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SPECIAL ARTICLE

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Availability of medicines in the European Union: results from the EURO-Medicines project

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Abstract *Objective*: There is at present no comprehensive directory of medicines available in European countries. Such a directory would be valuable to policy analysts, clinicians, regulatory agencies, pharmaceutical companies and consumer groups. The aim of this project was to compile such a directory of all medicines marketed in each of the European Union member countries.
Methods: Lists of medicines for each country, compiled from several national sources, classified by Anatomical-Chemical-Therapeutic (ATC) code. Census date was late 1998.
Results: A comprehensive directory was created using data from 14 of the 15 European Union countries. Numbers of trade names and of active ingredients varied widely, from Germany with 18,554 and 1973, respectively, to Denmark with 1915 and 1016, respectively. In individual therapeutic areas, there were variations in the numbers of active ingredients available: the least variation between countries was in antineoplastic medicines (ATC code L, maximum number available in any country 101, minimum 60) and wider variation in alimentary (ATC code A, maximum 256, minimum 103) or cardiovascular (ATC code C, maximum 269, minimum 112). Only 7% of all the active ingredients were available in all the countries studied. The Scandinavian countries had the greatest proportion of active ingredients (60%) available in all other countries. Each country had a number of active ingredients available only in that country – Italy had the largest number of these.
Conclusions: The directory illustrates the wide variations in the availability of medicines across the European Union. The range of drugs available in each country represents differences in regulatory and market policies, as well as cultural and historic differences. This directory lends itself to many further analyses.

Keywords Medicines · Europe · Regulation

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Introduction

The development of centralised drug licensing in the European Union is an example of the harmonisation of European institutions [1, 2]. This follows from a system of individual national licensing agencies acting independently that has not entirely disappeared but which is far less important than before. A result of this previous system is that many older drugs are available in only one or some of the European states but not in others, or that the doses and indications may vary between countries. Other discrepancies have existed and continue to exist in the patterns of drug use with relatively few drugs being widely used in more than one country [3, 4], in expenditure on medication and in drug prices. Some of the most widely used medicines in some countries have even been withdrawn or were never licensed in others. There is rarely any scientific rationale for these discrepancies.

A system of improved communication between national and pan-European regulatory agencies and the pharmaceutical industry was proposed in the early 1990s [5], particularly with regard to regulatory activity, pharmacovigilance and medicinal product authorisations. The general public was to have access to this information. Part of this was a directory of medicines,

the European Product Index (EPI), itself a by-product of the European Community Pharmaceutical Information project [6]. The aims of this project were to ensure market transparency [7], support pharmacovigilance and provide technical information by creating a repertory of drugs available in the European Union. Early trials suggested that the system would be of great value, but various difficulties have meant that the EPI has never been developed. European regulatory agencies depend on a drug dictionary produced by the World Health Organization (WHO) and on a commercial directory produced by a for-profit organisation. The former, although useful, does not contain dosage form and some other information. The latter is not available to other groups except at great expense.

Identifying the discrepancies in availability of medicines can therefore be difficult, since at present there exists no directory of all medicines available in each European state. Such a directory would be of value to regulatory agencies, to those agencies negotiating drug prices, to manufacturers and those charged with promoting good prescribing. Other potential users of such a directory would be those with direct responsibility for patient care who need to identify the medicines a patient is using and consumers. To fill this gap, we undertook the "EURO-Medicines" project, funded by the Commission of the European Communities under the IV Research programme (Biomed 2-Area 6, Public Health). Its aims were to define drugs available in member states and, using these data, to compare the performance of each member state in regulating its drug market. The objectives (tasks) of this project were threefold:

- Task 1 – to undertake a comprehensive survey of all medicines marketed in each of the 15 European Union members
- Task 2 – to examine selected medicines identified from the list developed in task 1 as being available in most or all countries by reviewing the summary of product characteristics (SPC), since this represents the uses of the medicines approved in each state by the regulatory agencies
- Task 3 – to list active ingredients withdrawn for reason of safety or ineffectiveness from any of the countries identified from official lists and from published data and to examine if these ingredients were still available in other countries

This paper describes task 1.

