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External Price Referencing: A Network Analysis of the 27 European Union Member States

Claire REMY

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Professional advisors: Mme Girard and Mme Bucher, Pierre Fabre

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Abstract

External Price Referencing: a Network Analysis of the European Union

Introduction: In the context of an economic crisis, medicines price is a key concern for both health authorities and pharmaceutical companies. External price referencing - taking into account foreign prices for setting the national price of a new drug- is widely used in the European Union. Understanding price interdependencies is essential in order to support market access decisions, such as launching a new medicine in a country, but also to clarify negotiations between public authorities and medicines producers. This paper aims to provide a general comprehension of the external price referencing system in the European Union (EU), namely by providing an up-to-date overview of reference practices, and by identifying the most influential players. This study was conducted for Pierre Fabre's Pricing and Market Access department.

Material and methods: The study includes the 27 EU Member States. A literature review was conducted to clarify the current state of knowledge. A summary table and reference matrix were updated, which was the basis for network analysis. The primary indicator of influence chosen was the eigenvalue.

Results: Within the very dense European influence network, France, Spain, Germany, Greece, the UK and Italy were identified as the most influential countries in order of eigenvalues, which is in line with the scarce information available in literature. The summary table and reference matrix can be used as tools to analyse the effects of external price referencing when need be.

Conclusions: The use of external price referencing in the EU complicates pricing processes and negotiations, particularly in influential countries. Further research would be necessary to understand influences and identify the needs of both public and private parties in the different Member States to work towards a common European Health technology assessment of new medicines.

Résumé

Le référencement des prix des médicaments étrangers: une analyse de réseau de l'Union Européenne

Introduction: Dans un contexte de crise économique, le prix des médicaments constitue un enjeu majeur pour les autorités de santé et entreprises pharmaceutiques. La prise en compte des prix étrangers lors de la fixation du prix d'un nouveau médicament au niveau national est une pratique majoritaire dans l'Union Européenne. Il est ainsi crucial d'acquérir une meilleure compréhension du système d'influences des prix des médicaments en Europe, afin de soutenir les décisions d'accès au marché au sein des entreprises du médicament, et faciliter les négociations entre autorités publiques et entreprises privées. Cette étude a pour but d'apporter une vue d'ensemble du réseau d'interdépendances des prix dans l'Union Européenne (UE) et d'identifier les pays à forte influence. Cette étude est menée pour le département des Affaires Economiques de Pierre Fabre.

Matériel and méthodes: Les 27 Membres de l'UE ont été retenus. Une revue de littérature a été menée pour identifier l'état de l'art actuel. Un tableau synthétique et une matrice des référencements inter-pays ont été mis à jour et constituent le matériel de base pour l'analyse de réseau. L'indicateur principal d'influence est la valeur propre.

Résultats: Les pays les plus influents du réseau très dense de l'UE par ordre des valeurs propres sont la France, l'Espagne, l'Allemagne, la Grèce, le Royaume-Uni et l'Italie. Ces résultats concordent avec la littérature, bien que celle-ci soit très limitée. Le tableau synthétique et la matrice des référencements peuvent être utilisés comme outils d'analyse.

Conclusion: Le référencement des prix étrangers dans l'UE complexifie la fixation des prix et les négociations nationales, particulièrement dans les pays influents. Une évaluation médico-économique des nouveaux médicaments commune à l'UE nécessiterait plus de recherche sur les influences et les besoins des partis privés et publics dans les différents Etats Membres.

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List of acronyms

EEA: European economic area

EU: European Union

EOF: The Greek national organisation for medicine

EPR: External price referencing

ERP: External reference pricing

G-BA: The German Federal Joint Committee

WHO: World Health Organisation

List of tables and figures

Introduction

In a context of global financial constraint, the cost of medicines is a key concern for both health authorities and pharmaceutical companies. While firms push the prices up in order to sustain their activity, public payers face a dilemma opposing on the one hand the will to reward and encourage innovation, and on the other hand the need to curb public expenditure. Generally speaking, setting the price of a new medicine can reveal a complex business, involving stakeholders with very different interests. Indeed, the highly regulated pharmaceutical market cannot follow a classical economic model where the price level reflects the equilibrium between supply and demand. The price of a new drug usually depends on its clinical benefit relatively to comparable treatments. This was indeed decided in most Member States, which are responsible for pricing medicines entering their national markets.

However, EU Members often take into account prices in other States, most of the time in neighbouring countries or economically comparable countries. This is called ‘external’ or ‘international’ ‘referencing’ and sometimes ‘benchmarking’. The OECD defines external price referencing as ‘the practice of comparing pharmaceutical prices across countries’. It is widely used in the EU: 24 of the 27 Member States use it. Each country has its own rules, defines its own basket of reference countries and its price calculation method. Overall, cross-references result in a complex system of price interdependencies through which countries influence one another.

Most of the time, external referencing is used as supportive information for the pricing decision. Therefore, the external price calculation methods are not always abided by as clear set rules. Prices observed thus differ from what they would be if external referencing was the sole method of pricing, or if its rules were always strictly respected.

It is difficult to quantify the effect that external price referencing can have on a company’s turnover, because price variations are subject to a multitude of factors. Nevertheless, the network of price influence is strong enough to drive decisions such as withdrawing a medicine from a market, as it occurred in Greece during the economic crisis. Entering a national market, withdrawing a drug from a country, or setting a drug launching sequence are thus crucial decisions for pharmaceutical companies, and depend a lot on the knowledge of inter-country influences. It is obviously very valuable for pharmaceutical companies to understand the external price reference system.

Moreover, it is also worthy for health authorities to understand the external price referencing system. Understanding price-interdependencies and to what extent some countries are more influential than others is key information when negotiating with international players and ensuring that a valuable medicine is available in a country.

Since the game of influences in the EU results in a real network of medicine price information flows, it can indeed be analysed as a network, therefore using network theory. This theory is a part of graph theory and has been used in many sciences including biology or computer science. It is more recently used in social sciences and it continues to grow. It will be used in this paper as a mean to assess influences between European prices.

In addition, not only is the European network of price influences dense, but it also changes continuously. Information seeking, and even more up-to-date information seeking, can turn out to be very laborious.

This study was carried out for Pierre Fabre's market access and pricing department, as a Master of Public Health internship project at the EHESP. It aims at providing a general comprehension of the external price referencing (EPR) system in the EU, namely by providing an up-to-date overview of reference practices, and by identifying the most influential players using network analysis.

The outline of this paper is as follows: Material and methods will be presented. Results will be shown and interpreted. Finally, the results of this paper will be discussed along with policy implications.

