ATC code	L02AE03, Cytostaticum hormones	**Average cost per IMS standard unit prior to patent expiry (IMS)**	307 EUR
Patent expiry in Europe	Ranges from 2001/12 – 2006/01, in some cases 2008	**Average price for 3.6 ml injectable implant in 2010 (PPI)**	120 EUR (ex-factory originator)
Originator brand name	Zoladex©	**Total originator sales 12 months prior to patent expiry (IMS)**	Considerable variation in sales: in UK 68 Mio EUR and in FR 1.1 Mio EUR
Pharmaceutical forms and strengths	Pre-filled syringe with implant: 3.6mg (1 month), 10.8mg (3 months)	**Originator company** **Further distributors**	Astra Zeneca Cell Pharma, Genus Pharmaceuticals, Acino Pharma (Cimex)

Source: EMINet 2010, IMS 2008

12 months prior to patent expiry IMS standard unit cost – that takes all marketed strengths/preparations of the given substance into account – amounted to around EUR 300.–.

[12] In November 2010 further companies like Teva Pharma or Sandoz entered the market.

Graph 3.4
Ex-factory unit price comparison of originators and followers of Goserelin (injectable implant) 3.6 mg in EUR, September 2010



DK, FI, NL, SE, UK: ex-factory prices were calculated with average mark-ups as published in Austrian regulation on the calculation of the EU-average price[13]

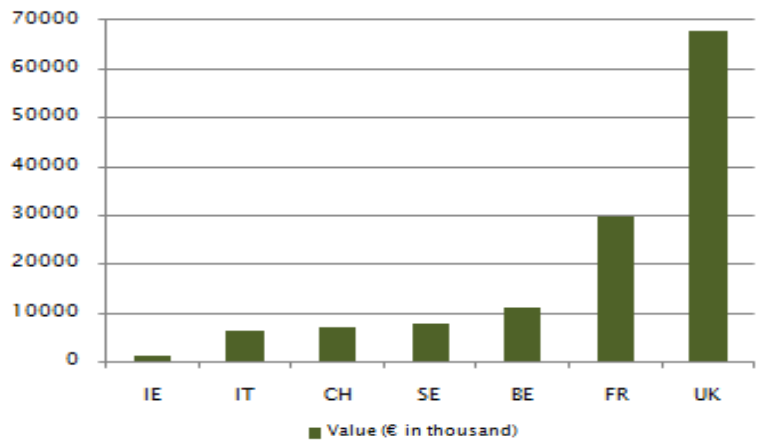
Source: PPI 2010

In 2010, the average unit ex-factory price of one 3.6 mg injectable implant of Zoladex was 120 EUR in Europe (based on the PPI data). Even though the patent was already expired in 2010 followers were only found in three markets (Germany, United Kingdom and Switzerland).

12 months prior to patent expiry also Goserelin sales varied to a great extent in the analysed markets. In Ireland sales value amounted to less than 1.1 Mio EUR; whereas in the United Kingdom it was 68 Mio EUR (cf. Graph 3.5), i.e. the UK consumed per capita five times more.

[13] http://www.bmg.gv.at/cms/site/standard.html?channel=CH0723&doc=CMS1078931881119

Graph 3.5
Sales (in EUR 1,000) of Goserelin in Europe 12 months prior to patent expiration



Source: IMS 2008

Despite the huge market by the end of 2010 only two generics distributors were on the market in the UK, three in Switzerland and merely one in Germany. This outcome supports the hypothesis that – even if the potential market is huge – complex pharmaceutical forms (in this case an injectable implant) that require 1) dedicated manufacturing facilities and 2) even might be acquainted with further patents are an additional market barrier. This finding was confirmed by our Sandoz interview partner who stated that due to the complex pharmaceutical form of Goserelin less generic followers are marketed than it would be the case with for instance standard oral forms. However, this might not always be the case if generic manufacturer seek to develop a new formulation or route of administration.

Goserelin is again a good example that the "rule of thumb" threshold of EUR 11.8 Mio. sales to be an "attractive" generic market could not be verified.

Flumazenil

Flumazenil is an example of an active substance with a low sales value that nonetheless attracted many generic competitors. According to IMS data total sales 12 months prior to patent expiry of Flumazenil amounted to a total of 1.78 million EUR in Europe (AT, DE, DK, FI, IE, IT, PT, SE, CH, and UK).

The product is mainly prescribed to patients who become excessively drowsy after the use of benzodiazepines either applied for diagnostic or therapeutic procedures (anaesthetics). It is also employed as an antidote in the treatment of benzodiazepine overdoses.

The originator manufacturer of Flumazenil is Roche and the brand name is Anexate. Despite the low sales still a great number of companies market Flumazenil in Europe; some of those companies are: B. Braun, Mylan, Biokanol, Actavis, Hexal, Hikma Pharma, Fresenius and TEVA.

Market availability of Flumazenil is quite diverse in Europe; in some countries only the originator was available, in other countries (DK, EE and CY) only generics could be found and in a few countries the active substance was authorised but not included in the reimbursement list (cf. Table 3.1); here again, it is not clear whether the originator's manufacturer decided not to apply for reimbursement or if reimbursement eligibility was denied. The later could be due to the fact that it may primarily used in hospital settings. In Denmark, for instance the first provider (out of currently three) entering the market was Fresenius Kabi in January 2007.

Table 3.4 gives detailed information on Flumazenil with regard to pharmaceutical forms, patent expiry, average price per unit in 2010 and total sales as well as cost per unit 12 months prior to patent expiry.

Table 3.4
Factsheet Flumazenil September 2010

Active substance	Flumazenil		
ATC code	V03AB25, all other therapeutic substances	**Average cost per IMS standard unit prior to patent expiry (IMS)**	19 EUR
Patent expiry in Europe	Ranges from 2000/09 – 2007/02	**Average price for 0.1 mg/ml ampoule per 5 ml in 2010 (PPI)**	15 EUR (ex-factory price originator)
Originator brand name	Anexate©, Lanexat©, Mazicon©	**Total originator sales 12 months prior to patent expiry (IMS)**	1.78 Mio EUR
Pharmaceutical forms and strengths	Ampoules: 0.5mg, 1mg; Vials: 0.5mg (0.1mg/ml)	**Originator company** **Further distributors**	Roche B. Braun, Mylan, Biokanol, Actavis, Hexal, Hikma Pharma, Frensenius, TEVA, Inresa, Matrix, Pharmaselect, Genfarma, Baggerman, Combino Pham, GES EFG, Fresenius Kabi, Aguettant, Hameln, Pharmachemie, Bowmed

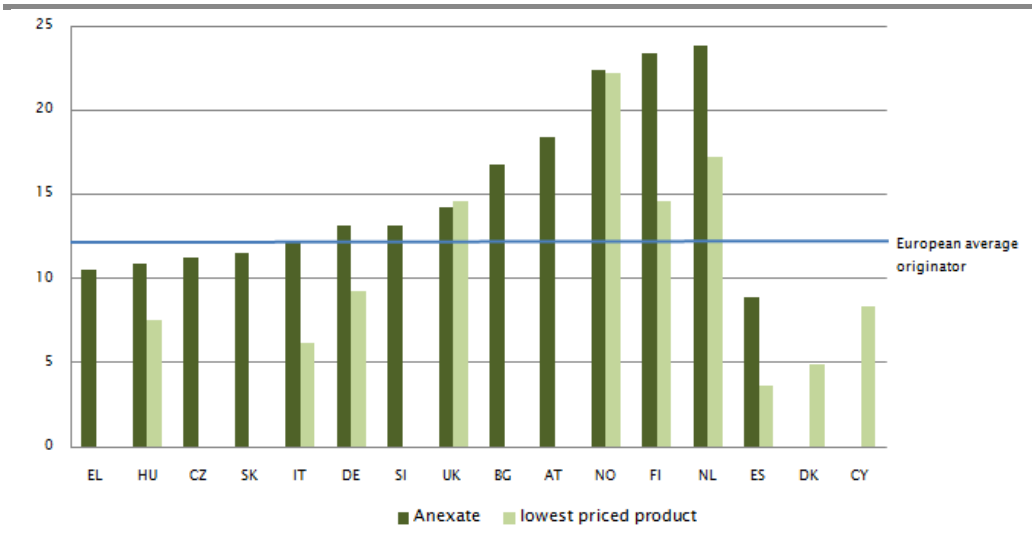
Source: EMINet 2010, IMS 2008

The IMS average standard cost 12 months prior to patent expiry was 19 EUR. The 2010 PPI average ex-factory unit price for one 0.1 mg/ml Flumazenil ampoule was 12.4 EUR (cf. Graph 3.6). By summer 2010, 17 countries had followers of Flumazenil on the

market (cf. Table 3.1); however pricing was – probably because of hospital use – only available for eight countries.

The 2010 PPI price analyses also demonstrated that, in general, the price of followers is much lower than the originator's price. This is especially the case. Norway is an exemption as the price of the generic and the originator are almost similar. The reason could be that the product – due to its low sales – is not part of the Norwegian step-price system that regulates prices of generics due to their sales.[14]

Graph 3.6
Ex-factory unit price comparison of originators and followers of Flumazenil (ampoule per 5 ml) 0.1 mg/ml in EUR, September 2010



DK, FI, NL, SE, UK: ex-factory prices were calculated with average mark-ups as published in Austrian regulation on the calculation of the EU-average price[15]

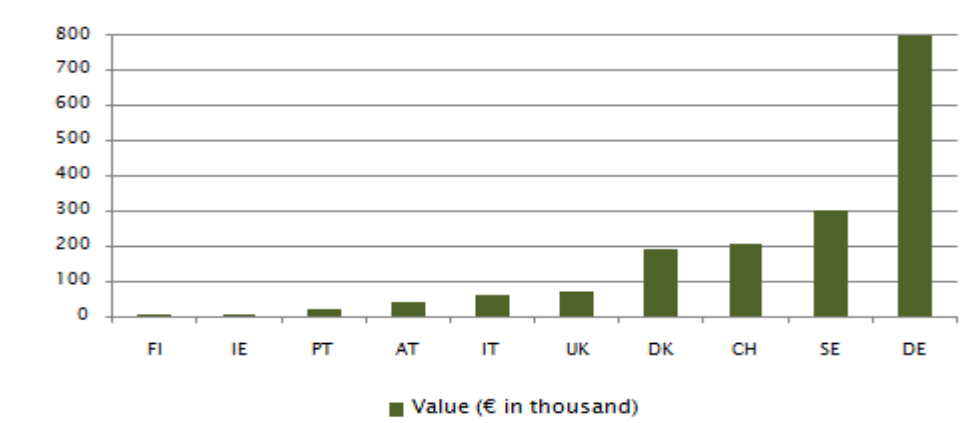
Source: PPI 2010

The most likely reason for lacking generic followers, for instance in Bulgaria, is the overall low sales of Flumazenil that makes it – as our interview partners have confirmed – unattractive to produce product leaflets in local language. Graph 3.7 shows the IMS sales value of Flumazenil 12 months prior to patent expiry in ten European countries. Germany tops the ranking with 873.162 EUR whereas in Finland it only generated sales of 4.217 EUR.

[14] PPRI Profile Norway 2008, cf. http://pprig.goeg.at → Publications

15 www.bmg.gv.at/cms/site/standard.html?channel=CH0723&doc=CMS1078931881119

Graph 3.7
Sales (in EUR 1,000) of Flumazenil in Europe 12 months prior to patent expiration



Source: IMS 2008

Additional reasons for low genericisation were stated by EGA and our interview partners from industry: Generally speaking the production of generic followers in markets with low sales doesn't make sense if initial investment cost, e.g. for extra labelling or translation of the package or for the registration of medicines are deemed too high. The production cost of the molecules themselves were not seen as a barrier to enter a low sales market, as the medicines are manufactured for multiple countries and these countries can be accessed, if necessary, via centralised authorisation procedures. The companies also mentioned the national administrative procedures – not only linked to authorisation, but also to pricing and reimbursement – as major barrier for launching generic followers.

According to EGA members most small countries like Belgium, Malta or the Baltics are not considered as an „attractive" generic market, but due to historical reasons, some generic companies are nonetheless present there. Especially mentioned were high legal and regulatory entry barriers in Belgium (e.g. the „no-switch list") or Cyprus with a strong market share of local industry and originator products (cf. section 4.3. for details).

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4 Factors that determine genericisation

4.1 Theoretical considerations

Microeconomic market theory can provide a conceptual framework and some insights to the analysis of off-patent medicines markets, and its expected behaviour, as well as on the factors that favour or oppose genericisation.

Off-patent markets are usually characterised by product differentiation, with one medicine, the originator, that has a high degree of consumer loyalty, because in spite of the evidence on bioequivalence of the generics some consumers feel that it is somehow superior and not perfectly substitutable by their generic versions. Product leadership is the result of early entry and strong advertising among potential prescribers. These characteristics result in a market structure called monopolistic competition where contrary to perfect competition, suppliers are not price-acceptant, and as result different prices might be found in the state of market equilibrium. The market can be defined so as to include all products that have the same active ingredient and formulation, or it may include several active ingredients of a therapeutic group which are highly substitutable, for instance, all statins or all ACE-inhibitors. There might further be more than one market leader. Moreover, as in most medicines markets, there are additional obstacles to perfect competition:

» on the supply side, there are entry barriers in the form of regulation of market entry, i.e. products require a specific market authorisation justified by the need to ensure efficacy, safety and quality;
» on the demand side, there is no perfect information by the patient/consumer on the characteristics of the medicine and limited price-sensitivity, mainly due to the fact that consumers usually do not pay the price, at least, not the full price, of the medicine, which is totally or partially paid by a third party payer (insurer or public health system). Finally, prices are not freely determined by demand and supply side forces, but subject to regulation.

Originators and generics manufacturers are for-profit entities; therefore the main incentive to develop and market a generic is the prospect of appropriate profits. The expected return on investment from developing and marketing generics depends on expected sales of the generic follower and on the costs of developing, manufacturing and marketing the medicine, which in turn depend on other factors such as future price of the originator, competition from other generic manufacturers and market regulations. Another argument is, that the larger the global sales potential is, the more likely generic producers will incur in the investment (fixed costs) required to develop and market a certain generic.

It can be further assumed that the basic decision of developing a generic and that of marketing it in different countries is based on different factors:

» potential global sales
» development costs
» global manufacturing and marketing costs.

But it will also consider the expected individual country's sales and the costs of marketing the product in individual countries, e. g. with regard to registration fees or labelling requirement in local language in order to conclude in which countries the medicine is actually launched. These two types of decisions are interrelated, as the global market potential is the sum of the expected individual national market sales. But even if a positive decision is taken for developing the medicine, the manufacturer might find unprofitable to incur the additional costs of marketing the medicine in a given country.

This is more likely to happen in small markets, where the expected price and sales might not seem sufficient to compensate the country-specific additional costs. Fixed costs of marketing the medicine in a small country have a larger impact than in big markets and there might be diseconomies of scale, such as those related to the production of relatively small batches.

In most cases, the lack of genericisation will be the result of multiple simultaneous factors, the most common ones are mentioned below:

» small population (e.g. due to the rareness of the disease)
» relatively low expected sales
» limited health insurance coverage of the molecule, leading to lower use
» complex pharmaceutical forms (e.g. implants, patches)
» strict registration requirements (e.g. fees, labelling and translation of package leaflets into national language)
» lack of appropriate demand polices (generic prescribing, generic substitution) or
» lack of appropriate supply side generic policies (e. g. too strict price control mechanisms).