Methods

Each medicine was to be classified by the WHO Anatomical Therapeutic Chemical (ATC) code [8] and identified by international non-proprietary name of its active ingredients. Other information to be recorded was the proprietary name (with details such as pharmaceutical form, strength and pack size), the marketing authorisation holder, the year of approval, whether reimbursed by the health service, prescription status (hospital only, prescription only, over-the-counter) and any special restrictions on its use (e.g. for opiates or other controlled drugs). Unbranded or generic medicines were treated in the same way with the exception of the proprietary name. Utilisation data and prices were also recorded when available. The census period for these lists was the second half of 1998.

A number of methodological difficulties were anticipated. We expected difficulty in finding complete national databases of good quality, despite a European requirement to have such a list available in each state [9]. We therefore aimed to use a variety of agencies in each of the member states to compile a list of available medicines, largely national formularies and also data from Ministries of Health or other national organisations, public or commercial as necessary. We also expected the data from such diverse sources to be of varying quality, and for quality assurance and standardisation of the data we followed the European Prestandard ENV 12610 (Medical Informatics – Medicinal Product Identification) [10].

Further difficulties were the definitions of what constituted a medicine. For licensed drugs, this is clear but for many over-the-counter (OTC) preparations, the distinction may be difficult. For OTC preparations such as vitamins, we decided to include a preparation only if we considered that it was clearly used therapeutically, and not as a simple food supplement, based on listing in the British National Formulary or similar source. Similarly, we decided to exclude herbal and homeopathic preparations where the range of products available varies enormously across Europe. We generally accepted the ATC code assignment on a national list where available, but for some countries it was necessary to undertake the assignment. The data were analysed using commonly available software (MS Excel 97 and Access 97).

Results

Data were received from a variety of sources. For only one country (Greece) was it not possible to obtain data. No source had all the information required, and the sources ranged from national lists provided by state agencies to prescribing databases, compendia of summaries of product characteristics, as well commercial directories of available medicines (Table 1). There are no data available at present on dermatological preparations in Portugal. The data on trade names for Austria, Belgium and Germany include not only the proprietary name but also the formulation and strength; these data are therefore not directly comparable to the data for the other countries which include only the proprietary name.

Numbers of medicines available

The numbers of medicines available varied widely among countries, with Germany having the largest number of both active ingredients (by ATC codes) and trade names and the Scandinavian countries the least (Table 2). The average ratio between trade names and active ingredients is higher in Germany than in other countries. Details by ATC code (1st level) are shown in Table 3.

Similarities and discrepancies between countries

The similarities and discrepancies between countries were further explored. Table 4 shows what percentage of the ingredients licensed in each country is available in the other countries, for those countries for which complete data are available. More than 60% of the ingre-

Table 1 Data sources used by country

Austria	Austria Codex
Belgium	Internal list from the Belgian Pharmaceutical Association Gecommentarieerd Geneesmiddelen-Repertorium. Heymans Instituut Compendium des Medicaments
Denmark	Laegemiddelstyrelsen. Apotekssforbeholdte Farmaceutiske Specialiteter, Specialitets Takst Laegemiddelkataloget
Finland	Internal list from the Laakelaitos Lakemedelsverket (National Agency for Medicines)
France	Dictionnaire Vidal French Translation of the ATC code by CNHIM – Centre National Hospitalier d'Information sur le Médicament
Germany	Internal file from Bundesvereinigung Deutscher Apothekerverbande, der Bundesapothekerkammer und des Deutschen Apothekerverbandes Rote Liste FachInfo Fachinformationsverzeichnis Deutschland
Ireland	Internal list from the Irish Medicines Agency Internal list from Irish Pharmaceutical Association MIMS (Ireland) – Monthly Index of Medical Specialities, Dec. 1998 Summary of Product Characteristics Compendium 1997–1998 (Irish Pharmaceutical Healthcare Association)
Italy	Informatore Farmaceutico. Edizione per il medico Supplemento ordinario alla Gazzetta Ufficiale della Repubblica Italiana REFI – Repertorio Farmaceutico Italiano
Luxembourg	Ministere de la Sante. Division de la Pharmacie et des Medicaments. Liste des medicaments admis a la vente dans le Grand-Duché de Luxembourg
Netherlands	Internal list from the Z-Index Association Lijst van Farmaceutische Producten. College ter beoorderling van geneesmiddelen
Portugal	Lista de medicamentos sujeitos e nao sujeitos a receita médica Lista oficial dos medicamentos comparticionados pelo Servico Nacional de Saùde
Spain	CEF. Catalogo de Especialidades Farmacéuticas Base de datos de Medicamentos ECOM (Base de Datos de la Direcciòn General de Farmacia y Productos Sanitarios)
Sweden	Internal list from the Lakemedelsverket (Medical Product Agency) FASS. Lakemedel i Sverige
UK	Internal list from the UK Medicines Control Agency Prescription Pricing Authority BNF – British National Formulary, Sept. 1998 ABPI Compendium of Data Sheet and Summaries of Product Characteristics 1997–1998