Material and Methods

Material

It was decided to restrain the analysis to the 27 EU Member States, where cross-country references are very dense. Although external price referencing is used worldwide, interactions within Europe are by themselves very complex. In addition, being a Member of the EU results in sharing common regulatory issues.

Methods

Literature Review

A literature review was conducted in order both to clarify the state of knowledge of the European external pricing system and to extract the material which will be the basis for the analysis. A structured literature review was thus carried out in March 2013 on Sciencedirect, Pubmed and EBSCO databases, using mesh terms (as shown in annex 1). It was further completed with a non-systematic review mostly with documents found on the EU, the WHO or national health authorities' websites, as shown in Figure 1 below.

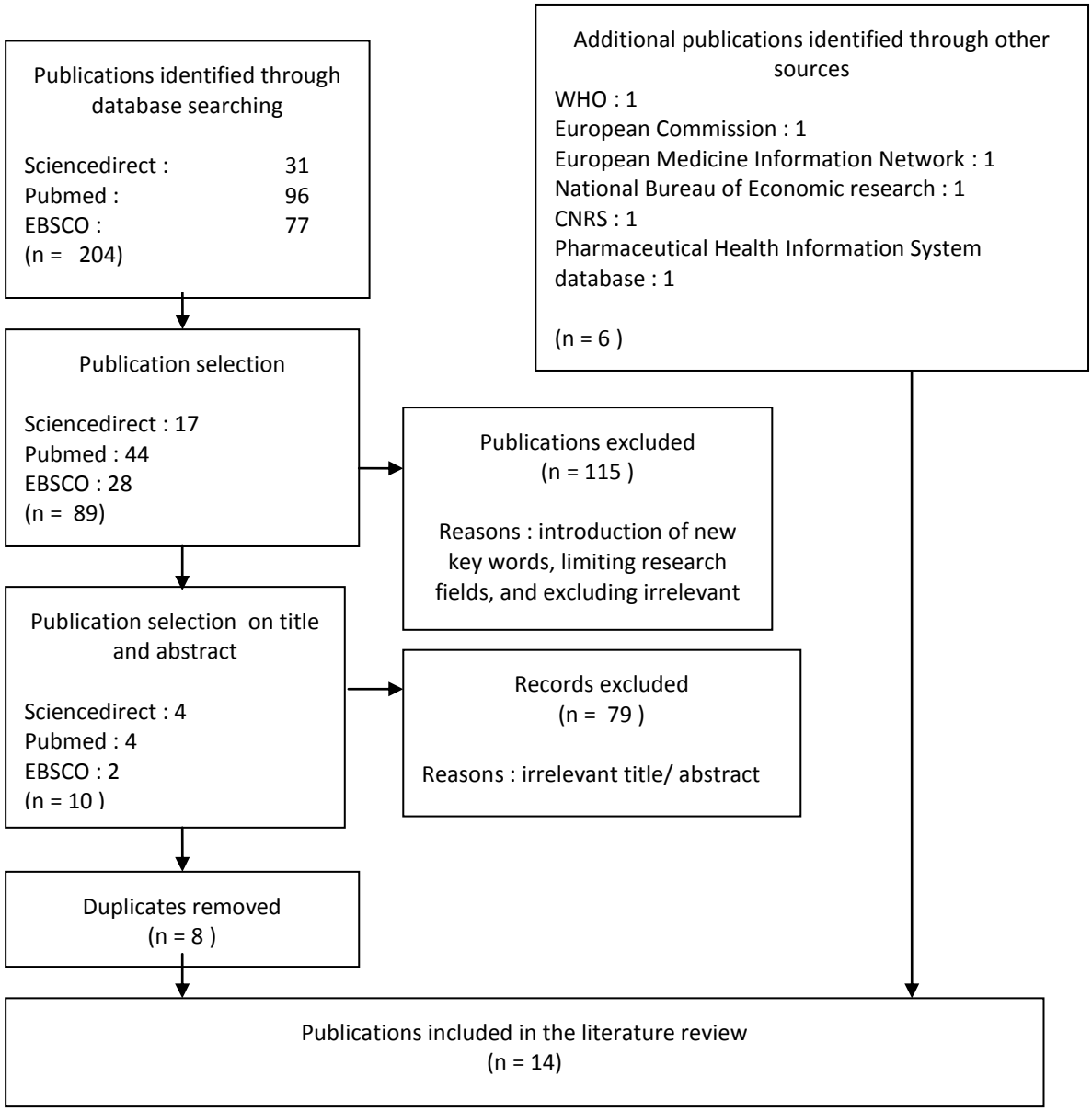

Figure 1: Flow chart of the literature review

Summary table and matrix construction

The aim of the summary table is to provide a descriptive overview of the use of EPR in the EU 27 and of the countries' main characteristics. The matrix will be the basis for the network analysis. Both the summary table and reference matrix of this paper are based on Leopold et al's works (2012), found in an economic paper of the European Commission by Carone et al. (2012) related to "Cost-containment policies in public pharmaceutical spending in the EU".

The table by Leopold et al which summarizes the main characteristics of external price referencing in the EU 27 such as the scope medicines, the price level or the calculation method of the reference price, was adapted to this paper by extracting the main elements and by adding national expenditure per capita and GDP per capita to show the countries' market share and wealth.

In Leopold et al's matrix (annex 3), the EU 27 Member States are put in lines and columns. A coloured box indicates that the country in line references the country in column (and a blank box indicates that the country in column is not referenced by the country in line).

The table and matrix were updated and adapted for this study according to information available in grey literature mostly. The first adaptation of the matrix consists in marking references by the number 1 instead of colouring. In addition, the euro-zone countries were marked for Spain, and the additional countries which appear in the original matrix were not taken into account. Also, Italy takes into account EU prices but has no specified basket of reference countries. While no countries were marked in Leopold et al's matrix, it was decided on the contrary to include all EU countries in Italy's basket. Moreover, regulation has changed in several countries since 2012. The following updates were brought to the table and matrix:

- Slovakia :Tesar (2012), in an article entitled "International reference pricing in the Slovak Republic", wrote that "In the present time, the ex-factory price is fixed at the second lowest price in the EU". This change in the price calculation method was brought to the table.

- Bulgaria: On September, 10th 2012, PMR, a market research and consulting company, stated that "The Bulgarian government has approved an increase in the number of reference countries used in the establishment of the maximum prices of reimbursed medicines on the Positive Drug List […]. Italy, Finland, Denmark and Slovenia have, as a result, been added to the reference countries. The price proposed by the manufacturer cannot now exceed the

equivalent of the lowest producer price of a drug on the reference markets of Denmark, Estonia, Finland, France, Greece, Italy, Lithuania, Portugal, Romania, Slovakia, Slovenia and Spain." The table and matrix were adapted accordingly.