4.2 Results from the literature review

The study by the DOH and the BPI (2002)[16] concluded that several conditions seem to be necessary to ensure effective generic competition once a medicine goes off-patent:

» the market needs to be very large (an annual turn-over of at least 11.8 Mio. EUR / 10 Mio. GBP)
» the medicine needs to have a certain level of generic prescribing
» the manufacturing process must be relatively straightforward and
» there must not be other major inhibiting factors.

Moreover, it found that most significant medicines (with an annual net ingredient cost of 3.5 Mio. EUR / 3 Mio. GBP or more at the time of patent expiry) faced some generic competition but the extent of generic entry was variable.

The results of an econometric regression analysis carried out in the Pharmaceutical Sector Inquiry (2009)[17] confirm that high sales value is associated with a higher likelihood of generic entry. Other variables that characterise the regulatory environment and are also positively associated to generic entry are:

» compulsory substitution by pharmacist
» absence of price caps or compulsory discounts to generic medicines.

Although the analysis does not include smaller European markets[18], some relationships, such as the effects of small market size, can probably be extrapolated to the missing small markets. In any case, in the 17 countries included the share of generic entry by country does not show a clear association between market size and generic entry. Time to entry (the gap between the active substance in question lost exclusivity and the first generic entry) was found to be 13 months on average.

Again there is a clear market size gradient in this variable: between 18 and 20 months for the medicines in the 3 lower quintiles[19], that drops to approximately 8 and 4 months for the second and first quintile, respectively. Regression analysis confirms these findings and the positive effect of regulatory variables such as compulsory substitution, physicians' incentives to generic prescription and the absence of generic price regulation on manufacturer level.

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16 www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009600

17 http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/index.html

18 Slovakia, Croatia, Bulgaria, Slovenia, Lithuania, Cyprus, Latvia, Estonia, Iceland and Malta

19 Quintile were formed according to sales value one year prior to expiry

The degree of generic competition is approximated in the analysis of the Pharmaceutical Sector Inquiry by the number of generic companies in the market for a given medicine. According to the results presented, one year after patent expiry that number rises on average to seven companies and after three years it goes beyond nine. There is again the expected market size gradient: the number of companies in the highest quintile is almost four times larger than that in the lowest quintile. The medicines market size becomes clearly a driver of competition when the number of generic companies by country is compared. The five larger explored EU markets (DE, FR, IT, UK and ES) plus the Netherlands and Portugal have more than six companies per active substance on average. Finally, the regression analysis in the Sector Inquiry suggests that regulatory policies requiring pharmacists to dispense generic products when available and encouraging doctors to prescribe the substance (as opposed to a particular brand), tend to have a positive effect on the degree of generic follower penetration. The same is true for policies involving reimbursement of medicines at the level of the lowest priced product and a frequent adjustment of reimbursement levels to take account of price developments in the market. By contrast, the analysis indicates that policies involving price caps/mandatory discounts for generics appears to reduce the level of generic penetration relative to the regimes without such price caps/mandatory discounts.

A recent report by IMS (2010)[20] comments the limited penetration of generics in some large markets, such as Italy and Spain, and states that "*Reducing the price of generic medicines in low volume markets can severely challenge the sector's sustainability. In these countries the cost of maintaining the essential infrastructure related to registration costs, pharmacovigilance and other legal requirements will not be covered by the revenues generated*." They conclude that the right way to promoting generics is by removing regulatory barriers and implementing policies that increase the demand for generics. From the authors perspective no comprises are possible on safety issues.

Bae (1997) found a negative relationship between an originator's sales revenue and the time to generic entry. Scott Morton (1997) concluded that larger revenue markets attract more entry. Regarding policy variables, Magazzini et al (2004) found that administered prices (price control) leads to lower generic penetration, and Garattini and Tediosi (2000) associated price regulation with speed of entry. Simoens (2007) associates no price control and the existence of a mature generics market with higher market penetration.

No literature could be found that explicitly analysed the relations between low genericisation and patent protected pharmaceutical forms. Low generic availability associated

[20] www.imshealth.com/imshealth/Global/...TL/Generic_Medicines_GA.pdf

with national requirements such as packaging and labelling in national language were only rarely mentioned in literature.

4.3 Views from the generics industry

This section includes a short summary of an EGA report dealing with the problem of small markets as well as statements by representatives of the generic industry who answered in written the questionnaire and in personal interviews. A summary of the filled out questionnaires are included in the Annex.

A report by EGA (2009)[21] states that the key barriers for generic medicines when entering the European markets are mostly the result of the following inadequate policies:

» failure of governments to create long-term generic medicines policies
» linkage of generic prices to originators/reference product prices
» delays in pricing and reimbursement decisions
» lack of appropriate incentives for physicians, pharmacist and patients to prescribe, dispense and request generic medicines.

The report does not explicitly mention or address the issues of small sales volume or small markets as a barrier to generic entry. However, it states that "...*reducing the price of generic medicines in low volume markets can severely challenge the sector's sustainability. In these countries the cost of maintaining the essential infrastructure related to registration costs, pharmacovigilance and other legal requirements will not be covered by the revenues generated. More affordable and lower-price treatments will be a natural result of increasing the demand for generic medicines and will raise the level of completion in all markets.* "[22]

In line with the findings of EGA, the interviewed individual generic manufacturers explained that the following factors are taken into account when considering the potential development of a follower:

» market potentials
» technical feasibility of development (for instance, not requiring dedicated facilities)

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[21] www.egagenerics.com/.../ega_increase-patient-access_update_072009.pdf

[22] Bongers F and Carradinha H. How to Increase Patient access to Generic Medicines in European Healthcare Systems. EGA (European Generic Medicines Association) June 2009, p.4

» adjustment to the current portfolio of the company and
» the timeliness of the expected launch, i.e. possibility of having the medicine ready to enter the market by the end of the originator's exclusivity period.

Other factors mentioned by some respondents were the availability of active ingredient of good quality, the expected profitability (revenues minus costs over the product's lifecycle), the predicted development cost, the cost of raw material, and sales at launch, price erosion, overall generic penetration and market share. The patent situation linked to medical devices was not explicitly stated as a criterion.

Different speculations on rough indications of critical market size or threshold in terms of sales or volume under which a generic is not likely to be developed or marketed have been stated by the mentioned DOH/BPI report 2002 (cf. section 4.2)[23]. As part of our investigation among generic manufacturers the authors also assessed their opinion on potential thresholds. One respondent stated that less than 7.5 Mio. EUR expected sales would probably be a too low figure for making medicine attractively for a major company. A second one said that sales of the originator before patent expiry below 20 Mio EUR in the big EU markets would probably make the development of a generic impossible. Another mentioned that 100.000 EUR for one year could be nice for a small market like Austria, provided that the registration fee is not too high and that there are no further market barriers. The interview partners claimed these figures to be estimates and that the actual expected sales would vary depending on the company and on the development/marketing cost involved to penetrate the market.

European countries considered as small or low volume markets by all interview partners from industry are: Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta, Slovakia and Slovenia.

According to the industry representatives, the main factors that constitute entry barriers to (small) markets for generic companies are:

» Factors related to market conditions like the reduction of originator's prices upon generic entry (as this is the case in Austria or Belgium or Norway) leading to the effect that generics do not enter the market as the prices of originators are too low to compete with or too small patient population not allowing for a reasonable distribution (too small orders).
» Factors related to regulation: high regulatory fees, lengthy and costly administrative pricing and reimbursement procedures, requirement of package in national lan-

[23] www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009600

guage[24], low entry prices due to price control based on external reference pricing, compulsory price decreases after launch, frequent changes and long-term unpredictability of regulations, extensions of patent protection and threat of patent litigation by originators.

For the eleven active substances included in the study sample factors that might limit the interest for marketing followers, according to the survey respondents, were:

» Some of the products require high technical expertise and are subject to difficult regulatory requirements (e.g. biologicals). According to a respondent, this applies to Octreotide, Somatropin, Leuprorelin, Teicoplanin, Fentanyl and Goserelin.

» Products administered through devices (Fentanyl and Goserelin) present an additional barrier, as they require more marketing efforts.

» Very low sales. This applies to Flumazenil, Aztreonam, Cilastatin + Imipenem, Rifabutin and Apraclonidine

» Moreover, antibiotics are not attractive because of usually low prices.

» In the case of biosimilars, the lack of substitution regulations.

4.4 Results of the statistical analysis

The methodology used in the statistical analysis is described in detail under section 2.3.3. The data of the statistical analysis is based on the 2010 PPI survey covering 30 EU countries (EU-27 plus Iceland, Norway and Switzerland).

In a first step the association between socio-economic as well as generic policy related variables with genericisation was analysed. The results of this analysis is summarised in tables 9.1-9.8 in the annex. With respect to generic policy related characteristics the results show that the majority of the countries have generic price control (86.2 %) at ex-factory price level. 65.5 % of the countries use international price comparison and in 58.6 % of the countries the decision is linked to the originator medicine. 13.8 % of the countries apply tendering-like practices in the out-patient sector and half of the countries (40.9 %) have an accelerated/specific procedure in place for pricing a/o reimbursement decisions of generics. Three quarters (75.9 %) of those countries feature a reference price system and the majority of the countries apply prescribing by INN i.e. by active substance rather than product name (86.2 %). In case of INN pre-

[24] The statements included in this section have been made by representatives of the generic industry in the answers to a survey (see Annex 1) and in personal interviews.

scribing or generic substitution biologicals are often considered as non substitutable. Usually country have list of so-called "interchangeable" medicines.

In a second step an analysis of the variables associated with availability and generic competition was performed. In order to facilitate the reading, the results are presented sequentially according to the study objectives:

Objective 1: to assess the present situation of availability and generic competition by means of a descriptive analysis of a sample of off-patent medicines in the EU markets.

The statistical analysis showed that in the case of Rifabutin and Apraclonidine availability of generics was significantly higher in countries with stronger purchasing power (measured by the price level index for pharmaceuticals), higher per capita total expenditure on health, higher gross national income per capita and higher per capita government expenditure on health.

Countries that used international price comparisons for generics and pricing and/or reimbursement decisions linked to originator showed less availability of Apraclonidine.

Objective 2: to explore to what extent availability and market competition in off-patent medicine markets of Europe is associated with global sales volume, market size and a set of economic, demographic and regulatory characteristics.

The analysis revealed that countries with larger pharmaceutical market values and larger populations are more likely to apply generic price control and thus show higher values for competition indicators 1 and 2. Countries with higher pharmaceutical price levels demonstrated higher values for competition indicator 2 (= availability of a follower), whereas countries with generic price control had lower values of competition indicators 1 and 2, i. e. were less likely to have followers respective more than one generic on the market (cf. table 6).

Objective 3: To assess which policies options might promote or limit genericisation of low sales medicines and in small markets.

Countries with larger populations, huge pharmaceutical sales, greater expenditure on health as percentage of GDP and a larger pharmaceutical market value showed a higher number of followers, both biosimilars and generics, on the market. Generic policies and pricing and/or reimbursement decisions linked to the originator's price were associated with a lower number of followers.

5 Policy options to promote genericisation

Is the lack of genericisation a relevant problem for health systems, insurers and consumers? Assuming that to promote generic competition is not an objective in itself, but a mechanism to lower medicine prices and, as a consequence, improve access and reduce expenditure, the ultimate benefits of generic competition to health systems, insurers and consumers are mainly of an economic nature. The lack of genericisation implies losing the opportunity to attain potential cost-containment and increase access to medicines. Of course, when the cost of the medicine is not appropriately covered by the health system or affordable out-of-pocket by the users, the lack of generics might limit the access to needed medicines and have a negative impact on health.

A report of a task force of the Working Group Pricing of the Pharmaceutical Forum "Ensuring availability of medicines in small national markets" indicates the steps required to make a medicine available on a national market once it has been successfully developed[25]. It also points to the specific problems small markets might face and suggests some approaches to overcome them. The most important points are:

» Production of multi-lingual single packs for multiple national markets, as the production of packs for small national markets typically have lower quantities and is therefore more expensive per unit produced. Producing multi-lingual packs is allowed by Community law under Article 63 of Directive EC/2001/83 and is e. g. in place in Belgium where packs are adapted to language requirements in Dutch, French and German.

» Public authorities should apply public service obligations on all wholesaling actors or else organise distribution themselves for medicines that are not efficiently delivered through private wholesaling. Small national markets face availability problems due to higher costs of transport and wholesaling.

Representatives of the generics industry furthermore suggested as options for small countries:

1. to limit compulsory price reductions[26],
2. to allow and encourage generic prescribing,
3. to increase incentives to prescribers and dispensers of generics,

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[25] http://ec.europa.eu/pharmaforum/docs/ev_20081002_frep_en.pdf, p. 88

[26] Referring to e.g. the policy of a few countries like Austria to set the (reimbursement) price of the follower as percentage of the originator's price.

4. to launch information campaigns for patients and professionals regarding generics,
5. to reduce pricing and reimbursement administrative costs,
6. to have clear / strict legislation rules (terms and conditions) for reimbursement and
7. that in the context of the reference price systems, only the lowest price of a group of equivalent products should be reimbursed.

5.1 Experiences from countries

Luxembourg

Luxembourg is an example of a small country that decided to link its pricing decisions to the country of origin as well as to Belgium. With respect to cross-border price comparisons Luxembourg takes the price of the originator country and has only this country in its basket. Luxembourg is not only linked to Belgium with respect to pricing and reimbursement procedures but also regarding the language of the packages and the information leaflet. This reduces the threshold to enter the market for generic companies to a great extent, as mentioned by a representative of the generic industry.

Malta

Malta is another example of a small market that links its authorisation process as well as its pricing and reimbursement procedures and the language of the packages to a bigger country – the United Kingdom. This gives generic companies the incentive to enter also Malta as no additional costs for translation of patient leaflets or for marketing authorisation occur.

Iceland, Latvia and Estonia

These countries are examples of small markets (based on market capitalisation and population size) that are facing difficulties with genericisation. In an expert panel with members of the PPRI network on 8 June 2010 at the PPRI network meeting in Oslo, they reported the following problems:

» Lack of generic industry in the national markets; Iceland for instance has only three generic companies on the market of which the Actavis Group is the dominating player as it covers the whole portfolio. This does not create competition among the different players on the 300,000 person market which consequently does not

lead to lower medicine prices. Further, companies don't enter the market because they need to provide all information (patient leaflets, labels) in Icelandic.

» Pricing and reimbursement policies: Estonia reported that the current wholesale and pharmacy margin system means that the retailing of high price medicines is more lucrative and there is no system in place that give doctors or pharmacists incentives to prescribe / dispense low(er) priced followers. Latvia mentioned that originator companies already lowered their prices quite substantially thus even reducing the chances for generic companies to reach significant market shares in their 1.3 million inhabitant market.

» Authorisation: Another example reported by Estonia was that the marketing authorisation holder has to pay a "safety monitoring fee / annual fee" to the Medicines Agency for every marketed preparation. The fee amounts to 2,500 EEK/160 EUR per preparation. Latvia also commented that such registration fees may constitute entry barriers to market entry for generic companies.

» Vertical integration: Wholesalers have already established good service contracts with already existing generic companies, hence leaving almost no room for new generic competitors. Enhanced public service obligations could be a solution for this problem.

6 Discussion

The discussion on lacking generic entry in small markets (with regard to the possible number of patients) respectively countries with low sales volumes is centred around two main points 1) potential general barriers for genericisation (e.g. problems related to the production process or economy of scales) and 2) issues related to the different national pricing and reimbursement frameworks.