Table 2 Numbers of active ingredients and trade names by each country and ratio of trade names to active ingredients. *ATC* Anatomical-Therapeutic-Chemical

Country	Number of active ingredients (ATC codes)	Number of trade names	Mean number of trade names per active ingredient
Austria[a]	1727	8643	5.01
Belgium[a]	1483	6118	4.13
Denmark	1016	1915	1.88
Finland	1130	2282	2.02
France	1514	4089	2.70
Germany[a]	1974	18,554	9.40
Ireland	1352	3751	2.77
Italy	1693	5070	2.99
Luxembourg	1537	3204	2.08
Netherlands	1290	3359	2.74
Portugal	1398	4355	3.12
Spain	1338	4100	3.06
Sweden	1041	1954	1.88
UK	1366	3635	2.66

[a]For Austria, Belgium and Germany, the "trade name" includes not just the proprietary name but also the preparation form and strength. The figures for trade name in these countries is therefore not directly comparable with those in other countries

dients licensed in the Scandinavian countries are available in all the other states. The extreme figures are for Germany and Sweden: 83% of the active ingredients licensed in Sweden are available in Germany, but only 42% of the ingredients approved in Germany are available in Sweden.

Table 3 Total number of active ingredients by ATC code 1st level, by country. *A* alimentary tract and metabolism, *B* blood and blood-forming organs, *C* cardiovascular system, *D* dermatologicals, *G* genitourinary system and sex hormones, *H* systemic hormonal preparations, excluding sex hormones and insulins, *J* anti-infectives for systemic use, *L* anti-neoplastic and immunomodulating agents, *M* musculoskeletal system, *N* nervous system, *P* anti-parasitic products, insecticides and repellents, *R* respiratory system, *S* sensory organs, *V* various

Country	A	B	C	D	G	H	J	L	M	N	P	R	S	V	Total
Austria	217	101	231	158	105	38	173	82	89	217	15	137	86	77	1727
Belgium	191	75	166	132	98	26	147	69	63	210	22	128	104	51	1483
Denmark	103	62	119	81	62	22	96	60	53	162	19	70	56	51	1016
Finland	130	60	118	78	72	20	116	73	60	144	11	75	66	107	1130
France	197	82	172	135	104	33	151	79	68	198	42	135	79	39	1514
Germany	256	124	269	184	119	40	178	101	91	258	28	141	116	82	1974
Ireland	219	75	138	141	64	31	125	68	60	192	15	103	70	51	1352
Italy	216	90	198	156	109	35	178	75	92	203	22	136	118	65	1693
Luxembourg	183	83	202	130	90	27	156	80	67	222	23	127	96	51	1537
Netherlands	148	75	164	93	81	28	124	82	47	184	22	84	78	78	1290
Portugal[a]	199	82	212	–	90	31	157	66	93	176	26	130	96	40	1398
Spain	171	73	142	146	72	30	147	64	71	183	13	118	80	27	1338
Sweden	124	73	112	63	64	23	126	74	49	137	18	70	52	52	1041
UK	162	51	190	107	82	30	173	79	58	207	28	113	73	13	1366