- The case of Greece: The economic turmoil in Greece led the government to change its pricing system in October 2012. It is now value-based (reference price per therapeutic category 4th level). The national organisation for medicine (EOF) announced in 2012 that "The current Greek pricing system is based on the exceptional and harsh economic, social and medical factors that are specific to Greece". Since we do not know how long this 'exceptional situation' will last and whether Greece will one day go back to its previous pricing system, external price referencing was considered not applied. In addition, the EOF required other countries to stop referencing Greek prices the same year: 'The Greek Ministry of Health asks competent Authorities in other Countries not to refer to those prices in their national pricing and reimbursement decision-making process.' However, there is no proof that other countries have abided. Therefore, the reference to Greece in the other scope countries was kept as such.

Portugal: The reference basket changes every year. In 2013, it includes Spain, France and Slovakia. The changes have been made in the matrix accordingly.

Network analysis

The external price referencing system in the EU was analysed according to network theory. It included a graphic visualisation of the network and network measures such as density and centralisation. Influence was calculated by centrality measures: degree, degree '2 steps' and namely eigenvalues, ranging from 0 to 1. In-degree is the reference frequency of a country. It is therefore representative of a country's influence. On the contrary, out-degree is the number of countries included in the reference basket of a State; it is a measure of the influence which a country is subject to. Degree '2 steps' measures direct and indirect ties: a high in-degree '2-steps' thus means that the country is highly referenced directly and indirectly and a high out-degree '2 steps' means that the country is highly influenced both directly and indirectly. In a way, degree '2 steps' can be considered a relevant measure of influence in the long-run because it takes a time for a medicine to have a price in all countries, and sometimes indirect ties are only taken into account after a first round of price revisions, that is to say in a few years time. The third centrality measure, eigenvalue, is usually considered the most relevant measure of influence. It accounts not only for a

country's direct influence, but also for the influence of the countries it is connected to. For example, a State which is referenced by influential countries has more influence than a State which is referenced by non-influential countries. Correlation between centrality measures was studied. Namely, we analysed the link between influencing and being influenced. Finally, we identified the structure of the network, whether a core of influential countries and a periphery of influenced countries exist, or whether countries are grouped in clusters of influence. Clusters were identified via Tabu search, which means that countries have been grouped according to similarities in their ties.

Analyses were conducted on excel, UCINET and Netdraw.

Results

Results of the literature review

The primary finding of the literature review is that publication on external price referencing for medicines is scarce. This was also pointed out in several articles. In a recent working paper of the WHO/HAI by Espin et al (2011), a literature review brought evidence that "an unexpectedly low number of articles existed on the consequences, impact, scope and limitations of using ERP [External Reference Pricing]." A few papers discussed the impact of external referencing, mainly on prices, but very few dealt with the interactions between countries. Surprisingly enough, particularly considering the importance EPR can have on pharmaceutical firms' bottom lines and on national health expenditures, few publications on influences through external referencing in Europe were found.

Only one congress abstract by Lindgren and Akerborg (2011) dealt directly with our research topics: "Analyzing the European External price referencing System Using Spectral Graph Theory". The most influential countries found in terms of eigenvector centrality were "Germany and France followed by Italy, Spain, Hungary ahead of a group of six countries of about equal impact". When edges were weighted by the size of their pharmaceutical markets, the most influential countries were Germany, Italy, the UK, France and Spain. Another congress abstract entitled "Then and now : the Evolution of International Reference Pricing Globally" by Bharat and Ando (2011) identified the EU 5 (i.e. France, Germany, Italy, Spain and the United Kingdom) as "leading countries", that is to say the most referenced countries, between 2006 and 2011. In addition, the working paper "External referencing and pharmaceutical price negotiation" by Mariñoso et al. (2011) offers some insight when it states both that "a country has an incentive to engage in ER [external referencing] if copayment

levels are high as compared to the other country's" and that "In a nut shell, only small countries should be observed to engage in ER and/or ER should be based on large countries (or a large group of countries)". This indicates that countries like the EU 5 Members, since they are large countries, should appear as the most influential in the external reference network. However, pricing rules have changed in several countries since the publication of these articles, and most importantly in Germany where the Act on the reorganisation of the Pharmaceutical Market (AMNOG) was introduced in January 2011. It can also be pointed out that being a wealthy country (part of the EU5 for example) or a large market is in a way a factor of influence.

Finally, at this stage of our literature review, only one study used spectral graph theory, and little information is available since it was a congress abstract

The summary table and matrix

Table 1: Summary table of external price referencing in the EU

Country	Code	Scope Medicines	Price	Calculation	Total expenditure on pharmaceuticals (million €)	GDP per capita 2011 (US$)
Austria	**AT**	Reimbursed	Ex factory	average of all countries	3761	49581,46
Belgium	**BE**	All	Ex factory	average of all countries	5926	46607,69
Bulgaria	**BG**	Prescription-only	Ex factory	lowest price of the reference basket	857	7282,52
Cyprus	**CY**	Imported, prescription-only and OTC in private sector	Pharmacy purchase	average of the 4 lowest +3%	218	30670,31
Czech Republic	**CZ**	All	Ex factory	average of all countries	2217	20676,90
Germany	**DE**	Specific reimbursed	na	na	42383	44021,22
Denmark	**DK**	EPR not applied	//	//	1942	59889,01
Estonia	**EE**	Innovative reimbursed	Ex factory	not defined	198	16534,26
Greece	**EL**	EPR not applied	//	//	4515	25629,81
Spain	**ES**	Innovative	Ex factory	not defined	18500	31984,73
Finland	**FI**	Reimbursed	Pharmacy purchase	Checking of the price level and the range of the prices in EEA countries according to this ranking: NL, BE, BG, ES, IE, IS, UK, IT AT, EL, CY, LV, LI, LU, MT, NO, PT, PL, FR, RO, SE, DE, DK, SI,	2216	48811,77
France	**FR**	Innovative	Ex factory	prices "similar" to those in the reference countries	36006	42379,26
Hungary	**HU**	Reimbursed	Pharmacy purchase	lowest price per basket	2544	14042,64
Ireland	**IE**	Prescription-only (incl.	Pharmacy	average of all countries	2646	47478,13