6.1 Barriers to genericisation

Low global sales seem to be one of the main obstacles to the development of followers as it offers less potential opportunities for generic manufacturers to obtain large market shares. Orphan medicinal products constitute a specific problem in this sense as by definition these medicines have a limited number of potential patients and therefore are less "attractive" markets from an economic perspective. However, in the case of orphan medicinal products there is an issue of health needs of individuals which might not be covered if the medicine is not available; whereas in the case of lacking generic availability of blockbuster medicines, the problem is mainly an economic one. As most orphan medicinal products tend to be costly a lack of followers results in higher public expenses for pharmaceuticals than necessary. Nonetheless, for ultra rare orphan medicinal products the potential economic benefits of genericisation are likely to be modest as very often countries have only 2-3 patients, thus the economic incentive for manufacturers of biosimilars is low.

Our statistical analysis supported this finding as the bivariate analysis showed that countries with larger populations, higher pharmaceutical sales, greater expenditure on health as percent of GDP and a pharmaceutical market capitalisation had a larger number of generics on the market. This means that not only medicines with low sales but also **small markets with respect to patient populations** are reasons for low genericisation. In addition, the results of the mapping of availability analysis also came to the conclusion that the threshold of around 11.8 Mio. EUR to develop generics seems, if at all, to be mainly relevant for complex pharmaceuticals (cf. Goserelin in section 3.2).

Nonetheless, it could **not be verified that such a "rule of thumb" threshold in terms of critical market size / value really exists.** Industry interview partners mentioned broad ranges from 100.000 EUR to 20 Mio EUR sales and confirmed that investment decisions are based on a number of criteria that may differ to a large extent between companies, e.g. depending on their size or business strategy. Manufacturing decisions are linked to other factors such as the cost for packaging, labelling and in how far the national pricing and reimbursement system supports or even promotes the use of

generics. Obviously some industry representatives claimed, both in articles, meetings and personal talks that some national pricing and reimbursement authorities do not promote generic use.

It was interesting to see that still for "small" substances like Flumazenil a much higher number of generic competitors were observed on the market than for substance with high sales. The reason could be that it is, compared to some other complex products of the eleven surveyed substances, comparably easy to manufacture.

In addition, we observed two more factors of high relevance with respect to genericisation: **complex pharmaceutical forms**, e. g. injectable implants, spray etc. and **complex active substances** e.g. growth hormones seem to reduce the number of followers on the market**.** Companies mentioned that development costs in general are not market barriers as they develop their products for multiple countries. However, with respect to the selected active substances (e. g. Goserelin, cf. section 3.2) companies do require high technical knowledge as well as specialised equipment ad dedicated manufacturing facilities. This leads to higher development costs which might not be in relation to the expected turnover. In addition, special regulatory requirements are applied for products that are marketed in complex pharmaceutical forms.

Summing up, in most cases multiple factors, namely limited demand (because of small patient populations or size of the national pharmaceutical market), the complex and thus costly manufacturing of the molecule in the case of biosimilars and potential patent infringement issues related to the pharmaceutical form influence or even hinder genericisation.

6.2 National policy framework

Another major entry barrier for generic manufacturers that we could identify is **cost associated with placing the product on the market**. Companies in particular mentioned that not the translation cost of the dossiers for marketing authorisation but having to produce small amounts of country-specific packages and leaflets leads to diseconomies of scale.

High costs of country-specific packs for a small country could for instance be addressed if the language coincides with that of a large country, a factor of which Malta and Luxembourg have taken advantage of. This does not need to imply giving up some sovereignty, as long as the final decision is retained by the small country.

Additional causes of generic unavailability in small markets seem to be some **pricing and reimbursement policies and measures at country level** that discourage generic manufacturers to launch their products like the following:

» Factors linked to regulatory policy: high registration fees but also list published by the national Medicines Agency that recommends not to switch or not to prescribe active substances for certain therapeutic areas, e.g. trans-dermal systems like Fentanyl patch and oncologic medicines. These cases are listed in a document, which creates a "scare" effect for prescribers and there is a tendency that companies decide not to launch generic versions of molecules mentioned in the list. In Belgium, for instance the Federation of Belgian Generics Manufacturers claims such a "no-switch[27]" list to make it unattractive to place certain followers on the market.

» Factors linked to prescribing habits: There may be little incentive for doctors to prescribe cost-effectively, like e.g. prescription targets, which would enhance the prescription of followers. In addition, still in five Member States and EFTA countries prescribing by INN is forbidden, in further eight INN prescribing is only indicative and generic substitution by the pharmacist is not allowed in eight countries.

» Factors linked to dispensing: lack of differentiated margins in absolute value for pharmacists when dispensing generic and originators and different dispensing habits e.g. dispensing one month supply in one market and three months' supply in another market (e.g. 28 tabs per pack and 98 tabs per pack) can make it difficult to market the medicine with the pack size that suits the consumers best. Sweden has tried to tackle this problem by allowing pharmacists to charge an additional add on (1.08 EUR/10 SEK) when dispensing a generic rather than an originator brand in case of off-patent medicines with the exception of biosimilars. Another policy option that could favour generics is the trend to dose dispensing in Europe.

» Factors linked to reimbursement: financial difficulties of smaller markets lead to delays in payments of reimbursable medicines. Greece, for instance, is well known to pay up to two years later. This fact makes a small market even less attractive.

» Factors linked to pricing: too low prices for originators and as a consequence for potential followers constitute high barriers from a provider's perspective. For instance, Belgian authorities have implemented an obligatory price decrease of -42 % for generic followers in comparison to the reference medicine, and in Austria the first follower of products listed in the green and yellow box of the positive list need to reduce their price by 48 % to be reimbursed.

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[27] Propositions pour l'application pratique dans la pratique medicale et pharmaceutique et dans lae dossier medical electronique, description on DCI, 10 March 2010

Due to these facts and the barriers because of low national demand especially small / low volume markets need to put an emphasis on the enforcement of policy measures that trigger genericisation.

Examples of medium sized countries (Sweden, Denmark) show that the introduction of generic policies (e.g. mandatory generic substitution) boosts the demand for followers and thus contribute to savings. However, the same is true for larger markets: France, for instance, made prescribing by INN compulsory a year ago. According to IMS Health data, cited by the health insurance group Mutualité Francaise, less than one in eight prescriptions in France were written by INN before.[28]

Finland is another example of a smaller country that implemented an incentive system which led to satisfying cost-containment result for the third party payer, and because of the percentage co-payment system, for patients: In 2003 generic substitution and in 2009 reference pricing was implemented in Finland. Reference pricing provided financial incentives to support the use of generic substitution. As a result, 54 percent of the 19.2 Mio. EUR prescriptions dispensed by pharmacies in the six reviews months were covered by reference pricing and 69 % of them involved generic substitution. The highest savings derived from medicines groups that had the most exposure to generic substitution like Statins.[29] In this line the European Generic Medicines Association (EGA) stressed the importance for European governments to put in place coherent healthcare policies incentivising patients, physicians and pharmacists to use generics to ensure affordability and sustainability of healthcare. [30]

Spain, like many other countries, implemented price cuts in 2010 to respond to the financial deficits due to the financial crises. In April 2010, the health administration decided to cut the prices of generic by 25 %. However this measure was accompanied by a specific plan to promote generics through mandatory generic INN prescribing and the compulsory dispensing of generics by pharmacists. According to information by the Director of the Spanish Generic Medicine Association, Spain expected savings of 320 Mio. EUR between July and December 2010. According to IMS the measures were already effective as sales of generics increased by 13 % in value and 17 % in volume in the months to August 2010 sales of generic.[31]

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28 Generics bulletin, 6 July 2010, p. 8

29 Generic bulletin, 6 August 2010, p. 13

30 Generic bulletin, 7 May 2010, p.13

31 IMS Pharma Pricing and Reimbursement, November 2010, Vol. 15, p. 331

Some generic policies are perhaps less suitable for small markets than for larges ones. Small markets need to consider that, e.g. in case of the implementation of **tendering systems** which mainly aim at price competition**,** like in Germany or the preference policy in the Netherlands, this may lead to the effect that smaller generic manufacturers cannot afford to invest in these markets (as they would need to serve the full market any time) and rather refrain from it.

Looking at the example of the Netherlands and its preferential policy, we could see that Octreotide, one of the analysed active substances, was also included in the Dutch preference policy since summer 2009 and our price analysis showed that generic followers of Octreotide were really marketed. The price of the originator product is around the EU-average of 8 EUR and the unit price of the generic follower is in line with the EU average of 6.35 EUR. By the end of 2010 it is expected that the number of active ingredients covered by the Dutch preferential policy will reach 200, but the number of included active substances varies significantly between insurers (e.g. Achmea includes 129 molecules and UVIT at total of 52 and Agis just 6). UVIT – one of the Dutch insurers – e.g. incorporated off-patent biological medicines (e.g. erythropoietin, filgrastim and somatropin) into the preference policy only in July 2010, but reversed the decision just one month later following widespread criticism from doctors and others.[32]

The Association of the Dutch Generic Medicines Industry claimed that it is no longer attractive to market selected generics in the Netherlands – due to the low price – resulting in reducing their product portfolio.[33] However, preferential pricing is a good example of the economic fact that lower prices may be only obtained if generics manufacturers achieve higher (guaranteed) volumes.

Summarising it can be said that as both, the cause (total sales) and the effects of the problem (no development of a generic) are global, the remedies should preferably be also supranational. This means, for instance, any kind of EU-wide coordinated measures to promote generic development such as: reduction of administrative fees and pricing and reimbursement procedures of low sales generics or granting a period of exclusivity to the first generic entering the market would be valuable to boost generic penetration besides a consequent implementation of already existing generic policies like mandatory generic substitution. A solution for products excluded from generic substitution like some biosimilars could be to initially prescribe them rather than the originator brand.

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[32] IMS Pharma Pricing and Reimbursement, November 2010, Vol. 15, p. 327

[33] IMS Pharma Pricing and Reimbursement, November 2010, Vol. 15, p. 330

7 Conclusions

The problem of lacking genericsised medicines in small markets exists. Our mapping exercise showed a connection between the availability of medicines in a given market and the overall "attractiveness" of the product and/or the market and the regulatory conditions there.

In September 2010 no generic versions were marketed in 30 European countries for three (Aztreonam, Apraclonidine and Rifabutin) out of the eleven claimed off-patent active substances analysed (cf. section 2.3.2 on methodology). For the remaining eight molecules at least one generic or biosimilar follower, irrespective of strength and pack size, was available in at least one of the EU/EEA countries. In 13 countries we found five generics out of the eleven substances on the market, but in a few countries we found hardly generics at all.

Availability of generics was especially low in the Baltics as well as in the Czech Republic, Slovenia, Hungary Bulgaria, Romania and Iceland. This was due to the fact that also no originator versions of the selected active substances were marketed in these countries. This does not necessarily explain the lack of generics as especially for Flumazenil in the Czech Republic, in Denmark; in Estonia and in Malta only generic followers were included in the national reimbursement systems. Germany was the country with the highest number of generic alternatives for the eleven active substances (n=7). The analysis indicated that the likelihood of followers being marketed is higher in countries with higher purchasing power.

Consequently, the often quoted threshold of 11.8 million EUR[34] as critical market size to attract followers in a market could not be verified, not even as rule of thumb. The decision to produce a generic version of a medicine depends more on other factors than the actual market size, a very important one being the complexity of the molecule and of course also the complexity of its presentation / pharmaceutical form. Though all generic manufacturers are able to produce "normal oral forms" as one of our interview partners said, a dedicated manufacturing facility is needed, e.g. to produce a substance like Goserelin that comes a) in a complex form and b) is a hormone.

A larger market potential for complex biological products stimulates competitors better than "simple" products with low volumes like Apraclonidine: For Octreotide – with annual sales in 2008 above 125 million Euro in Europe – 14 competitors were on the market and Somatropin (sales around 135 million Euro) was distributed by ten companies.

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[34] www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009600

A further potential "hurdle" to genericisation besides market size and the advanced technology and input needed to manufacture biological are complex pharmaceutical forms (e.g. implantable sticks) that, sometimes because of additional patents related to the form of the product rather than the chemical molecule or the manufacturing process, could delay the market entry of generics. We recognise the problem of generic manufacturers in hesitating to invest in active substances that require medical devices.

In case of biologicals market barriers are generated through high launch expenses as additional clinical studies are mandatory.

As generics are an effective way to contribute to a more rational use of medicines with the added value of containing pharmaceutical expenditure the lack of marketing in individual countries with small markets is an issue that should be addressed by national authorities. Also the case of generics not being developed might optimally have to be addressed at a supranational level, because the development and marketing is of economic interest for the public payer.

We conclude that especially small markets should aim at providing incentives to generic development and marketing – for instance:

» Promotion of generic prescribing linked with financial incentives
» Tendering should not be awarded for a too long time period
» Mandatory generic substitution for pharmacists linked with possible financial benefits for pharmacists to dispense generics

However, these measures might have substantial implementation costs which should be carefully evaluated before implementing them by reviewing previous experiences – when available – and by carrying out prospective impact analyses and monitoring the results if the policies are actually implemented.

We also conclude that small countries may link their registration requirements e.g. language of the labelling and the leaflets to those of larger neighbouring countries, as this might save generic manufacturer investment costs and thus encourage the launch of followers. Examples of countries that have done so are Malta (to UK) and Luxembourg (to Belgium).

Small countries should also consider that if the cost of marketing a medicine in a small country is relatively higher than in a larger market because of the production of small batches or delivering small orders, it might not be feasible to impose local prices at the same or at a lower level than those of larger markets. This is also a frequent criterion in the context of price regulation based on external price referencing, unless the small country's cost differential is somehow subsidised or compensated. Unlike originators, which enjoy a larger profit margin as a result of market exclusivity and

later of brand loyalty, generic manufactures must compete on prices and usually operate with tighter profit margins.

Summarising, our analyses showed that there is a lack of followers for some medicines in some – especially smaller – markets and in countries with less purchasing power. But we also learned that there is a variety of possible policy measures – that carefully need to be customised to the needs and system framework of the given market – to stimulate the development and launch of followers.

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9 Annexes

9.1 Response by EGA on the list of 11 active substances

EGA commented the selection as follows:

There are no specific objections regarding your choice of products, but possible reasons for late and limited generic competition are:

» Octreotide: Complex biological product
» Somatropin: Complex biological product
» Leuprorelin: Complex biological product
» Flumazenil: Low sales
» Aztronam: Low sales (and dedicated facilities)
» Cilastatin + Imipenem: Low sales (and dedicated facilities)
» Teicoplanin: Low sales (and dedicated facilities)
» Rifabutin: Low sales, low price (and dedicated facilities)
» Apraclonidine: Low sales and low price
» Fentanyl: Complex pharmaceutical dosage form
» Goserelin: Complex pharmaceutical dosage form

There are various reasons for limited generic competition for the selected products. The most common reasons are technical barriers, low sales and increased investment for development, and as such are inherently less open to competition. The generic industry in Europe has developed considerably in the recent years. There were very few European generic companies that had capabilities of marketing complex products and products that needed dedicated manufacturing facilities. The regulatory pathway was also not well defined for biological products. With highly developed, global pharmaceutical industry and well defined regulatory pathways we can expect a competitive generic market for these complex products in the near future. For products with low sales however, developing a generic version in general doesn‘t make sense. We would also add that some of the assumptions around patent dates for these products seem incorrect, and in addition to some of the more complex biology products included in this study, there is substantial uncertainty about the regular pathway and about the standards required for regulatory approval.[35]

[35] Note of authors: patent expiry is based on IMS data of 2008

As for Latvia, only 5 of the products are marketed in Latvia and generics are available only for 2 of them. The rest of the products are not marketed and sometimes even registered in Latvia.