		Generics)	purchase			
Italy	**IT**	Reimbursed	Ex factory	average of all countries	24872	36130,45
Lithuania	**LT**	Prescription-only (incl. Generics)	Ex factory	Declared manufacturer price is compared with 95% of the average manufacturer prices in reference countries	528	14099,99
Luxembourg	**LU**	All	Pharmacy retail	lowest price per basket	246	114231,75
Latvia	**LV**	Reimbursed	Ex factory	third lowest price and not higher than the price in LT + EE	293	13726,91
Malta	**MT**	na	na	na	92	21379,73
Netherlands	**NL**	Prescription-only	Pharmacy retail	average of all countries	6715	50085,06
Poland	**PL**	Reimbursed	Ex factory	lowest price per basket	5613	13351,70
Portugal	**PT**	Prescription-only and reimbursed OTC (excl. Generics)	Pharmacy retail, ex factory	average of all countries	3450	22484,95
Romania	**RO**	Prescription-only	Ex factory	lowest price per basket	1816	8874,32
Sweden	**SE**	EPR not applied	//	//	4212	57113,93
Slovenia	**SI**	Reimbursed	Ex factory	95% of the average of the 3 countries	621	24132,03
Slovakia	**SK**	Reimbursed	Ex factory	second lowest price in the EU	1567	17782,02
United Kingdom	**UK**	EPR not applied	//	//	18154	38974,32

			OECD Health Data 2012; Eurostat Statistics Database.	The World Bank
Source		Adapted from Carone, Schwierz, Xavier (2012)		

Referenced countries →

Referencing countries ↓

	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK	UK
AT		1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1
BE	1			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1
BG	1				1	1				1	1		1		1						1	1	1		1	1	
CY	1								1			1												1			
CZ								1	1	1		1	1		1	1						1					
DE	1	1			1		1		1	1	1	1		1	1					1		1		1	1		1
DK																											
EE													1			1		1									
EL																											
ES	1	1		1		1		1	1		1	1		1	1		1		1	1		1			1	1	
FI	1	1				1	1		1	1		1		1	1		1			1		1		1			1
FR						1				1					1												1
HU	1	1			1	1			1	1		1		1	1						1	1			1	1	
IE	1	1				1	1			1	1	1								1							1
IT	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1
LT					1			1					1					1			1					1	
LU																											
LV								1								1											
MT				1	1			1	1				1			1		1			1	1			1	1	1
NL		1				1						1															1
PL		1			1	1	1		1	1		1	1	1	1	1	1			1		1		1			1
PT										1		1														1	
RO	1	1	1		1	1			1	1			1		1	1					1					1	
SE																											
SI	1					1						1															
SK	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1
UK																											

Figure 2 : Reference matrix of the EU

Network analysis results

As shown in figure 3, the matrix was visualised in ‘spring embedding’. In other words, bound countries are closer on the graph, and countries which are not directly linked are further apart.

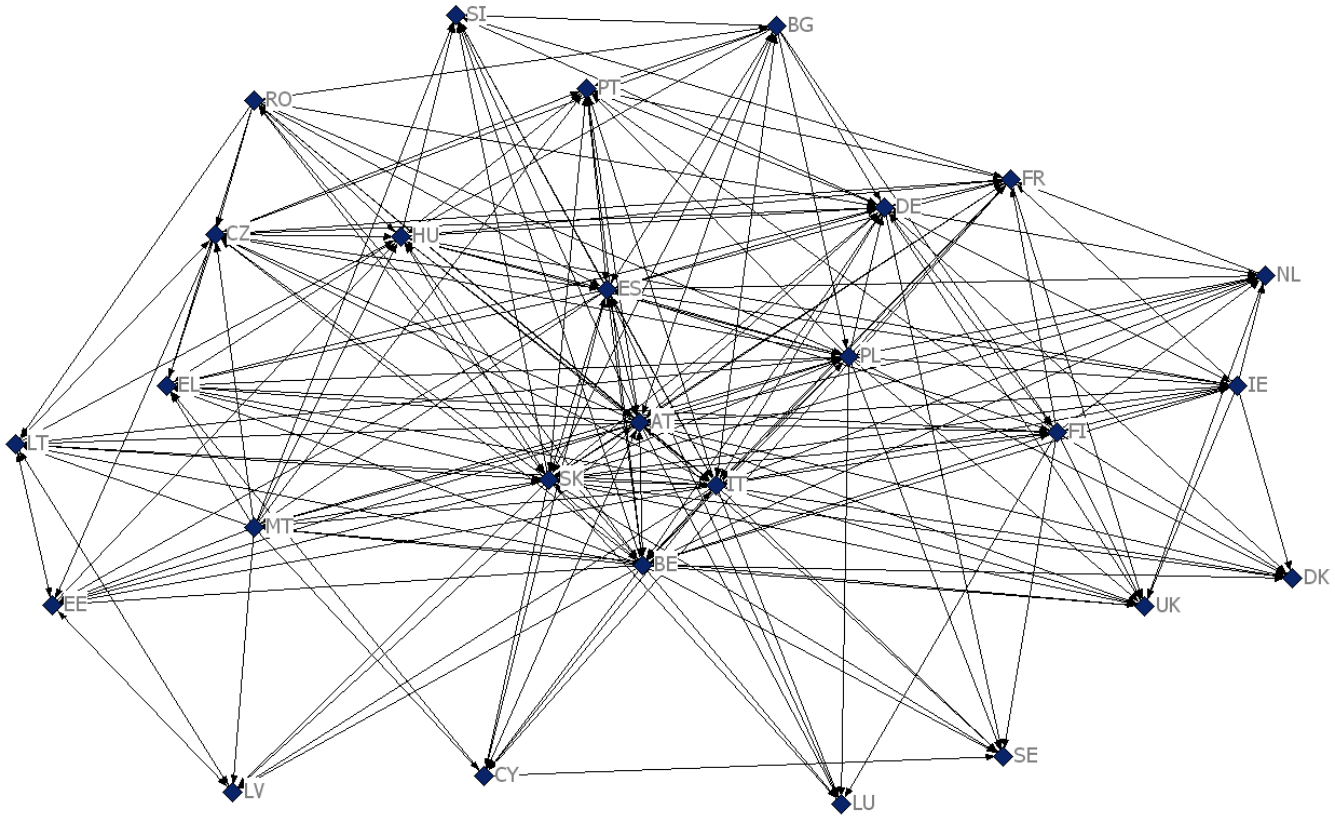

Figure 3: Network of EPR among the 27 EU Member States

A great density is shown by the network visualisation. Slovakia, Austria, Italy, Belgium, Spain, Germany, Poland, Greece, Hungary and Portugal are in the centre, which suggests that some countries will be identified as the main leaders or the main followers. Countries which do not apply external referencing or which do not reference many countries such as the UK, Luxembourg, Estonia, the Netherlands or Denmark, stand at the periphery. Some of the countries standing at the periphery will probably be identified as the least influenced or the least influential.

The 27 Member States reference one another 256 times. The density of the network is equal to 0.37, which is high since 37% of the potential total links exist. The network diameter is equal to 3, which means that countries do not need to go through more than one other

Member State to reach any other country. The network is not very centralised: network in-degree centralisation is equal to 22.92%, which suggests that many different countries are referenced by others. On the contrary, the out-degree centralisation is relatively high, with a value of 68.61%, which means that a smaller group of countries are highly influenced.

Centrality measures are given in table 2. France, Spain, Germany and Greece were identified as the most influential countries in order of in-eigenvalue and in-degree. In-degree '2 steps' shows that all countries except Romania and Bulgaria can be reached directly or indirectly by 19, 20 or 21 countries. The least influential countries are Romania, Bulgaria and Malta for the three measures. Countries identified as the most influenced in terms of out-degree and out-eigenvalues are Slovakia, Italy, Austria and Belgium. Out-degree '2 steps' shows that a large majority reference all EU Member States directly or indirectly.

Table 2: Centrality measures of ERP for the 27 EU Member States

	Outdegree	Indegree	OutEigenvalue	InEigenvalue	Outdegree 2 Steps	Indegree 2 Steps
AT	24	12	0,86	0,71	26	20
BE	24	11	0,86	0,70	26	20
BG	12	3	0,76	0,15	26	15
CY	4	6	0,11	0,41	24	19
CZ	8	11	0,33	0,61	26	21
DE	15	14	0,56	0,86	26	20
DK	0	8	0,00	0,54	0	20
EE	3	9	0,11	0,58	16	21
EL	0	13	0,00	0,79	0	21
ES	16	14	0,68	0,88	26	20
FI	14	8	0,51	0,54	26	19
FR	4	15	0,23	1,00	26	20
HU	13	11	0,71	0,58	26	21
IE	9	9	0,40	0,63	24	20
IT	26	12	1,00	0,75	26	20
LT	6	10	0,28	0,55	26	21
LU	0	7	0,00	0,48	0	20
LV	2	7	0,04	0,44	6	21
MT	12	5	0,36	0,37	26	19
NL	4	9	0,17	0,63	24	19
PL	16	9	0,56	0,47	26	21
PT	3	12	0,20	0,75	26	20
RO	12	3	0,78	0,15	26	15
SE	0	8	0,00	0,52	0	20
SI	3	9	0,17	0,58	24	20
SK	26	10	1,00	0,58	26	21
UK	0	11	0,00	0,75	0	20

Pearson correlation coefficients between countries' centrality measures are given in Table 3 As expected, in-degree is strongly correlated with in-eigenvalues and out-degree with out-eigenvalues. This suggests that being connected to influential countries does not fundamentally change the countries' order of influence. In and out-degrees '2 steps' are not as strongly correlated with in and out-degrees or eigenvalues. This suggests that the countries with the strongest direct influence are not always those with the strongest indirect influence. In fact, in such a dense network, countries influence themselves indirectly a lot and while there are differences in direct influences, almost all countries are indirectly influential. More interestingly, 'in-measures' and 'out-measures' are poorly correlated, which means that influential countries are not necessarily the least influenced or that the most influenced countries are not necessarily the least influential.

Table 3: Pearson correlation coefficients between centrality measures

	Outdegree	Indegree	Outdegree 2 Steps	Indegree 2 Steps	OutEigenvalue	InEigenvalue
Outdegree	1.000	0.168	0.642	-0.069	0.954	0.070
Indegree	-	1.000	0.089	0.642	0.074	0.966
Outdegree 2 Steps	-	-	1.000	-0.215	0.686	0.010
Indegree 2 Steps	-	-	-	1.000	-0.261	0.601
OutEigenvalue	-	-	-	-	1.000	-0.045
InEigenvalue	-	-	-	-	-	1.000

A core-periphery structure was identified with a relatively good fitness (0.621). The core includes Austria, Belgium, Italy, Spain, Finland, Germany, Hungary, Poland and Slovakia with a density of 83.3% and the periphery comprises the remaining Member States. The core is composed of countries which reference themselves a lot, but which also reference the periphery a lot (density of 70.4%). However, the periphery does not reference the core or the remaining countries many times, since densities are below 30%.

Similarly, five clusters were identified using Tabu search with a fit score of I0.146I and an R-square of 0.127. The first cluster includes Austria Belgium, Germany, Spain, Finland, France, Ireland, the Netherlands and Slovenia with a density of 75%. The second one includes Denmark, Luxembourg and the UK with a density of 0 since they do not apply external price referencing. The third cluster includes Cyprus, Greece and Sweden with a density of 33%. The fourth includes Estonia, Lithuania, Latvia and Malta with a density of 75%. And the last cluster gathers Bulgaria, Czech Republic, Hungary, Italy, Poland, Portugal, Romania and

Slovakia with a density of 71.4%. Annex 5 shows the densities between clusters, and the matrix in the annex shows in more detail the links between the five clusters and within clusters as well.

Discussion

Our study contributes to improve the current knowledge by clarifying the complex and scarce information available on EPR and by providing a new analysis of this system, using Leopold et al's matrix and table. This paper is the first of this type to provide a network analysis of the EU EPR system, which can be of great interest for both public health authorities and pharmaceutical companies.

The countries identified as the most influential in order of eigenvalues include France, Spain, Germany, Greece, the UK and Italy. These results are in agreement with literature because influential countries are large, and the top 6 leading countries include the EU 5. However, small differences can be noticed: the only study abstract which uses eigenvalue by Lindgren and Akerborg (2011) finds that leading countries in order of influence are Germany and France, Italy, Spain and Hungary. Moreover, the article by Bharat and Ando (2011) which uses in-degree finds that the EU 5 are leading when our order by in-degree includes Greece in the top 5 leading countries and only identifies the UK in the seventh position after Portugal and Austria. These differences may be due to the changes in regulation since the publication of the articles, or to the scope of countries taken into account. In addition, we found that the least influential countries include low-price countries such as Bulgaria and Romania, and small countries such as Cyprus and Malta. And the most influenced countries, taking away Italy for which the bias is too strong, are Slovakia, Austria, Belgium and Spain. In addition, we found that being influenced does not correlate with being influential.