In addition, EGA sent direct comments from some of their members:

None of the mentioned countries is considered an interesting generic market to enter, but due to historical reasons, some generic companies are present on these markets; eg high legal and regulatory entry barriers in Belgium, Cyprus with strong market share of local industry and originator products.

The actual barriers for a generic company to enter a market is the market size and expected price. Development costs, including for registration, are in general not barriers, since we are developing for multiple countries, and all these markets can be accessed via DCP, CP and MRP procedures (although the national phase in Cyprus can be horrendous). However, there is potentially some improvement to be made in the regulatory process in the smaller markets, specifically allowing for a reduced scale, accelerated regulatory process for companies to include the smaller countries at a later date after we have commercialised the product elsewhere. Reduced in-country delays would increase the attractiveness of these markets as would any steps available to reduce the administration required in order to market a product, such as immediate pricing & reimbursement.

One initiative that could increase access in the smaller markets for smaller products would be for the smaller Member States to allow the use of the same packaging in those markets where those products have the same underlying market authorisation. A good example of this is Malta which allows use of the UK packages.

Other basic conditions to trigger generic entry to a market, besides critical market size and volumes, are the policy incentives (supply side/demand side).

As for Latvia, this topic is very critical, because of in accordance to the latest official data from 4,296 products registered only 3,152 are really available on the market, which means that 23 % are not marketed.

Finally, EGA nominated representatives from four generic companies present in all Member States, namely Actavis, Teva Pharmaceuticals, Sandoz and Mylan. In addition, three national generic associations – from Belgium, Norway and Latvia – were recommended.

9.2 Interviews with representatives of the generics industry

In order to obtain the perspective of the generics industry on the issue of low volume and small size generics a semi-structured questionnaire was designed and sent to a list of companies and manufacturers associations, which was suggested by EGA. They were sent a presentation letter with a brief description of the study objectives, a list of the 11 molecules selected for the analysis and a questionnaire. They were offered to respond to the questionnaire in writing or at a telephone conference. As a result four interviews were made with two representatives of generic companies and two of national generic manufacturers associations. In addition, a background interview war made with another national generic association, EGA was involved in the discussion as well.

A summary of the answers to the eight questions is summarised below, first the answers made by all or most respondents and afterwards those made by one or two of them.

Summary of the answers

1. *Which factors does a generics company take into account when considering the potential development of a medicine? Please list up to three factors in order of priority.*

Market potential. Technical feasibility of development (not requiring dedicated facilities). Adjustment to the current portfolio of the company. Timeliness of expected launch, i.e. possibility of having the product ready by the end of the originator's exclusivity period.

Factors mentioned by some respondents were the availability of active ingredient of good quality. Expected profitability (revenues minus costs over the product's lifecycle)

2. *Which factors does a generics company take into account when considering the potential launching of a product in a given (country) market? Please list up to three factors in order of priority*

Market potential (according to originators sales of the medicine and to the value of the therapeutic group). Number of expected competitors. Pricing and reimbursement policies. Timeliness of launch. Patent situation.

3. *Do companies use any formula or algorithms that take into consideration the said factors in order to assist decisions on developing and launching generics*?

The answer varied. Respondents mentioned the use of a present value calculations to support a business case. The elements considered are predicted development cost, cost of goods, sales at launch, price erosion, generic penetration and market share.

4. *Is there a critical market size / threshold in terms of sales or volume under which a generic is not likely to be developed or marketed?*

It depends on the company and on the development costs. One responded suggested that less than 7.5 Mio. / USD 10 Mio. would probably be a too low figure for making the product attractive. A second one said that sales of the originator before patent expire below 20 EUR Mio. in the big EU markets would probably in future make the development of a generic impossible.

5. *Which European markets would you consider as small or low volume generic markets?*

Countries indicated by all respondents were: Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta, Slovakia and Slovenia

Countries indicated by some, but not all respondents were: Belgium, Bulgaria, Greece, Ireland, Netherlands, Norway, Romania, and Switzerland.

6. *Which regulatory procedures or other factors present entry barriers to (small) markets for your companies? Please list in order of priority*

High regulatory fees. Lengthy and costly administrative pricing and reimbursement procedures. Requirement of package in national language. It is sometimes difficult to place all the information required in a multilingual package. Small orders (it is sometimes difficult to merge orders from several (small) countries because the dispensing habits – and consequently the pack sizes – differ across countries. Reduction of originator's prices to generic entry. Price control at entry based on external reference pricing leading to a too low price. Compulsory price decreases lined to originator. Frequent changes and long-term unpredictability of regulations. Extension of patent protection and threat of patent litigation by originators. One respondent (multinational company) mentions discrimination against foreign companies. It also suggests as an option for small countries to link authorisation and pricing and reimbursement procedures and packaging language to a large country, such as done by Luxembourg (with Belgium) and Malta (with UK)

7. *What would be the basic conditions in terms of policy incentives to trigger generic development and create competition in the case of small market generics? List examples with respect to pricing, reimbursement, prescribing, dispensing, patients behaviour, and others in order of priority.*

Limited compulsory price reductions. Increased incentives to prescribers and pharmacists. Information campaigns to patients and professionals. Removal of pricing and reimbursement administrative costs. Set up and enforce clear/strict legislation and rules (terms and conditions) for reimbursement. Reimburse only the lowest price of a ERP group of equivalent products.

8. *The list of products in the attached file (Octreotide, Somatropin, Leuprorelin, Flumazenil, Aztreonam, Cilastatin+Imipenem, Teicoplanin, Rifabutin, Apraclonidine, Fentanyl, Goserelin) has been selected as a sample for analysing the problems of small market generics. Could you comment on the validity of that information on the table, especially on the expire dates and whether in your opinion the non-availability problems in some countries might be due to small market or to other factors.*

Several factors that reduce the attractiveness of developing and marketing one or more of the former medicines were mentioned.

a) Some of the products require high technical expertise and are subject to difficult regulatory requirements (e.g. biologicals). According to a respondent, this applies to Octreotide, Somatropin, Leuporelin, Teicoplanin, Fentanyl and Goserelin

b) Products administered through devices (Fentanyl and Goserelin) present an additional barrier, as they require more marketing efforts.

c) Very low sales. This applies to Flumazenil, Aztreonam, Cilastatin + Imipenem, Rifabutin, Apraclonidine.

d) Moreover, antibiotics are not attractive because of usually low prices.

e) In the case of biosimilars, the lack of substitution.

Questionnaire answered by Ms. Julia Pike, Sandoz

1. *Which factors are taken into account by a generics company when considering the potential development of a medicine? Please list up to three factors (in order of priority).*

    1. High value market. (Both global sales and sales in a specific market). How molecule fits in traditional portfolio.
    2. Technical feasibility for making the product (for example, oncology medication), with the equipment. Not requiring dedicated facilities.
    3. If the active ingredient is available at good quality
    4. Expected turn over (Development cost in relation to expected turnover (e.g. patches, inhalators and other administration devices require high development costs).
    5. Development costs (sometime difficult returns)
    6. If the product fix with the portfolio of the company
    7. Timeline. Possibility of having the generic ready by the end of originator's exclusivity.

2. *Which factors are taken into account by a generics company when considering the potential launching of a product in a given (country) market? Please list up to three factors (in order of priority).*

    1. What is the original strategy regulatory? Central procedure. Time limitations for using central procedure (it has additional costs)
    2. Value by sales of the product in that country market.
    3. Number of expected competitors
    4. Generic policies (mainly, pricing and reimbursement of generics). Likely price that will be given to the product. In some countries, there is price cut when the product comes inside the market or external reference pricing of generics. "Branded approach". For some products there might not be automatic substitution. Central and Eastern European countries application of ERP: Lowest price in Europe less 10 %
    5. Costs considered: registration fees; marketing (in small countries the company might not have local branch/office: this adds costs to distribution.
    6. Another problem with some of the smaller markets at the moment is their financial difficulties. Looking for example at a number of the CEE markets, we are often waiting for over a year to be paid for our products. Greece is well

known to pay as much as 2 years late. When the market is already not very attractive, this delayed payment makes it even less attractive.

3. *Do companies use any formula or algorithm when considering the factors you cited above to assist them in making decisions on developing and launching generics?*

They make an estimation of (present) value calculation, taking into account all the previous factors (regulation cost, etc.). Exceptions might be made for strategic purposes in the case of individual products.

4. *Does a critical market size/threshold exist, in terms of sales or volume, under which a generic is unlikely to be developed or marketed?*

No internal rule of thumb. Thinking of the molecule in a global way. Less than 7.5 Mio. EUR/10 Mio. USD might be too low. But it depends of development costs.

5. *Which European markets would you consider to be small or low-volume generic markets?*

Bulgaria, Cyprus, Estonia, Greece, Ireland, Latvia, Lithuania, Luxembourg (but connected to Belgium), Malta (but connected to UK), Romania, Slovakia, Slovenia. Moreover, Greece and Slovakia are considered "distributors" markets and Greece a "strongly branded" market.

6. *Which regulatory procedures or other factors present entry barriers to (small) markets for your companies? Please list them in order of priority.*

    1. Long delays in market authorisation, pricing and reimbursement. Malta and Luxembourg do not need marketing authorization because they accept market authorisation in the UK and Belgium, respectively.
    2. Local companies having preferential treatment.
    3. Differential treatment in pricing (in some Central and Eastern European countries) to local companies.
    4. IP management issues.

7. *In terms of policy incentives for small market generics, what basic conditions would be necessary to trigger generic development and create competition? Please list examples with respect to pricing, reimbursement, prescribing, dispensing, patient behaviour, and others (in order of priority).*

There is a problem with small markets with their own language. Harmonize the marketing authorization and accept pack and labelling from other countries, as Luxembourg and Malta with Belgium and UK. It is not as much the translation of dossiers v. packages, but having to produce small amounts of country-specific packages and leaflets (diseconomies of scale)

8. *The list of products in the attached file (Octreotide, Somatropin, Leuprorelin, Flumazenil, Aztreonam, Cilastatin + Imipenem, Teicoplanin, Rifabutin, Apraclonidine, Fentanyl, Goserelin) has been selected as a sample for analysing the problems of small market generics. Could you comment on the validity of the information contained in the table, particularly on expiration dates and whether, in your opinion, the problems affecting non-availability in some countries might be due to small market or other factors.*

Somatropin (biosimilar) and Teicoplanin: high regulatory requirements in showing quality, effectiveness and bioequivalence.

Leuprorelin and Octreotide: require high level of technical expertise

Cilastatin+Imipenem and Aztreonam: Not attractive as prices of antibiotics is usually very low.

Fentanyl: Difficult technical development (patch). Originators claim that its product is better. It would require substantial marketing efforts.

Goserelin: Double technical difficulty: Hormone and implant.

Questionnaire answered by Ms. Gudbjorg Edda Eggertsdottir, Actavis

1. *Which factors are taken into account by a generics company when considering the potential development of a medicine? Please list up to three factors (in order of priority).*

Financial feasibility, Technical capabilities, Cost/Risk

2. *Which factors are taken into account by a generics company when considering the potential launching of a product in a given (country) market? Please list up to three factors (in order of priority).*

Patent situation, Sales, Generic competition

3. *Do companies use any formula or algorithm when considering the factors you cited above to assist them in making decisions on developing and launching generics?*

Business Case is prepared based upon predicted development cost, cost of goods, sales at launch, price erosion, generic penetration and market share.

4. *Does a critical market size/threshold exist, in terms of sales or volume, under which a generic is unlikely to be developed or marketed?*

Products with annual brand sales below € 20m in the big EU 7 markets would rarely be feasible for generic development.

Minimum order quantities (quantities dependent on product). Sometimes it is possible to combine artwork/packaging (multi-language pack) and orders with other markets.

Sometimes the reference product (from the originator) has been withdrawn from the small market.

Some markets refer to a "price basket" (average of price in certain European countries) resulting in a very low price on the target market.

5. *Which European markets would you consider to be small or low-volume generic markets?*

No answer given.

6. *Which regulatory procedures or other factors present entry barriers to (small) markets for your companies? Please list them in order of priority.*

Local registrations can be expensive and take considerable time. Pricing and reimbursement also takes very long in some countries.

Language requirements. Native language needed on packaging and PIL. The amount of information to be placed on the packaging sometimes makes it difficult to prepare a multi-language packaging.

Different dispensing habits, e.g. dispensing one month supply in one market and three months' supply in another market (e.g. 28 pcs pack and 98 pcs pack) can make it difficult to obtain the product with the pack size that suits the market.

Substitution between different dosage forms e.g. oral dosage forms of tablets, dispersible tablets, capsules etc.

7. *In terms of policy incentives for small market generics, what basic conditions would be necessary to trigger generic development and create competition? Please list examples with respect to pricing, reimbursement, prescribing, dispensing, patient behaviour, and others (in order of priority).*

Generic substitution in pharmacies is essential. Fee for generic substitution and other financial benefits to pharmacies promote generic penetration.

Reimbursement systems: Reimburse only the lowest price and patients pay the difference if a more expensive product is prescribed and/or dispensed.

Tenders should not be awarded for too long time periods.

Generic prescribing promotes generic penetration.

Dose dispensing is in favour of generics.

Harmonization of OTC drugs in Europe would help the smaller markets.

Patient behaviour can be influenced by encouragement of health authorities to use generic products.

8. *The list of products in the attached file (Octreotide, Somatropin, Leuprorelin, Flumazenil, Aztronam, Cilastatin+Imipenem, Teicoplanin, Rifabutin, Apraclonidine, Fentanyl, Goserelin) has been selected as a sample for analysing the problems of small market generics. Could you comment on the validity of the information contained in the table, particularly on expiration dates and whether, in your opinion, the problems affecting non-availability in some countries might be due to small market or other factors.*

The main reasons for lack of competition for the products are the following:

Octreotide, Somatropin, Leuprorelin, Teicoplanin, Fentanyl and Goserelin: Advanced technology, very few generic companies had the capability of developing and producing these products. Recently some generic products have been launched. Generic competition is increasing in this kind of products.

Flumazenil, Aztreonam, Cilastatin+imipenem, Rifabutin and Apraclonidine: The market is very small and few generic companies have found it feasible to develop these products.

9. *Other comments:* The interpretation of article 126A is very different between countries and the interpretation can hinder or promote generic penetration.

Questionnaire answered by the Federation of Belgian Generics Manufacturers

1. *Which factors are taken into account by a generics company when considering the potential development of a medicine? Please list up to three factors (in order of priority).*

- Sales of reference product
- Time to launch: possibility to launch at date of patent expiry
- Portfolio strategy: Type of product/position in current portfolio
- Complexity of development

2. *Which factors are taken into account by a generics company when considering the potential launching of a product in a given (country) market? Please list up to three factors (in order of priority).*

- Evolution market share/sales of reference product and equivalent products (same therapeutic group)
- Time to launch/Number of players for same molecule/Company of reference product to launch its own generic?
- Price/Reimbursement conditions

3. *Do companies use any formula or algorithm when considering the factors you cited above to assist them in making decisions on developing and launching generics?*

Some companies do, depends on company-specific strategy

4. *Does a critical market size/threshold exist, in terms of sales or volume, under which a generic is unlikely to be developed or marketed?*

The threshold is defined on a company-specific basis

5. *Which European markets would you consider to be small or low-volume generic markets?*

Belgium is a low-volume/small-market share generic market. I cannot give information on the other countries.