Interestingly, while many argue that EPR is used as a cost-containment measure, the most referenced countries are not particularly low-price countries since they include Germany, France and the UK. Still, Greece, Italy and Spain are a good 'balance' since they are relatively low-price for so large countries. Nevertheless, the 'lowest price per basket' calculation methods, which appear at least eight times in the summary table, are not taken into account in the analysis and back up the idea that EPR is used to contain medicine prices. Moreover, although prices which are referenced are publically available, it should be reminded that they rarely correspond to real prices. Indeed, negotiations between national

agencies and pharmaceutical companies are not often made public (like price-volume agreements in France for example). Therefore “low-price” or “high-price” countries refer to publically available prices.

Apart from the medicine price level, countries’ wealth and market share were referred to as potential factors of influence in literature. The correlation coefficients between GDP per capita and in-eigenvalue (0.24), and between national expenditure and in-eigenvalue (0.68) show that wealthier countries and countries with the largest market share tend to be more influential. It may also be argued that countries are referenced for the trust in their pricing authorities. Paradoxically, this may explain why the UK only reaches the seventh position in terms of reference frequency. Indeed, while the NICE’s competency is worldwide acknowledged, few countries in Europe use medico-economic evaluation. Member States may decide to follow the recommendations of countries with the similar type of evaluation, and this may be the reason why the UK is not as referenced as France.

Generally speaking, the results of this paper are in agreement with literature, where the most influential countries are some of the largest in the EU, but where the influence factors are not obvious. Indeed, EPR has no real theoretical foundation (contrary to value-based pricing). Therefore, it is difficult to assess which factors weigh the most, and it seems that experimental research is needed to find elements of answers.

Spill over effects can have a huge impact on pharmaceutical companies’ turnover. Understanding the EPR system in the EU may be used for several pricing and market access decisions. Deciding whether to commercialise a medicine in a country is crucial, and the order of the launch sequence is essential. However, in such an intertwined network, it is hard to assess whether using complex and expensive launch sequence simulation tools drags better results than having a general comprehension of influences between countries. This paper provides some help in this sense. Indeed, the matrix and table provide in relatively short time information on which countries will potentially be affected by a price change and the price calculation method helps calculate the size of the effect. Particular attention should be given to the countries identified as the most influential. A few countries on the contrary are not very influential and can potentially be granted a lower price without triggering a negative spiral effect on European prices. The core-periphery analysis showed that a group of nine countries were highly influenced both between themselves but by the rest of the EU as well. Special attention should be given to them in case of a price decrease for instance. On the opposite, medicine prices in the countries of the periphery are more independently determined. (The blocked agency matrix and density matrix are given in annex 4). The use of

clusters can also help assess potential spill over effects in more detail. For instance, when there is a price change, one can identify the countries in the same cluster which will be affected, and one can identify with the density table which other clusters will be affected. The clusters matrix may also be used to identify launch sequences. Indeed, the matrix of densities in the annex gives a snapshot of influences between clusters. For instance, one can decide to launch a medicine from the most influential clusters to the least influential. It could also be decided to launch a medicine in five phases starting with the cluster of countries which do not apply EPR but which are still influential (Denmark, Luxembourg, the UK). Although these tools remain basic, and despite the fit and r-square showing that interpretation remains limited, they can potentially help in the decision-making process.

Although important, the findings presented in our paper have to be interpreted with caution since our study has a number of limitations.

Influence was defined in terms of degree and eigenvalue, based on the number of references solely. However, the way EPR is used also counts. Indeed, as shown in the summary table, countries use EPR differently. For most, it is used as supportive information. Only Bulgaria, Malta and Hungary use EPR as the sole method for setting medicine prices (reference: Phis data base). They are thus more influenced than appears in the analysis. On the contrary, some countries only use EPR in specific cases. For example, Germany uses it only in case negotiations between the Federal Joint Committee (G-BA) and the pharmaceutical company fail. Germany therefore appears more subject to external influence in this paper than it is in reality.

The scope of medicines also differs. A country which uses external referencing only for a certain type of medicine will overall be less influenced than countries which use it for all commercialised drugs. Generating different matrices for the different types of drugs may be an interesting continuation of this paper. However, most countries use EPR for a relatively wide range of medicines (prescription medicines or reimbursed medicines). Only Estonia, Spain and France use it solely for innovative drugs. These countries may appear more influenced in this paper than they actually are. One has to keep in mind that the influence they are subject to is only relevant if we are dealing with innovative medicines. Nevertheless, it can be argued that referencing external prices for innovative drugs, and therefore more expensive drugs, has a greater influence on the national price level than referencing external prices for non-innovative drugs.

The price which is set or negotiated is also not always the same. The network analysis of the paper does not take this information into account. Still, 15 of the 23 countries where EPR is used base their calculation on the ex-factory price.

Importantly, price calculation methods differ as well. For rules like 'the national price should not exceed the lowest price in a set of countries', all cited countries were counted as references. However, low-price countries are in fact the ones that are eventually referenced. Therefore, there may be a bias consisting of overestimating high-price countries and underestimating the others. Analysing price differences for a specific type of medicines and applying these rules (take the lowest price countries instead of all countries referenced for example) could also be an interesting continuation of this study.

In addition, only the EU 27 was taken into account. Other countries referenced (like Norway, Switzerland, Iceland or Russia) were not taken into account. However, only Bulgaria, Finland and Poland referenced non-EU Members. Similarly, references by other countries were out of the scope of this paper. The size of the network may also have limited the power of the cluster analysis.

The country of origin of the drug was also referenced several times but was not accounted for in the analysis. In order to identify the high drug producers, EU 27 Member States with Switzerland and Norway were ranged in order of pharmaceutical production (in million € in 2010). The top countries representing 90% of the total production include Switzerland, Germany, Italy, France, the UK, Ireland, Spain, Denmark, Sweden, Belgium and the Netherlands. Switzerland is out of scope but the other countries' influence may be underestimated. Nevertheless, only Estonia and Luxembourg reference the country of origin of a drug and in addition, many countries identified as great producers are already identified as influential.

Italy's basket of reference countries was not defined and all EU Members were included in its basket for the analysis. Therefore, Italy appears as the most influenced country when it is probably not the case. However, the main aim of the analysis is to identify influential countries more than influenced countries. Since all States can potentially be referenced by Italy, this had to be taken into account. Indeed, although it adds one reference to each EU 27 Member State, relative influence varies. For example, without Italy, France would have been referenced 14 times and Romania twice, that is to say seven times less, but counting Italy, Romania is referenced 5 times less than France (3 vs 15).

The scarcity of literature is also a limitation, since our results can only be confronted to very few comparative data.

Despite these limitations, our results have some implications on drug pricing and policies. They can also be of use to authorities, in order to be well-informed and prepared for price negotiations with pharmaceutical companies. Both parties can benefit from understanding influence effects in the EU, and it is also beneficial for pharmaceutical companies that the issue of spill over effects is taken into account by national authorities

A more abundant literature on EPR would be necessary to feed a reflection on the interest of a single European price. Until now, both experimental and theoretical research on this subject is weak, while healthcare financing is fundamental and even more so in a period of financial difficulty and European political questioning. Indeed, price differences within the EU trigger supplementary costs for both pharmaceutical companies which have to pay for information seeking and pricing processes in the separate Member States, not to mention parallel trade. But the States also suffer from high expenses because drug evaluation requires time and competence. However, challenges for a single European price are huge. Are countries with different health financing systems and different cultures ready to cooperate within the EU? Would a single European price be economically optimal at a macro-European level? Is it economically and ethically relevant to have a single price for medicines in countries with different purchasing powers?

Nevertheless, a common economic evaluation for European Members is probable. It can be a way to reduce costs while leaving national decisional power untouched. Still, research is needed in order to find answers to the challenges that this would bring. Among these difficulties, can medico-economic models be adapted to such a wide range of countries if comparable treatments differ?

Conclusions and recommendations

EPR is widely used in the EU and most countries influence themselves either directly or indirectly. In such an intertwined network, France, Spain, Germany and Greece appear to be the most influential countries. On the contrary, Slovakia, Austria and Belgium turn out to be the most subject to external influence. Countries which are influential can either be influenced or not. It is in fact difficult to determine what the factors of influence are. A core of

nine countries could be identified as being at the same time influential and influenced. Particular attention should be given to them in the pricing process of a new medicine. On the opposite, countries in the periphery tend to be more independent. The cluster analysis divides this periphery in four clusters of density.

The updated matrix, the summary table and the analysis of clusters and core-periphery can be used as tools to assess the impact of a price change in a country on the rest of the European Union and on identifying a logical launch sequence. For example, the question of launching a drug in highly influential countries like Greece or Portugal can be delicate, and analysing the potential impact of the setting of certain price level becomes crucial. Regarding launch sequences, they are case specific and depend a lot on the prices obtained as the processes go along in the different countries. One cannot recommend a ready-made optimal launch sequence.

Overall, the EPR system in the EU is complex, and many costs for both authorities and pharmaceutical companies could be avoided if the pricing process was simplified. While setting a single European price does not seem probable in the short-run, efforts towards a common European economic assessment of medicines could be very beneficial. Still, more theoretical and experimental research on medicine pricing in the European Union would need to be carried out in order to be able to face the challenges which may emerge in the future.

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List of annexes

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Annex

Annex 1: Search strategy

Table 1: Search strategy for Sciencedirect

Search	Strategy	Criteria	Results
#1	Articles published after 2007 which include the words “drug”, “pharmaceutical” or “medicine” and have “external price referencing” or synonyms in their title, key words or abstracts	Pub-date > 2007 and tak(international OR external)AND tak(reference OR referencing) AND tak(pricing OR price OR benchmark OR benchmarking) AND (medicine OR drug OR pharmaceutical)	31
#2	Limit search to relevant fields of research	#1 AND Fields : (Decision Sciences, Economics, Econometrics and Finance, Medicine and Dentistry, Nursing and Health Professions, Pharmacology, Toxicology and Pharmaceutical Science, Social Sciences)	25
#3	Exclude irrelevant topics	#2 AND exclude topics : "Latin America, Norway, Palestine refugee, saydam hygiene, scor model, scor template, sme sector, societal perspective, southeast Asia, supply chain"	17

Table 2: search strategy for Pubmed

Search	Strategy	Criteria	Results
#1	Articles published after 2007 which include the words “drug”, “pharmaceutical” or “medicine”, “external price referencing” or synonyms	(international OR external)AND (reference OR referencing) AND (pricing OR price OR benchmark OR benchmarking) AND (medicine OR drug OR pharmaceutical) > 2007	96
#2	Inclusion of other key words	#1 AND (interdependency OR impact OR consequence OR influence) OR (launch OR launching) OR (EU OR European OR Europe) OR (regulation OR rules OR updates)	44

Table 3: search strategy for EBSCO

Search	Strategy	Criteria	Results
#1	Articles published after 2007 which include the words “drug”, “pharmaceutical” or “medicine”, “external price referencing” or synonyms	(international OR external)AND (reference OR referencing) AND (pricing OR price OR benchmark OR benchmarking)AND (medicine OR drug OR pharmaceutical) > 2007	77
#2	Inclusion of other key words	#1 AND (Europe OR EU OR European OR launch OR launching OR interdependency OR impact OR consequence OR influence)	28

Annex 2 : Leopold et al's table

Table 5 – Characteristics of external reference pricing

	Scope	Price level	# of countries in basket	Calculation of reference price
Austria	Reimb.	ExFP	24	Avg. of all countries
Belgium	All	ExFP	24	Avg. of all countries
Bulgaria	POM	ExFP	9	3 lowest prices
Cyprus	Imported POM and OTC (in private sector)	PPP	4	Avg. of the 4 lowest plus 3% to cover
Czech Republic	All	ExFP	8	Avg. of all countries
Germany	Specific reimb. medicines	n.a.	15	n.a.
Denmark	ERP not applied	-	-	-
Estonia	Innovative reimb.	ExFP	4	Not defined
Greece	All excl. generics	ExFP	22	Avg. of the 3 lowest prices
Spain	Innovative reimb.	ExFP	Not defined	Not defined
Finland	Reimb.	PPP	16	Checking of the price level and the range of the prices in EEA countries according to this ranking: NL, BE, BG, ES, IE, IS, UK, IT AT, EL, CY, LV, LI, LU, MT, NO, PT, PL, FR, RO, SE, DE, DK, SI,
France	Innovative reimb.	ExFP	4	Prices "similar" to those in the reference countries (DE, ES, IT, UK)
Hungary	Reimb.	PPP	14	Lowest price per basket
Ireland	POM incl. generics	PPP	9	Avg. of all countries
Italy	Reimb.	ExFP	Not defined	Avg. of all countries
Lithuania	POM incl. generics	ExFP	6	Declared manufacturer price is compared with 95% of the average manufacturer prices in reference countries
Latvia	Reimb.	ExFP	2	Third lowest price and not higher than the price in LT + EE
Luxembourg	All	PRP	1	Lowest price per basket
Malta	n.a.	n.a.	12	n.a.
Netherlands	POM	PRP	4	Avg. of all countries
Poland	Reimb.	ExFP	17	Lowest price per basket
Portugal	POM and reimb. OTC (excl. generics)	ExFP, PRP	3	Avg. of all countries
Romania	POM	ExFP	12	Lowest price per basket
Sweden	ERP not applied	-	-	-
Slovenia	Reimb.	ExFP	3	95% of the average of the 3 countries
Slovakia	Reimb.	ExFP	26	Avg. of the 6 lowest countries in the basket
United Kingdom	ERP not applied	-	-	-