6. *Which regulatory procedures or other factors present entry barriers to (small) markets for your companies? Please list them in order of priority.*

- Obligatory price decrease of -42 % in comparison to the reference product (too high for small molecules)
- Threats of patent litigation by originator companies
- Extension of market exclusivity for the reference product by filing for an additional 6-months 'paediatric exclusivity' by the reference companies

- Communication Medicines Agency in relation to no-INN for biologicals and no-Switch for molecules with a Narrow Therapeutic Index, oncology medication, etc. (see attachment). In this document, the Medicines Agency recommends not to switch or not to prescribe on INN for certain classes of medicines. This document creates a 'scare' effect for prescribers and there is a tendency now that companies decide not to launch generic medicines anymore of which the molecule is mentioned in this specific document.

- Communication reference companies or Key Opinion Leaders paid by reference companies in relation to generics and biosimilars ('scare tactics' cfr. Report sector inquiry Neelie Kroes)

- Long Price and Reimbursement procedure which can take to 180 days + 2-3 months for publication

7. *In terms of policy incentives for small market generics, what basic conditions would be necessary to trigger generic development and create competition? Please list examples with respect to pricing, reimbursement, prescribing, dispensing, patient behaviour, and others (in order of priority).*

Pricing/Reimbursement

- Limited compulsory price decrease in case of small-market molecules

Prescribing

- Incentives for doctors for cost-effective prescriptions

- Increase the prescription targets for generic medicines

Dispensing

- Identical margin in absolute value for pharmacists when dispensing generics and originator products (at this moment, the pharmacist earns less by dispensing a lower priced, generic medicine)

Patient Behaviour

- Information campaigns of the government towards the patients in relation to generics

Others

- Active information campaigns from authorities towards Health Care Professionals when new small generic molecules are launched

8. *The list of products in the attached file (Octreotide, Somatropin, Leuprorelin, Flumazenil, Aztronam, Cilastatin+Imipenem, Teicoplanin, Rifabutin, Apraclonidine, Fentanyl, Goserelin) has been selected as a sample for analysing the problems of small market generics. Could you comment on the validity of the information contained in*

the table, particularly on expiration dates and whether, in your opinion, the problems affecting non-availability in some countries might be due to small market or other factors.

The patent expiry dates have not been checked.

Octreotide

- One generic on the market in BE

Somatropin

- Biological medicine
- On the No-INN list in BE (see attachment)
- Somatropin Sandoz (Omnitrope) on the market in BE
- Negative communication Key Opinion Leaders in relation to regulatory framework and interchangeability of biosimilars

Leuprorelin

- Cytostatics are on the No-Switch list in BE

Flumazenil

- No generics in BE
- Very low sales

Aztreonam

- No generics in BE
- Very low sales

Cilastatin+Imipenem

- No generics in BE
- No information available

Teicoplanin

- No generics in BE
- No information available

Rifabutin

- No generics in BE
- Very low sales

Apraclonidine

- No generics in BE
- Very low sales

Fentanyl

- Fentanyl is on the No-Switch list when dealing with a difference in duration of application

Goserelin

- No generics in BE
- No information available

9. *Other comments.*

Questionnaire answered by the Latvian Generics Manufacturers Association

1. *Which factors are taken into account by a generics company when considering the potential development of a medicine? Please list up to three factors (in order of priority).*

a) Company expertise in selected field:. market (volume, structure etc.), market potential of the molecule; potential market size
b) Market potential: competitors activities, strong evidence based data about the molecule, potential number of competitors
c) Market growth: prices and compensation level, synergy of portfolio Licensing

2. *Which factors are taken into account by a generics company when considering the potential launching of a product in a given (country) market? Please list up to three factors (in order of priority).*

a) Market potential: Market (volume, structure etc.), Market potential, Market potential: originator product's or molecule's market share and sales, Potential market size
b) Representation in selected field/niche: Prices and availability of compensation, Possibility to put individual product in particular niche, Number of potential competitors (molecules, companies), Reimbursement conditions
c) Expected profitability: Competitors (quantity of generics in the market etc.), Pricing situation, Reimbursement conditions, Competitors and price level

3. *Do companies use any formula or algorithm when considering the factors you cited above to assist them in making decisions on developing and launching generics?*

YES, those are only my personal comments as a country manager

4. *Does a critical market size/threshold exist, in terms of sales or volume, under which a generic is unlikely to be developed or marketed?*

YES, depends from local market; not possible to compare with other markets. Depends on country, company turnover in the country, sales force allocation.

5. *Which European markets would you consider to be small or low-volume generic markets?*

Belgium, Bulgaria, Estonia, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Slovakia, Slovenia, Switzerland

6. *Which regulatory procedures or other factors present entry barriers to (small) markets for your companies? Please list them in order of priority*.

1. High regulatory fees to Authorities: One of the highest registration fee and annual fee, package in national language, patent prolongation or supplementary protection certificates, administrative high costs in the case of reimbursement application

2. Long reimbursement procedure: expertise fee for medicine including in compensation list, small volumes of initial orders compared with minimal quantity possible, decrease of Originator product price along with first generic entry in market to generic price level, reimbursement yearly maintenance fees
3. Blockade by originators, artificial pricing: market/sector depends on laws and regulations and their un-predictability in a long term, fees for entered to reimbursement list, weak Government support, annual maintenance fees for registered products
4. Too sharp uncontrolled price erosion: often changes in the regulatory framework negatively affect producers' activities
5. Lack of resources to change customer's habits within branded market;

Vertical integration, liberalised pharmacy market and power of mask monopoly situations

7. *In terms of policy incentives for small market generics, what basic conditions would be necessary to trigger generic development and create competition? Please list examples with respect to pricing, reimbursement, prescribing, dispensing, patient behaviour, and others (in order of priority).*
1. Dispensing: improving of inspection of pharmacy market to avoid illegal activities by competitors, PR company for cost saving from country and patient side, strong Government support for generics: strict legislation, strictly defined terms and conditions for inclusion in reimbursement list, educational activities, control, to exclude administrative costs in reimbursement
2. Reimbursement: to improve compensation budget and system, to avoid often changes in pricing, PR company for quality from generics company, patient Organisation participation in education of patients, automatic inclusion in the reimbursement list after price application, but without additional submission
3. Behaviour: to avoid prescribing of INN, brand name prescribing,
4. Fees to Authorities: to improve patient behaviour
5. To strengthen compliance of ethical code by companies, pharmacy chains and physicians

8. *The list of products in the attached file (Octreotide, Somatropin, Leuprorelin, Flumazenil, Aztronam, Cilastatin+Imipenem, Teicoplanin, Rifabutin, Apraclonidine, Fentanyl, Goserelin) has been selected as a sample for analysing the problems of small market generics. Could you comment on the validity of the information contained in the table, particularly on expiration dates and whether, in your opinion, the problems affecting non-availability in some countries might be due to small market or other factors.*
Mainly small markets & type of access path (few originator loyal KOLs – high prescribers the same time); Our company is not working in these markets. Majority of those products are presented on Latvian market and reason should be small market size and limited reimbursement situation

9.3 Results of the statistical analysis

This chapter contains the data and research outcomes of the statistical analysis of factors determining genericisation in table format. The finings are summarised in section 4.4

Table 9.1
List of independent (demographic and economic) variables

Indicator	Definition	Source
Population	Population in a country as of 1 July of the year 2008.	WHO HFA DB[36]
Price level index for pharmaceuticals (PLI)	The PLI for a country indicates its price level compared to the average price level of the 25 countries that made up the EU in 2005.	EUROSTAT [37]
Gross National Income (GNI)	Gross expenditure on the final uses of the domestic supply of goods and services valued at purchasers values less imports of goods and services.	World Bank Database[38]
Total expenditure on health as % of GDP	Level of total expenditure on health expressed as a percentage of gross domestic product (GDP) (year 2008).	WHO HFA DB[26]
Per capita expenditure on health	Total expenditure on health Expressed in Purchasing power parity (PPP) international dollar (year 2008).	WHO HFA DB[26]
Per capita general government expenditure on health	Level of public expenditure[39] on health expressed in Purchasing power parity (PPP) international dollar (year 2008).	WHO HFA DB[26]
Pharmaceutical market value	Pharmaceutical sales, at ex-factory prices, through all distribution channels (pharmacies, hospitals, dispensing doctors, supermarkets, etc.), whether dispensed on prescription or at the patient's request. Samples and sales of veterinary medicines are excluded (year 2007 in € million).	EFPIA[40]

All raw data are available from ESIP's research team

Source: ESAP 2010

36 http://data.euro.who.int/hfadb/

37 http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/

38 http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf

39 Public health expenditure incurred by public funds (state, regional and local government bodies and social security schemes). Cf. health expenditure.

40 http://www.efpia.org/Content/Default.asp

Table 9.2
Descriptive analysis of the countries' characteristic (n=30)

	Mean (SD)	Range
Population	16913.07 (22341.33)	315 – 82264
Pharmaceutical market value	4849.38 (7106.80)	77 – 25501
GNI per capita	28460.67 (11537.99)	10620 – 59250
Price level indices for pharmaceutical products	96.55 (25.60)	68 – 187
Total expenditure on health as % of GDP	8.19 (1.72)	4.7– 11.8
Per capita total expenditure on health	2773.60 (1302.40)	592 – 5734
Per capita government expenditure on health	2107.80 (1146.55)	475 – 5212
Ind 1	0.2907 (0.15)	0.1 –0.7
Ind 2	0.398 (0.17)	0.1 – 0.9
Ind 3	1.286 (1.01)	0.11 – 4.80

Source: EASP 2010

Table 9.3
Generic policies applied in the countries (n=29)

		N (%)
Generic Price Control (Manufacturer level)	No	4 (13.8 %)
	Yes	25 (86.2 %)
International price comparison for generics	No	10 (34.5 %)
	Yes	19 (65.5 %)
Pricing a/o Reimbursement decision linked to originator	No	12 (41.4 %)
	Yes	17 (58.6 %)
Tendering-like practices applied in the outpatient sector	No	25 (86.2 %)
	Yes	4 (13.8 %)
Reference Price System	No	7 (24.1 %)
	Yes	22 (75.9 %)
Accelerated/specific procedure in place for pricing a/o reimbursement decision	No	13 (59.1 %)
	Yes	9 (40.9 %)
INN prescribing	No	13 (13.8 %)
	Yes	25 (86.2 %)
Pharmacists generic substitution	No	8 (27.6 %)
	Yes	21 (72.4 %)

Source: EASP 2010

Table 9.4
Demo-economic characteristics of the countries (n=30)

Country	Population (in thousand)	Pharmaceutical market value	GNI*	Price level indices	Total expenditure on health % GNI	total expenditure on health+	Government expenditure on health+	Index1	Index2	Index3
Austria	8.337	2.736	37.360	107	10,1	3.763	2.875	0,27	0,27	0,91
Belgium	10.590	3.932	35.380	106	9,4	3.323	2.461	0,18	0,45	0,73
Bulgaria	7.593	542	11.370	72	7,4	835	477	0,13	0,13	0,25
Cyprus	862	174	24.980	102	6,6	3.034	1.383	0,17	0,33	0,33
Czech Re	10.319	1.586	22.890	71	6,8	1.626	1.385	0,10	0,10	1,10
Germany	82.264	25.241	35.950	128	10,4	3.588	2.758	0,60	0,70	1,30
Denmark	5.458	1.860	37.530	121	9,8	3.513	2.968	0,20	0,40	0,29
Estonia	1.341	137	19.320	79	5,4	1.094	836	0,17	0,33	1,36
Spain	44.486	13.209	30.830	77	8,5	2.671	1.917	0,27	0,36	2,00
Finland	5.304	1.848	35.940	111	8,2	2.840	2.120	0,27	0,36	4,80
France	62.036	25.501	33.280	91	11,0	3.709	2.930	0,44	0,56	0,57
Greece	11.137	5.503	28.300	73	6,6	2.727	1.646	0,11	0,44	1,13
Hungary	10.012	1.955	18.210	74	7,4	1.419	997	0,29	0,29	2,82
Ireland	4.437	1.902	35.710	119	7,6	3.424	2.762	0,25	0,25	0,50
Italy	59.604	16.734	30.800	118	8,7	2.686	2.056	0,45	0,55	0,90
Lithuania	3.321	404	17.170	70	6,2	1.178	860	0,50	0,50	1,80
Latvia	2.259	257	16.010	79	6,5	1.112	663	0,20	0,20	1,50
Luxembourg	481	na	52.770	103	7,1	5.734	5.212	0,13	0,25	2,88
Malta	407	77	20.580	106	7,5	4.053	3.140	0,70	0,90	0,83
Netherlands	16.528	4.616	10.620	109	9,0	3.509	2.878	0,40	0,50	1,33
Poland	38.104	4.237	16.710	68	6,4	1.035	733	0,50	0,63	2,00
Portugal	10.677	3.490	22.330	94	10,0	2.284	1.613	0,29	0,29	0,11
Romania	21.361	1.601	13.380	70	4,7	592	475	0,30	0,30	1,82
Sweden	9.205	3.052	37.780	95	9,1	3.323	2.716	0,27	0,45	1,90
Slovenia	2.015	487	27.160	86	7,9	2.099	1.501	0,11	0,11	1,30
Slovakia	5.400	846	21.460	71	7,7	1.555	1.040	0,17	0,50	0,14
U K	61.231	14.493	36.240	93	8,4	2.992	2.446	0,45	0,45	1,00
Norway	4.767	1.360	59.250	120	8,9	4.763	4.005	0,30	0,50	0,20
Iceland	315	126	25.300	na	11,8	4.310	3.763	0,14	0,29	0,43
Switzerland	7.541	2.726	39.210	187	10,8	4.417	2.618	0,36	0,55	2,36

Source: EASP 2010

Table 9.5
Generic policies applied in the countries (n=29)

Country	Generic Price Control	International Price Comparison	P/R decision #	Tendering-like practices†	Pharmacists generic substitution	INN prescrib-ing	Procedure for pricing a/o reimbursement decision	Reference Price System
Austria	No	No	Yes	No	Yes	No	No	No
Belgium	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Bulgaria	Yes	No	Yes	Yes	No	No	Yes	n.a
Cyprus	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Czech Rep	Yes	Yes	Yes	Yes	Yes	No	Yes	n.a
Germany	Yes	Yes	No	No	No	Yes	Yes	No
Denmark	Yes	No	No	No	No	No	Yes	Yes
Estonia	Yes	Yes	Yes	Yes	Yes	No	Yes	n.a
Spain	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Finland	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
France	Yes	Yes	Yes	No	Yes	No	Yes	No
Greece	No	No	Yes	No	Yes	No	Yes	n.a
Hungary	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Ireland	Yes	No	Yes	Yes	No	No	No	No
Italy	Yes	Yes	Yes	Yes	Yes	No	Yes	n.a
Lithuania	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Latvia	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Luxembourg	Yes	No	Yes	Yes	Yes	No	No	No
Malta	Yes	Yes	No	No	No	Yes	Yes	n.a
Netherlands	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Poland	Yes	Yes	Yes	Yes	Yes	No	Yes	n.a
Portugal	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Romania	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Sweden	No	Yes	Yes	No	No	No	No	Yes
Slovenia	Yes	Yes	Yes	Yes	No	No	Yes	No
Slovakia	Yes	Yes	Yes	Yes	No	No	Yes	Yes
U K	Yes	No	No	No	No	No	No	No
Norway	Yes	Yes	Yes	No	No	No	Yes	No
Iceland	No	Yes	Yes	Yes	Yes	No	No	No