Sources: Leopold et al. (2012), Commission services (DG ECFIN).
Notes: In Germany the system has been introduced in 2012. In Belgium, ERP was used as supportive to the pricing decision only. From 2012 on, it is used as the main pricing criterion for all patented medicines, which have been at least 5 years on the market.
Reimb = Reimbursed medicines; POM = Prescription-only medicine(s); OTC = Over-the-counter (products); ExFP = Ex-factory price; PPP = Pharmacy purchasing price; PRP = Pharmacy retail price; n.a. = not available.

Annex 3: Leopold et al's matrix

Table 6 – Country baskets in external reference pricing

	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK	UK	Additional countries	Countries in basket
AT		■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■		24
BE	■			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■		24
BG	■				■					■			■								■	■	■	■			■	Russia	9
CY	■								■			■												■					4
CZ								■	■	■		■	■		■	■						■							8
DE	■	■			■		■		■	■	■	■		■	■					■		■		■	■		■		15
DK																													
EE													■			■		■										Country of origin	4
EL	■	■	■	■	■	■				■	■	■	■	■	■	■	■	■		■	■	■	■		■	■	■		22
ES																												Euro zone countries	
FI	■	■				■	■		■	■		■		■	■		■			■		■		■			■	Iceland and Norway	16
FR						■				■					■												■		4
HU	■	■			■	■			■	■		■		■	■						■	■			■	■		1 more	14
IE	■	■				■	■			■	■	■								■							■		9
IT																												Not specified	
LT					■			■					■					■			■	■				■			6
LU																												Country of origin	1
LV								■								■													2
MT				■	■			■	■				■			■		■			■	■			■	■	■		12
NL		■				■						■															■		4
PL		■			■	■	■		■	■		■	■	■	■	■	■			■		■		■			■	Switzerland	17
PT										■					■										■				3
RO	■	■	■		■	■			■	■			■		■	■					■					■			12
SE																													
SI	■						■					■																	3
SK	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■		23
UK																													
Reference frequency	11	10	3	5	11	11	8	7	11	14	6	13	11	8	12	10	6	7	3	8	9	11	3	7	8	8	11		

Sources: Leopold et al. (2012), Commission services (DG ECFIN).

Annex 4: Blocked agency matrix

	AT	BE	IT	ES	FI	DE	HU	PL	SK	BG	CY	FR	DK	CZ	EL	LT	LU	LV	MT	IE	EE	PT	RO	SE	SI	NL	UK
AT		1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1
BE	1		1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1
IT	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ES	1	1	1		1	1			1		1	1			1		1		1	1	1	1			1	1	
FI	1	1	1	1		1						1	1		1		1			1		1		1		1	1
DE	1	1	1	1	1							1	1	1	1					1		1		1	1	1	1
HU	1	1	1	1		1		1	1			1		1	1					1		1			1		
PL		1	1	1		1	1					1	1	1	1	1	1			1		1		1		1	1
SK	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
BG	1		1	1	1	1	1	1	1					1								1	1		1		
CY	1											1			1									1			
FR			1	1		1																					1
DK																											
CZ			1	1			1					1			1	1					1	1					
EL																											
LT							1	1	1					1				1			1						
LU																											
LV																1					1						
MT							1	1	1		1			1	1	1		1			1	1			1		1
IE	1	1		1	1	1						1	1													1	1
EE							1									1		1									
PT				1					1			1															
RO	1	1	1	1		1	1	1	1	1				1	1	1											
SE																											
SI	1					1						1															
NL		1				1						1															1
UK																											

Density matrix :

	1	2
1	0.833	0.704
2	0.253	0.134

Annex 5: Clusters matrix

	1 AT	2 BE	6 DE	10 ES	11 FI	12 FR	20 NL	14 IE	25 SI	27 UK	7 DK	17 LU	9 EL	4 CY	24 SE	19 MT	18 LV	16 LT	8 EE	3 BG	15 IT	22 PT	23 RO	5 CZ	13 HU	26 SK	21 PL
AT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		1.000	1.000		1.000	1.000	1.000	1.000
BE	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		1.000	1.000		1.000	1.000	1.000	1.000
DE	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		1.000		1.000						1.000	1.000		1.000			
ES	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000			1.000	1.000	1.000		1.000			1.000		1.000	1.000				1.000	
FI	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		1.000	1.000	1.000	1.000		1.000						1.000	1.000					
FR			1.000	1.000		1.000				1.000											1.000						
NL		1.000	1.000			1.000	1.000			1.000																	
IE	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		1.000	1.000																
SI	1.000		1.000			1.000			1.000																		
UK										1.000																	
DK											1.000																
LU												1.000															
EL													1.000														
CY	1.000					1.000							1.000	1.000	1.000												
SE															1.000												
MT									1.000	1.000			1.000	1.000		1.000	1.000	1.000	1.000			1.000		1.000	1.000	1.000	1.000
LV																	1.000	1.000	1.000								
LT																	1.000	1.000	1.000					1.000	1.000	1.000	1.000
EE																	1.000	1.000	1.000						1.000		
BG	1.000		1.000	1.000	1.000				1.000											1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
IT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
PT				1.000		1.000																1.000				1.000	
RO	1.000	1.000	1.000	1.000									1.000					1.000		1.000	1.000		1.000	1.000	1.000	1.000	1.000
CZ				1.000		1.000							1.000					1.000	1.000		1.000	1.000		1.000	1.000		
HU	1.000	1.000	1.000	1.000		1.000		1.000	1.000				1.000								1.000	1.000		1.000	1.000	1.000	1.000
SK	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
PL		1.000	1.000	1.000		1.000	1.000	1.000		1.000	1.000	1.000	1.000		1.000			1.000			1.000	1.000		1.000	1.000		1.000

Density Table

	1	2	3	4	5
1	0.750	0.593	0.444	0.278	0.292
2	0.000	0.000	0.000	0.000	0.000
3	0.074	0.000	0.333	0.000	0.000
4	0.028	0.083	0.167	0.750	0.313
5	0.611	0.375	0.458	0.375	0.714

Partition saved as dataset ClusterID