Source: EASP 2010

Table 9.6
Association between the countries socioeconomic characteristic and the competition indicators

	Ind 1		Ind 2		Ind 3	
	β	p	β	p	β	p
Pharmaceutical market value	0.000	0.008	0.000	0.031	0.000	0.837
Population	0.000	0.002	0.000	0.024	0.000	0.894
Gross national income per capita	0.000	0.778	0.000	0.572	0.000	0.715
Price level indices for pharmaceutical products	0.001	0.194	0.002	0.079	0.002	0.817
Total expenditure on health as % of GDP	0.014	0.425	0.023	0.241	−0.128	0.249
Per capita total expenditure on health	0.000	0.546	0.000	0.111	0.000	0.838
Per capita government expenditure on health	0.000	0.578	0.000	0.195	0.000	0.893

Source: EASP 2010

Table 9.7
Association between the variables related to the generic policies and the competition indicators

		Ind 1		Ind 2		Ind 3	
		β	p	β	p	β	p
Generic Price Control (Manufacturer level)	No Yes	−0.231	0.004	−0.255	0.006	0.457	0.413
International price comparison for generics	No Yes	−0.114	0.061	−0.158	0.021	0.236	0.562
Pricing a/o Reimbursement decision linked to originator	No Yes	−0.056	0.357	−0.076	0.266	−0.562	0.145
Tendering-like practices applied in the outpatient sector	No Yes	0.208	0.011	0.249	0.007	−0.350	0.523
Reference Price System	No Yes	0.064	0.359	0.086	0.273	0.0150	0.741
Accelerated/specific procedure in place for pricing a/o reimbursement decision	No Yes	−0.037	0.517	0.038	0.528	0.405	0.371
International non-proprietary name	No Yes	0.105	0.218	0.035	0.723	0.182	0.746
Pharmacists generic substitution	No Yes	0.101	0.122	0.087	0.251	0.398	0.355

Source: EASP 2010

Table 9.8

Bivariate analysis of the countries characteristic and the availability of individual medicine

	Flumazenil		Aztreonam		Cilastatin+Imipenem		Teicoplanin		Rifabutin		Apraclonidine	
	β	p	β	p	β	p	β	p	β	p	β	p
Population	0.000	0.236	0.000	0.164	0.000	0.142	0.000	0.397	0.000	0.095	0.000	0.322
Pharmaceutical market value	0.000	0.411	0.000	0.170	0.000	0.126	0.000	0.644	0.000	0.116	0.000	0.194
Gross National income per capita	0.000	0.942	0.000	0.098	0.000	0.292	0.000	0.095	0.000	0.057	0.000	0.003
Price level indices for pharmaceutical products	0.007	0.729	0.026	0.218	0.016	0.390	0.041	0.123	0.066	0.014	0.117	0.003
Total expenditure on health as % of GDP	0.319	0.312	0.448	0.098	0.259	0.286	0.022	0.928	0.399	0.106	0.466	0.068
Per capita total expenditure on health	0.000	0.959	0.000	0.412	0.000	0.430	0.000	0.217	0.001	0.022	0.002	0.004
Per capita government expenditure on health	0.000	0.804	0.000	0.545	0.000	0.645	0.001	0.178	0.001	0.018	0.002	0.003

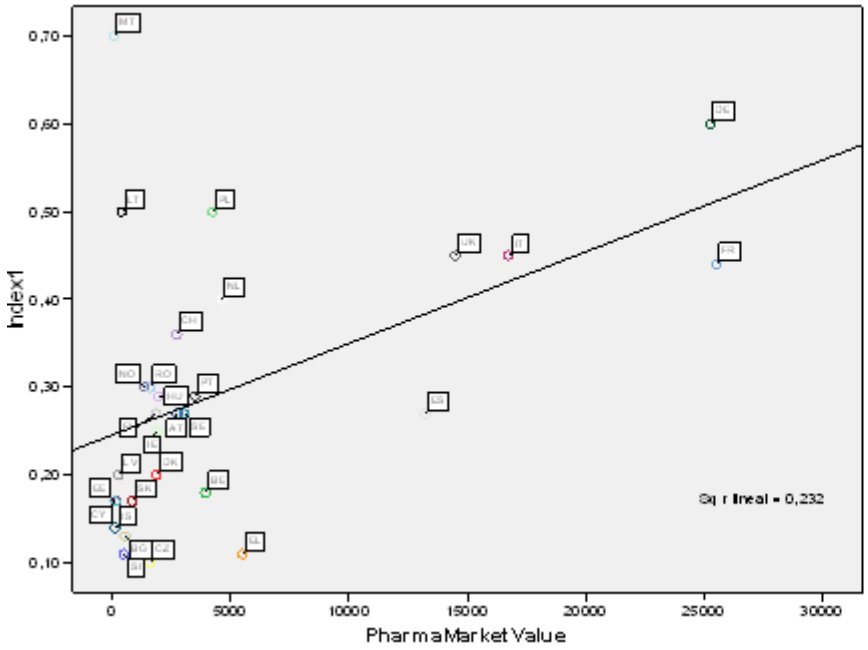
Source: EASP 2010

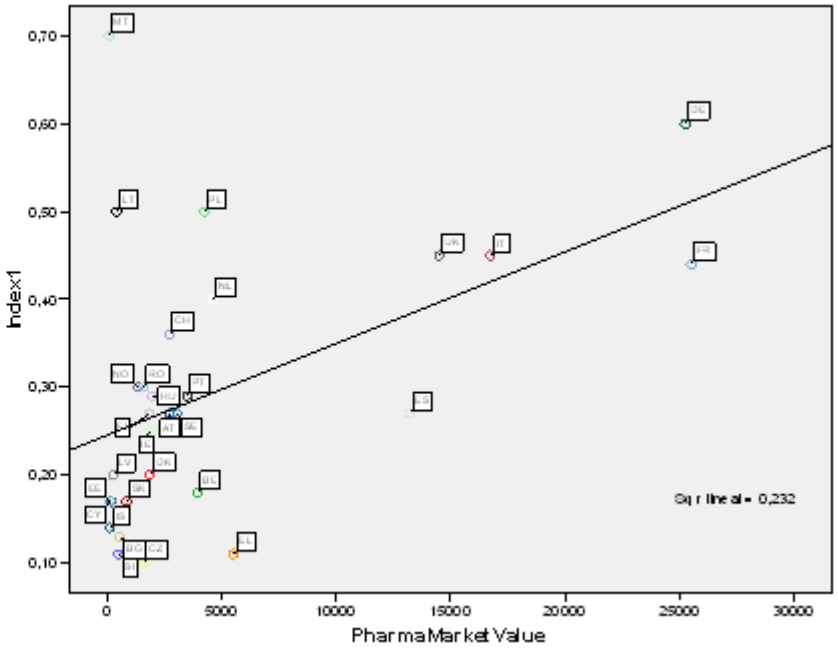
Table 9.9
Bivariate analysis of the generic policies and the availability of individual medicines

		Flumazenil		Aztreonam		Cilastatin & Imipenem		Teicoplanin		Rifabutin		Apraclonidine	
		β	p	β	p			β	p	β	p	β	p
Generic Price Control (Manufacturer level)	No Yes	-19.817	0.999	-20.962	0.999	0.754	0.488	-20.449	0.999	-21.283	0.999	-21.444	0.999
International price comparison for generics	No Yes	-20.173	0.999	-2.185	0.059	-0.308	0.713	-1.658	0.152	-0.953	0.251	-1.925	0.037
Pricing a/o Reimbursement decision linked to originator	No Yes	-1.219	0.306	-0.863	0.300	0.539	0.496	-2.041	0.077	-0.811	0.300	-1.705	0.042
Tendering-like practices applied in the outpatient sector	No Yes	19.817	0.999	-1.269	0.327	0.523	0.670	0.154	0.901	1.019	0.405	1.179	0.335
Reference Price System	No Yes	0.930	0.372	0.981	0.272	-0.357	0.706	0.065	0.947	-0.916	0.329	-1.099	0.242
Accelerated/specific procedure in place for pricing a/o reimbursement decision	No Yes	1.269	0.298	0.639	0.448	-0.588	0.514	0.783	0.426	0.539	0.549	0.847	0.346
International non-proprietary name	No Yes	-19.817	0.999	-0.762	0.534	-20.797	0.999	-0.154	0.901	0.241	0.823	-1.179	0.335
Pharmacists generic substitution	No Yes	0.693	0.500	-0.898	0.335	0.916	0.285	-20.717	0.999	-1.194	0.197	-2.431	0.036

Source: EASP 2010

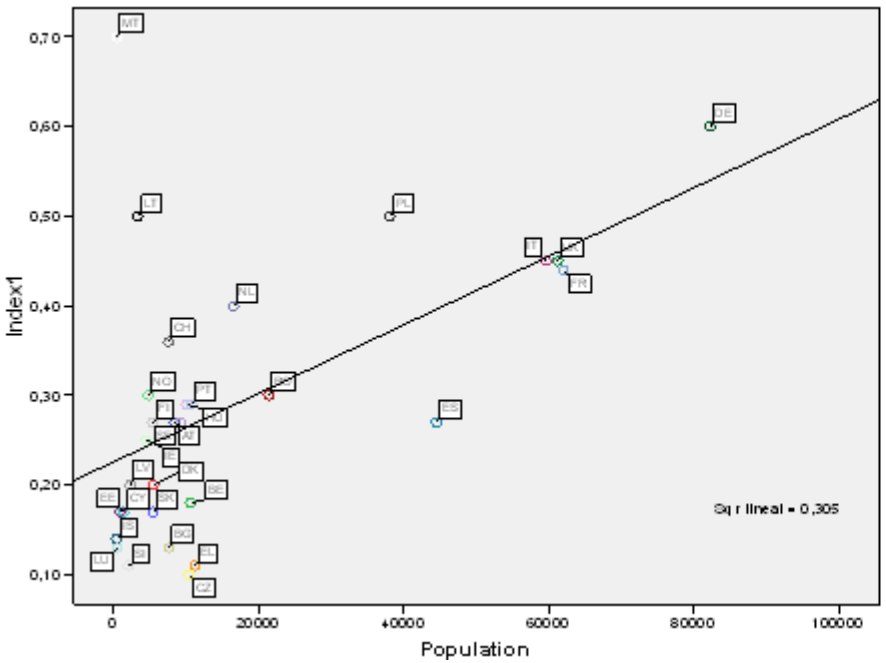
Table 9.10.
Association between competition indicators 1 and 2 and the pharmaceutical market value

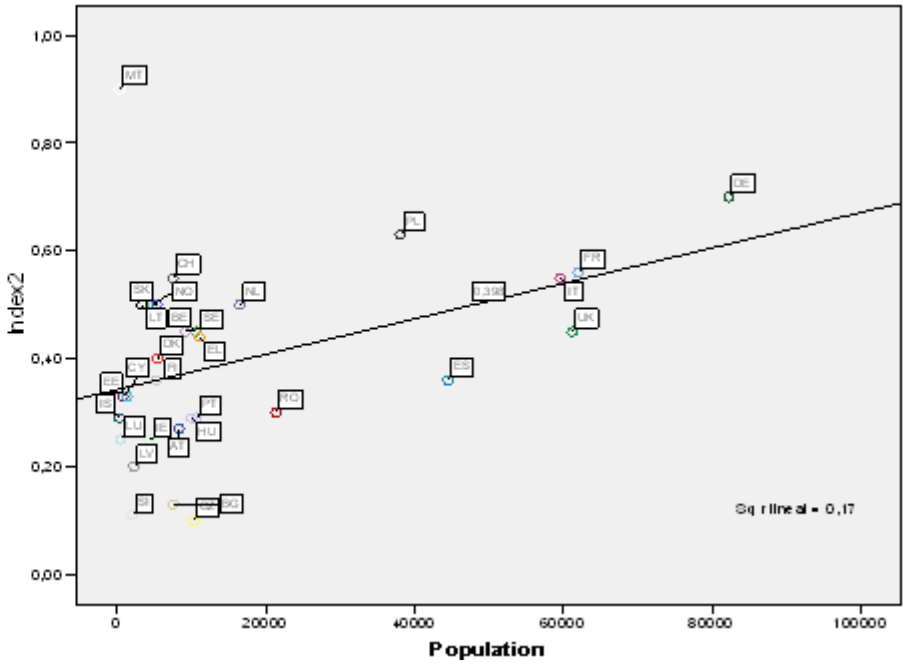




Source: EASP 2010

Graph 9.1
Association between competition indicators 1 and 2 and population size





Source: EASP 2010

Table 9.11

Number of observations for each medicine used in the country/product pair analysis

	Numbers (%)
Apraclodine	1 (0,9 %)
Aztreonam	2 (1,8 %)
Cilastatin plus Imipenem	9 (8,3 %)
Fentanyl	29 (26,6 %)
Flumazenil	16 (14,7 %)
Goserelin	4 (3,7 %)
Leuprorelin	7 (6,4 %)
Octreotide	15 (13,8 %)
Rifabutin	1 (0,9 %)
Somatropin	22 (20,2 %)
Teicoplanin	3 (2,8 %)

Source: EASP 2010

Table 9.12

Number of observations for each country used in the country/product pair analysis

	Numbers (%)			Numbers (%)
Austria	3 (2,8 %)		Lithuania	2 (1,8 %)
Belgium	5 (4,6 %)		Luxembourg	2 (1,8 %)
Bulgaria	1 (0,9 %)		Malta	8 (7,3 %)
Cyprus	3 (2,8 %)		Netherlands	5 (4,6 %)
Czech Rep	2 (1,8 %)		Norway	5 (4,6 %)
Denmark	4 (3,7 %)		Poland	5 (4,6 %)
Estonia	2 (1,8 %)		Portugal	1 (0,9 %)
Finland	4 (3,7 %)		Romania	3 (2,8 %)
France	5 (4,6 %)		Slovakia	3 (2,8 %)
Germany	7 (6,4 %)		Slovenia	1 (0,9 %)
Greece	4 (3,7 %)		Spain	4 (3,7 %)
Hungary	2 (1,8 %)		Sweden	5 (4,6 %)
Iceland	2 (1,8 %)		Switzerland	6 (5,5 %)
Ireland	2 (1,8 %)		U K	5 (4,6 %)
Italy	7 (6,4 %)			
Latvia	1 (0,9 %)			

Source: EASP 2010

Table 9.13
Analysis of the association of comp ind 3 (number of generic medicines in the markets with availability) and demo-economics characteristic

	OR (IC95 %)*	p
Population	1.000013 (1.000009 – 1.000016)	<0.001
Pharmaceutical market value	1.000034 (1.000023 – 1.000045)	<0.001
Gross National Income per capita	1.000007 (0.9999976 – 1.000016)	0.146
Price level indices for pharmaceutical products	1.00039 (0.9966392 – 1.004155)	0.839
Total expenditure on health as % of GNP	1.077758 (1.009936 – 1.150135)	0.024
Per capita total expenditure on health	0.9999448 (0.9998549 – 1.000035)	0.230
Per capita government expenditure on health	0.9999851 (0.9998789 – 1.000091)	0.783
Sales	1.001974 (1.00143 – 1.002517)	<0.001

*: Odds Ratio with confidence intervals 95 %.

Source: EASP 2010

Table 9.14
Analysis of the association of comp ind 3 (number of generic medicines in the markets with availability) and the generic policies applied

		OR (IC95 %)*	p
Generic Price Control (Manufacturer level)	No Yes	0.8047401 (0.6347654 – 1.02023)	0.073
International price comparison for generics	No Yes	0.9750842 (0.7888231 – 1. 205326)	0.816
Pricing a/o Reimbursement decision linked to originator	No Yes	0.7686932 (0.621369 – 0.9509474)	0.015
Tendering-like practices applied in the outpatient sector	No Yes	1.006865 (0.7813021 – 1.297548)	0.958
Reference Price System	No Yes	1.004566 (0.7756929 – 1.30097)	0.972
Accelerated/specific procedure in place for pricing a/o reimbursement decision	No Yes	0.8851258 (0.6923328 – 1.131606)	0.330
INN prescribing	No Yes	1.341448 (0.9497724 – 1.894647)	0.095
Pharmacists generic substitution	No Yes	1.186261 (0.9194192 – 1.530548)	0.189

*: Odds Ratio with confidence intervals 95 %.

Source: EASP 2010

Table 9.15
Multivariate analysis of the factors that explain comp ind 3 (number of generic medicines on the market)

	OR (IC95 %)*	p
Population	1.00003 (1.000018 – 1.000042)	<0.001
Pharmaceutical market value	0.9999488 (0.9999087 – 0.9999889)	0.012
Sales	1.00245 (1.001893 – 1.003008)	<0.001
Gross national income per capita	1.00001 (1 – 1.000022)	0.043

*: Odds Ratio with confidence intervals 95 %.

Source: EASP 2010

Table 9.16
Originator and generic availability a given market (country and product pair).

Country	Octreotide	Somatropin	Leuprorelin	Flumazenil	Aztreonam	Cil + Imip	Teicoplanin	Rifabutin	Apraclodine	Fentanyl	Goserelin
AT	1	1	3	3	3	3	3	3	3	1	3
BE	2	1	2	2	3	3	3	3	3	1	3
BG	3	3	3	3	3	6	3	6	6	1	3
CY	3	3	6	4	6	3	6	6	6	2	3
CZ	3	1	3	3	3	3	3	3	6	1	3
DE	1	1	1	1		1	3	3	3	1	2
DK	2	1	3	5	3	6	3	3	3	1	3
EE	6	3	3	4	6	3	6	6	6	2	3
ES	1	3	3	1	3	2	3	3	3	1	3
FI	2	1	3	1	3	3	3	3	3	1	3
FR	2	1	3	1	3	1	6	3	6	1	3
EL	6	2	2	3	3	4	3	6	3	2	3
HU	1	3	3	3	6	6	3	6	6	4	3
IE	3	1	3	6	6	6	3	3	3	1	3
IT	1	1	3	1	3	1	2	3	3	1	3
LT	6	1	3	6	6	6	6	6	6	1	3
LV	3	3	3	6	6	6	6	6	6	4	3
LU	3	1	3	6	6	6	3	3	3	2	3
MT	5	3	2	4	4	6	4	4	4	4	4
NL	1	1	3	1	6	2	3	3	3	1	3
PL	2	1	3	1	6	1	3	6	6	1	3

PT	3	1	3	6	3	6	6	6	6	1	3
RO	3	1	3	3	3	1	3	3	6	1	3
SE	2	1	2	1	3	3	3	3	3	1	3
SI	3	3	3	3	3	3	3	6	6	4	3
SK	3	1	2	3	6	6	6	6	6	5	3
UK	1	1	3	1	3	3	3	3	3	1	4
NO	2	1	2	1	3	3	3	6	3	1	3
IS	3	1	3	3	6	3	6	6	6	2	3

Source: EASP 2010

Table 9.17
Availability, competition indicators, sales and patent expiry dates of the medicines in the countries.

Country	Octreotide	Somatropin	Leuprorelin	Flumazenil	Aztreonam	Cil + Imip	Teicoplanin	Rifabutin	Apraclodine	Fentanyl	Goserelin
Availability	26	30	29	25	18	20	22	17	16	30	30
Index 1	0,27	0,70	0,03	0,56	0,06	0,30	0,05	0,06	0,06	0,80	0,10
Index 2	0,54	0,73	0,28	0,64	0,06	0,40	0,14	0,06	0,06	1,00	0,13
Index 3	0,8148	2,4667	0,2759	2,16	0,13333	0,8095	0,136	0,056	0,06	5,1	0,133
Sales	123,7	132,7	183,7	1,8	1,5	5,6	10,5	1,5	2,9	465,8	131,4
First Patent exp	2000	2006	2001	2000	2001	2000	2001	2000	2003	2005	2001
Last Patent exp	2006	2007	2007	2007	2004	2006	2006	2003	2007	2007	2006

Source: EASP 2010

Table 9.18
Number of followers in each market where the medicine is available

Country	Octreotide	Somatropin	Leuprorelin	Flumazenil	Aztreonam	Ci + Imip	Teicoplanin	Rifabutin	Apra-clodine	Fentanyl	Goserelin
AT	2	3	0	0	0	0	0	0	0	5	0
BE	1	2	1	0	0	0	0	0	0	4	0
BG	0	0	0	0	0		0			2	0
CY	0	0		1		0				1	0
CZ	0	5	0	0	0	0	0	0		6	0
DK	1	3	0	3	0		0	0	0	6	0
EE		0	0	1	0	0				1	0
FI	1	4	0	3	0	0	0	0	0	7	0
FR	1	5	0	4	0	2		0		6	0
DE	3	5	2	8		2	0	0	0	27	1
EL		1	1	0		1	0			1	0
IE	0	3	0				0	0	0	6	0
IT	4	7	0	4	1	5	1	0	0	9	0
LU	0	3	0				0	0	0	1	0
MT	1	0	1	1	1		1	1	1	1	1
NL	2	4	0	4		1	0	0	0	7	0
NO	1	4	1	4	0	0	0		0	5	0
PL	1	4	0	4		2	0			12	0
PT	0	2	0		0					3	0
RO	0	4	0	0		3	0	0		5	0
SK	0	4	1	0						7	0

SI	0	0	0	0	0	0	0			1	0
ES	3	0	0	8	0	1	0	0	0	8	0
SE	1	5	1	4		0	0	0	0	8	0
CH	0	2	1	2		0	1	0	0	6	1
HU	0	0	0	0			0			1	0
LT		2	0							2	0

Empty cells means that the drug is not available

Source: EASP 2010 based on PPI query summer 2010

9.4 Factsheets of 11 active substances

Active substance	Octreotide	**Originator brand name**	Sandostatin©
ATC code	H01CB02, Hypthalamic hormones	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	~ 90 EUR
Patent expiry in Europe	Ranges from 2000/11 – 2006/03	**Total originator sales 12 months prior to patent expiry* (IMS)**	125 Mio EUR
Pharmaceutical forms and strengths	Ampoule: 0.05mg/ml, 0.1mg/ml, 0.5mg/ml (Solution for injection or concentrate for solution for infusion) Vial: 1mg (0.2mg/ml), 5mg (1mg/ml) (Solution for injection or concentrate for solution for infusion)	**Originator company** **Further distributors**	Novartis Novo Nordisk, Ratiopharm, Hospira/Mayne, Bendalis, Hexal, GP Pharm EFG, Toscina, Italfarmaco, Chemi SpA, Lifepharma, Sandoz, AAH Pharmaceuticals, Sun Pharma-ceuticals

* IMS average cost per unit as well as total sales include Sandostatin and Sandostatin LAR

Active substance	Somatropin	**Originator brand name**	Genotropin©, Genotropin Miniquick©, Genotonorm©
ATC code	H01AC01, growth hormones	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	168 EUR
Patent expiry in Europe	Ranges from 2006/03 - 2007/10	**Total originator sales 12 months prior to patent expiry* (IMS)**	133 Mio EUR
Pharmaceutical forms and strengths	Pre-filled syringe: 0.2mg, 0.4mg, 0.6mg, 0.8mg, 1mg, 1.2mg, 1.4mg, 1.6mg, 1.8mg, 2mg; Refill cartridge: 5mg, 12mg	**Originator company** **Further distributors**	Pfizer and Eli Lilly Novo Nordisk, Sandoz, Merck/Serono, Ipsen, Ferring, Schwarz Pharma, Valeas, Biopartners

Active substance	Leuprorelin	**Originator brand name**	Daronda©, Ginecrin©, Lucrin©, Procren©, Procrin©
ATC code	L02AE02, cytostatic hormones	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	288 EUR
Patent expiry in Europe	Ranges from 2001/04 - 2007/11	**Total originator sales 12 months prior to patent expiry* (IMS)**	183 Mio EUR
Pharmaceutical forms and strengths	Powder with solution: 3.75mg, 11.25mg; Pre-filled syringe: 1mg; Vial: 14mg 5mg/ml	**Originator company** **Further distributors**	Abbott Sandoz, Hexal, Vianex, Orion

Active substance	Flumazenil	**Originator brand name**	Anexate©, Lanexat©, Mazicon©
ATC code	V03AB25, all other CNS drugs	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	19 EUR
Patent expiry in Europe	Ranges from 2000/09 - 2007/02	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 1.78 Mio EUR
Pharmaceutical forms and strengths	Ampoules: 0.5mg, 1mg; Vials: 0.5mg (0.1mg/ml)	**Originator company** **Further distributors**	Roche B. Braun, Mylan, Biokanol, Actavis, Hexal, Hikma Pharma, Frensenius, TEVA, Inresa, Matrix, Pharmaselect, Genfarma, Baggerman, Combino Pham, GES EFG, Fresenius Kabi, Aguettant, Hameln, Pharmachemie, Bowmed

Active substance	Aztreonam	**Originator brand name**	Azactam©
ATC code	J01DF01, OTH B-LACTAM EX PEN, CEPH	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	21.5 EUR
Patent expiry in Europe	Ranges from 20021/02 - 2004/01	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 1.5 Mio EUR
Pharmaceutical forms and strengths	Powder with/without solution: 0.5 g, 1g, 2g	**Originator company** **Further distributors**	BMS -

Active substance	Cilastatin + Imipenem	**Originator brand name**	Primaxin©, Tienam©, Conet©, Zienam©
ATC code	J01DH51, OTH B-LACTAM EX PEN, CEPH	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	15 EUR
Patent expiry in Europe	Ranges from 2000/09 - 2006/01	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 5.6 Mio EUR
Pharmaceutical forms and strengths	250mg/250mg; 500mg/500mg; 750mg/750mg	**Originator company** **Further distributors**	Merck & Co Mylan, Hexal, Fresenius, Teva, Ranbaxy, Sigmatau

Active substance	Teicoplanin	**Originator brand name**	Targocid©
ATC code	J01XA02, other Antibacterials	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	52 EUR
Patent expiry in Europe	Ranges from 2001/02- 2006/05	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 10.5 Mio EUR
Pharmaceutical forms and strengths	Powder with/without solution: 100mg, 200mg, 400mg	**Originator company** **Further distributors**	Sanofi-Aventis Teva

Active substance	Rifabutin	**Originator brand name**	Mycobutin©, Ansatipin©, Ansatipine©
ATC code	J04AB04, Rifampicin and Rifamycin	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	3.2 EUR
Patent expiry in Europe	Ranges from 2000/12 - 2003/06	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 1.5 Mio EUR
Pharmaceutical forms and strengths	Capsules:150mg	**Originator company** **Further distributors**	Pfizer -

Active substance	Apraclodine	**Originator brand name**	Iopidine©
ATC code	S01EA03, Miotics and Antiglauc. Preps	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	0.2 EUR
Patent expiry in Europe	Ranges from 2003/03 - 2007/11	**Total originator sales 12 months prior to patent expiry* (IMS)**	~ 3 Mio EUR
Pharmaceutical forms and strengths	Eye drops: 0.5 %, 1 %; Single dose pipettes: 1mg, 2.5mg	**Originator company** **Further distributors**	Alcon / Johnson & Johnson -

Active substance	Fentanyl	**Originator brand name**	Haldid©, Leptanal©
ATC code	N01AH01, narcotic analgesics	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	~ 11 EUR
Patent expiry in Europe	Ranges from 2005/07 - 2007/06	**Total originator sales 12 months prior to patent expiry* (IMS)**	Great variations in sales: in DE up to 250 Mio EUR and in CH only 6.4 Mio EUR
Pharmaceutical forms and strengths	Ampoules: 0.1mg, 0.5mg	**Originator company** **Further distributors**	Johnson & Johnson Actavis, 1A Pharma, Hexal, Sandoz, AWD Matrix, Swedish Orphan, B.Braun, Cephalon Nycomed, Nycomed), Richter, Ratiopharm, Mibel, Aluid, Betapharm, Mylan, Esparma, Heumann-Pharma, Krewel, Riemser, Stadapharma, Winthrop, CT Arzneimittel, Acino Pharma

Active substance	Goserelin	**Originator brand name**	Zoladex©
ATC code	L02AE03, cytostatic hormones	**Average cost per IMS standard unit prior to patent expiry* (IMS)**	307 EUR
Patent expiry in Europe	Ranges from 2001/12 – 2006/01	**Total originator sales 12 months prior to patent expiry* (IMS)**	120 Mio EUR
Pharmaceutical forms and strengths	Pre-filled syringe: 3.6mg (1 month), 10.8mg (3 months)	**Originator company** **Further distributors**	Astra Zeneca Cell Pharma, Genus Pharmaceuticals, Acino Pharma

9.5 Literature review

9.5.1 Literature search

The problems of generics of low volume drugs and generics in small markets do not seem to have been often addressed as a topic in itself in the literature and therefore there are no appropriate descriptors to make the search. A literature search was carried out in Pubmed using the expressions “generic medicine” (descriptor) and “small area” (no descriptor) and yielded 14 hits.

Additional searches were done combining “drug generics” with the following expressions: generic entry, generic competition, barriers, obstacles and small countries. This second set of searches gave 292 additional hits. Most of the references initially selected neither dealt with low sales generics nor with small markets and were therefore not directly relevant to this study. A few of them were retained as they address issues or reached conclusions which can indirectly provide some evidence or policy suggestions on the issues addressed here.

The selection of references, based on the title and the abstract, reduced the number of references retained to 11 articles:

Bae, J.P. Drug patent expirations and the speed of generic entry. Health Serv Res. 32(1): 87-101, April 1997

Dylst, P; Simoens, S. Generic Medicine Pricing Policies in Europe: Current Status and Impact. Pharmaceuticals 2010, 3, 471-481: pending review)

Editorial Countering delays in introduction of generic drugs. The Lancet. Vol. 359, Issue 9302, Pages 181, 19 January 2002

Garattini L; Tediosi F. A. comparative analysis of generics markets in five European countries. Health Policy; 51(3):149-62, April 2000

Godman B et al. Use of Generics – A critical Cost Containment Measure for All Healthcare professionals in Europe? Pharmaceuticals, 3, 2470-2494, 2010

Kaplan, Warren A and Laing, Richard Paying for Pharmaceutical registration in developing countries, HEALTH POLICY AND PLANNING; 18(3): 237-248 © Oxford University Press, 2003

King DR, Kanavos P. Encouraging the use of generic medicines: implications for transition economies. Croat Med J;43(4):462-9, August 2002

Magazzini L., Pammolli M. Dynamic Competition in Pharmaceuticals. Patent Expiry, Generic Penetration, and Industry Structure European Journal of Health Economics, Vol. 5, No. 2, pp. 175-182, 2004

Scott Morton, Fiona M., Entry Decisions in the Generic Pharmaceutical Industry (May 1997). Available at SSRN: http://ssrn.com/abstract=10992

Simoens S. Generic medicine pricing in Europe: current issues and future perspective. Journal of Medical Economics, Vol. 11, No. 1 : Pages 171-175, March 2008

Simoens S. International comparison of generic medicine prices. Curr Med Res Opin;23(11):2647-54, November 2007

Moreover, some grey literature studies previously know by the authors were included in the review. Especially relevant for this analysis were the following reports and surveys:

European Commission, DG Competition, Pharmaceutical Sector Inquiry, July 2009

UK Department of Health and Association of the British Pharmaceutical Industry. PPRS: The Study into the extent of competition in the supply of branded medicines to the NHS, 2002

IMS Report 2010 "Generic medicines: essential contributors to the long-term health of society", 2010

Bongers F and Carradinha H. How to Increase Patient access to Generic Medicines in European Healthcare Systems. EGA (European Generic Medicines Association), June 2009

EMINet 2009. Generic Matrix 2009, www.emi-net.eu

9.5.2 Summary of relevant findings

The main findings of the references found in the literature search which are relevant for this report are summarised below. References are presented according to the reviewer's judgement of its relevance for the present study.

DOH and the BPI, PPRS: The Study into the extent of competition in the supply of branded medicines to the NHS, Component 3, Competition on the Out-of-Patent Sector (2002).

The main publication found on the topic is a chapter of a broader study on the PPRS by the DOH and the BPI: Component 3, Competition on the Out-of-Patent Sector whose objective was ".. to chart the speed of availability and penetration of generics for products that have recently come off patent or which come off patent during the new scheme ..".

The key questions addressed were: "Overall, what was the scale of generic entry in product markets where the patent expired? What were the actual and potential savings for the NHS? Why did generic entry occur in some cases and not in others? Were there significant barriers to entry in certain cases? How fast was generic entry? Why was it faster in some cases than others? What happened to prices when generics entered the market?"

The study started with 137 chemical entities, which were identified as having lost patent protection in the UK between 1990 and 2000, but focussed on the 28 products which had "a Net Ingredient Cost (NIC) of at least GBP 3 million (EUR 3.5 Mio.) in the year in which their patent expired, since the major generic companies have said they are unlikely to be interested in smaller markets. These 28 products accounted for 82 % of total expenditure in 2000 on all products that have come off patent since 1990. "Out of these top 28 products, 22 are listed as having generic suppliers according to Chemist & Druggist's Generic List April – September 2001." By contrast, only 25 out of the 109 "minor" products are listed as having generic suppliers. In total, 47 out of 137 (some 34 %) of products are listed as having generic alternatives. 21 products were discontinued." The study also states that "IMS Retail data suggests that this is an under-estimate as it shows 42 % of products more than 10 years old have a generic alternative. The proportion decreases with total size of sales but is still 32 % for products with annual sales of less than GBP 100,000 (EUR 118,000)". The main findings of the study are: "several conditions seem to be necessary to ensure effective generic competition once a product comes off patent: the market needs to be very large (an annual turn-over of at least GBP 10 million (EUR 11.8 Mio.), the product needs to have a certain level of generic prescribing, the manufacturing process must be relatively straightforward, and there must not be other major inhibiting factors; most significant products (with an annual net ingredient cost (NIC) of GBP 3 million or more at the time of patent expiry) face some generic competition but the extent of generic entry is variable. In total, only 47 out of 137 products showed any generic entry by the end of 2000. 21 products had been discontinued and two products had recent patent expiry; the impact of generic entry has been variable; of the 28 significant products, four experienced generic erosion of 40 % or more (by value as opposed to volume), six between 20 % and 30 % and 14 products experienced no generic erosion or of less

than 20 %. The remaining four products were excluded either because the patent has only just expired, or because the product was withdrawn or because the market was substantially affected by decisions made by the Advisory Committee on Drugs; of the 109 smaller products with an annual NIC of less than GBP 3 million (EUR 3.5 Mio.), in only three cases (domperidone, dobutamine hydrochloride and mecillinam) has there been a significant impact on prices (25 % or more); even where generic entry has occurred, it has often been slow to make an impression on drug tariff prices although actual prices may have fallen more quickly than shown by this analysis. The top five products on the list are now showing substantial savings for the NHS from generic competition, but the price of four of the five only fell significantly at least one or two years after their respective patents expired. Ten other significant products have faced generic entry, but without a significant fall in price (less than 10 %). It appears that large-scale generic entry is needed to generate genuine price competition; overall expenditure on those products that came off patent between 1990 and 2000 is estimated to have been around a quarter lower than it would have been in the absence of generic competition; 124 analysis of individual products has identified some of the reasons why generic competition may be less effective in some markets than others, including the size of the market (generic companies are not interested in small markets), complexity/cost of manufacturing process, existence of additional manufacture/process patents, the significance of modified release forms, licensing procedures/requirements, nature of the product, variable generic prescribing rates, uncertainties created by court cases and availability of parallel imports/OTCs."

The findings or the DOH/BPI study are certainly relevant for our analysis. However, the fact that the study was restricted to the NHS market – a large market with a well established generics policy – limits the possibility of extrapolating the results to most European countries, especially to small markets with weak or poorly designed generic policies.

Pharmaceutical Sector Inquiry (2009)

The Pharmaceutical Sector Inquiry offered some relevant information on the entry of generics in EU countries. Impact of Generic Entry and Regulatory Factors Affecting Generic Competition addresses the overall impact of generic entry of the medicines that faced loss of exclusivity in the period 2000-2007. The analysis is based on a list of 75 high sales medicines.

The report analyses both the characteristics of generic entry – time to entry of generic companies, number of companies, etc – as well as the estimated effects on prices and market distribution. The analysis often provides the results for 17 EU Member States and by global volume of sales, and discusses the role that a small global or national market seems to have on the development and up-take of generics. The analysis

provides both descriptive statistics and econometric analysis of part of the relationships assessed.

The share of the medicines of the said list launched in the period 2000-2006 and experiencing generic competition in the first year after patent expiry was 46 % in number terms and 69 % in terms of market value in the 12 months before expiry. In the analysis by size the results show that the medicines in the lowest quintile the value share is approximately 25 %, while for the highest quintile it goes up to over 80 %. The results of the econometric regression analysis confirm that high sales value is associated with generic entry. Other variables that characterise the regulatory environment and are also positively associated to generic entry are compulsory substitution by pharmacist, absence of caps or compulsory discounts to generic medicines.

Unfortunately, this part of the analysis does not include the smaller markets and is therefore of limited utility to our study. In any case, in the 17 countries included, the share of generic entry by country does not show a clear association between market size and generic entry.

Time to entry (the gap between the INN in question lost exclusivity and the first generic entry) was found to be 13 month on average. Again there is a clear market size gradient in this variable: between 18 and 20 months for the medicines in the 3 lower quintiles, that drops to approximately 8 and 4 months for the second and first quintile, respectively. Regression analysis confirms these findings and the positive effect of regulatory variables such as compulsory substitution, physician's incentives to generic prescription and the absence of generic price regulation.

The degree of generic competition can be approximated by the number of generic companies in the market for a given product. According to the analysis of the Sector Inquiry one year after patent expiry that number rises on average to seven companies and after three years it goes beyond nine. There is again the expected market size gradient: the number of companies in the highest quintile is almost four times greater than that in the lowest quintile. The medicines market size becomes clearly a driver of competition when the number of generic companies by country is compared. The five larger EU markets (Germany, France, Italy, UK and Spain) plus the Netherlands and Portugal have more than six companies per INN on average.

Finally, the Sectors Inquiry analyses the impact of generic entry on prices and on generic penetration. The results show that generics enter the market on average at a price slightly under 80 % of the originators' price. Moreover, after three years the prices of both the originator and the generics have dropped on average to about 75 % and 55 %, respectively, of the originators' price at generic entry. The evolution of prices varies substantially across countries. As the analysis is done in terms of relative prices, it is difficult to explain the reasons for the variability found and the potential

role and interplay of regulation and competition. For instance, small decreases might be associated to lack of competition, but they can also be due to a strong regulation of the originator's price, which leaves less room for price competition after patent expiry.

The generic penetration rate in the first and second year is respectively 30 % and 45 % in terms of volume and 25 % and 38 % in terms of value. The results highlight large variations across countries. Germany is the country with the highest generic penetration in value two years after the first generic entry, 70 %, followed by the Czech Republic. Four countries (AT, DK, PT and the UK) attained penetration rates. At the other end of the continuum, three countries (EL, LU and IE) did not attain a 10 % penetration rate. As the report notes: Regression analysis suggests that regulatory policies requiring pharmacists to dispense generic products when available and encouraging doctors to prescribe the substance (as opposed to a particular brand), tend to have a positive effect on the degree of generic drug penetration. The same holds for policies involving reimbursement of medicines at the level of the lowest priced product and a frequent adjustment of reimbursement levels to take account of price developments in the market. By contrast, the analysis indicates that policies involving price caps/mandatory discounts for generics appears to reduce the level of generic penetration relative to the regimes without such price caps/mandatory discounts.

EGA. How to Increase Patient access to Generic Medicines in European Healthcare Systems. (2009)

A recent report by the EGA (2009) states that the key barriers to generic medicines when entering the European markets are mostly the result of inadequate policies: failure of governments to create long-term generic medicines policies, linkage of generic prices to originators/reference product prices, delays in pricing and reimbursement decisions, lack of appropriate incentives for physicians, pharmacist and patients to prescribe, dispense and request generic medicines.

The EGA report does not explicitly mention or address the issues of small sales volume or small markets as a barrier to generic entry. In fact, Figure 4 of the report shows that generic penetration seems unrelated to market size: three out of seven countries where generics have a market share lower than 20 %, Italy, Spain and France, are among the five largest European markets. And several countries than can probably labelled as "small pharmaceutical markets", Slovenia, Romania and Latvia, have a generic market share in the 60 %-80 % range.

IMS Report 2010. Generic medicines: essential contributors to the long-term health of society (2010)

Similarly, a recent report by IMS (2010) also point to the limited penetration of generics in some large markets, such as Italy and Spain and it further suggests that "Reducing the price of generic medicines in low volume markets can severely challenge the sector's sustainability. In these countries the cost of maintaining the essential infrastructure related to registration costs, pharmacovigilance and other legal requirements will not be covered by the revenues generated." The right way to promoting generics is by removing barriers and implementing policies that increase the demand for generics.

Bae (1997)

Based on a study of the factors that influence the speed and likelihood of generic drug entries which analysed 81 drugs that lost patent between 1987 and 1994 (in the US market?) using a proportional hazard method, Bae (Drug patent expirations and the speed of generic entry) found a negative relationship between an innovative drug's sales revenue and the time to generic entry. It also found that entry is slower when there is either very few of or a large number of competing brands and quicker for products that treat chronic conditions. He finally found that time to entry increased between 1987 and 1994.

Scott Morton (1997)

The author using data of generic entry between 1984 and 1994 concludes that larger revenue markets, markets with more hospital sales and products that treat chronic conditions attract more entry.

Magazzini et al (2004)

The article analyses products containing major molecules whose patent expired between 1987 and 1998 in four countries (USA, UK, Germany and France) and concluded that penetration by generic drugs tends to be more limited in countries that rely on administered prices in comparison to countries that rely on market-based competition.

King and Kanavos (2002)

Based on the review of experience of mature generic markets in developing countries (Canada, Denmark, Germany, Netherlands, the United Kingdom and the United States) King and Kanavos (Encouraging the use of generic medicines: implications for transition economies) offer a list of policy options for decision makers in Central and Eastern European Economies in transition)

Garattini and Tediosi (2000)

The authors suggest that common practice rather that regulations, which are highly harmonised, explain the differences in approval times among the countries analysed (France, Germany, Italy, Netherlands and the United Kingdom).
They point to the fact that no country has an efficient public information system on patent expiry and that financing has not been widely used to favour generics. Financial incentives have focussed on physicians rather than on pharmacists. They also find that generics have had more success in countries with flexible pricing policies. They conclude that a free market of wholesalers and pharmacists might enhance a comparative market and stimulate the success of unbranded generics.

Simoens (2007)

The author made an international comparison of generic drugs (15 molecules / strengths) in nine European countries and India in 2005 and found that India and the Scandinavian countries had the lowest prices. Prices varied by a factor of 3 to 36 and were usually higher in countries that adopt a free market approach and have a mature generic medicine market.

The Lancet, Editorial (2002)

Editorial of The Lancet highlighted some of the tactics used by originators to delay the entry of generics in the US: obtaining new patents on their products – e.g. for new claims that that an ingredient has active properties, or for new uses of the drug, testing the drug in children, which allows a 6-months patent extension, reaching agreements with generic companies in order to delay the entry of a generic version or falsely listing a patent claim.

Kaplan and Laing (2003)

In relation to the possibility of registration fees being an obstacle to marketing generics it is curious to note that Kaplan and Laing in their study Paying for Pharmaceutical registration in developing countries, conclude that "Our analysis suggests little relationship between DRA registration fees and drug approval times in developing countries" and that "developing countries could charge between 1-5 times their GNP per capita or between USD 17.000 and 80,000 for each USD 1000 spent per capita on public health"

9.5.3 Conclusions

The DOH-BPI (2002) study had objectives quite similar to those of the present study. However, it referred only to the UK, and its conclusions – such as the mentioned

annual turn-over threshold of at least GBP 3-10 million (Euro 3.5 to 11.8 Mio.) to make a market attractive to generic companies - cannot easily be extrapolated to other countries, especially not to small markets. On the other hand, the said thresholds mentioned in the report seem to refer only to the UK market. Being the UK one of the leading generic markets in Europe, it makes sense that companies are able to define the attractiveness of developing a generic according to the expected UK sales. But multinational generic companies are more likely to consider a broader set of country markets when making their product development decisions, as has been suggested by respondents to our survey.

The Pharmaceutical Sector Inquiry (2009) provides interesting information on the dynamics of the generics markets. Unfortunately, small markets are almost not represented in the 17 countries analysed in the Inquiry. In fact only four of these 17 countries (Belgium, Greece, Luxembourg, Netherlands) can somehow be included in the definition of small markets, but none of the more obvious "small markets" in Europe (such as Cyprus, Estonia, Latvia, Lithuania, Malta, Slovakia and Slovenia) were included in the data analysis. As a consequence the otherwise valuable information provided does not shed any light on the dynamics of small generic markets.

The EGA (2009) and IMS (2010) reports do not add much evidence to the topic of small markets, other that highlighting the fact that the degree of penetration/market share of generics is not unequivocally related to market size, as the cases of Italy, Spain and France shows: they are among the five largest European markets, but generic penetration is much lower – below 20 % – than several countries than can probably labelled as "small pharmaceutical markets", such as Slovenia, Romania and Latvia, which have a generic market share in the 60 %-80 % range. This suggests that other factors, probably, generic policies, might have a key role in determining generic penetration than population, income or pharmaceutical market size.

Market size has been associated to generic penetration and early entry by in several empirical studies (Bee, 1997; Scott Morton, 1997). The latter study also found that proportion of hospital sales and indication for a chronic illness are also positively associated to generic penetration.

Regarding policy variables, Magazzini et al. (2004) found that administered prices (price control) leads to lower generic penetration, and Garattini and Tediosi (2000) associate price regulation with speed of entry. Simoens (2007) associates no price control and the existence of a mature generics market with higher market penetration.