[a]Data on dermatologicals for Portugal not available

Table 4 Similarities between countries in terms of availability of active ingredients. The percentage of drugs [Anatomic-Therapeutic-Chemical (ATC) code] available in country 1 also available in country 2

Country 2→ ↓Country 1	Austria	Belgium	Denmark	Finland	Germany	Ireland	Italy	Luxem-bourg	Nether-lands	Spain	Sweden	UK
Austria	100	59	49	51	81	51	60	63	57	53	48	54
Belgium	72	100	55	54	79	60	67	82	66	61	52	60
Denmark	81	73	100	75	84	67	69	76	76	65	73	71
Finland	78	67	70	100	79	61	68	71	69	60	70	67
Germany	68	54	43	44	100	47	54	59	50	49	42	49
Ireland	65	63	53	51	72	100	58	64	59	55	50	66
Italy	62	56	43	45	66	46	100	58	50	54	42	50
Luxembourg	71	75	52	52	79	56	63	100	60	58	49	57
Netherlands	80	76	65	63	84	65	69	75	100	63	61	69
Spain	69	65	51	51	75	55	68	66	58	100	48	59
Sweden	79	71	74	76	83	65	69	73	72	62	100	70
UK	68	62	55	55	73	65	62	64	62	58	53	100

Only 7% of all the active ingredients are available in all the participating countries. The percentage differs among ATC classes: high for antineoplastic agents, systemic hormones (both 18%) and antiinfective agents (12%), low for dermatological agents, antiparasitic agents and various (1% each or less) and nootropics (none mutually available).

Number of exclusively available medicines

In each country, there is a small number of active ingredients exclusive to that country. Table 5 shows the number of drugs exclusively available in only one country for some ATC groups for those countries for which data are available.

Specific therapeutic areas

The data allow more specific examination of individual therapeutic areas. For instance, the numbers of active principles and available preparations in each of the major classes of cardiovascular or neurological medicines can be compared in each country. Table 6 shows the range of drugs within a particular class within each country, i.e. beta blockers, ACE inhibitors, peripheral vasodilators or nootropics (e.g. piracetam).

Discussion

We developed a directory of medicines available in the European Union at a single point in time. This directory lends itself to many analyses of which this paper presents only a small number. More detailed examination of this database will be of value to a range of bodies as suggested above. This database is available now to interested parties (regulatory bodies and academic research) and we intend to make it more widely available on a website (www.euromedicines.org). Its updating and maintenance as medicines are licensed and withdrawn would considerably enhance the value of this data source, and we intend to undertake this work periodically.

Table 5 Active ingredients exclusively available in one country [selected Anatomic-Therapeutic-Chemical (ATC) groups]. *A02B* drugs for treatement of peptic ulcers, *C* cardiovascular system, *G* genitourinary system and sex hormones, *H* systemic hormonal preparations, excluding sex hormones and insulins, *J01* antibacterials for systemic use, *J05* antivirals for systemic use, *L* antineoplastic and immunomodulating agents, *M01* antiinflammatory and antirheumatic products, *N* nervous system, *R03A* adrenergics, inhalants, *R03C* adrenergics for systemic use

Country	A02B	C	G	H	J01	J05	L	M01	N	R03A	R03C
Austria	1	11	1	3	0	0	2	4	10	1	2
Belgium	0	3	3	0	1	0	0	0	7	0	0
Germany	0	17	5	5	3	0	5	5	14	2	3
Denmark	0	0	1	1	0	0	1	0	1	0	0
Finland	2	1	2	0	0	0	1	0	3	0	0
France	0	10	8	4	4	0	0	2	19	0	0
Italy	2	30	9	4	9	1	3	4	25	2	3
Luxembourg	0	4	2	0	2	0	2	1	10	0	0
Netherlands	0	2	0	0	1	0	2	0	1	0	0
Portugal	2	9	3	0	2	0	0	2	7	0	0
Spain	0	8	3	2	10	0	2	4	13	0	0
Sweden	0	1	1	1	2	0	1	0	4	0	0
UK	1	19	5	2	6	0	1	0	13	2	2

Table 6 Number of trade names/active ingredients [Anatomical-Therapeutic-Chemical (ATC) codes] in four selected therapeutic groups. *ACE* angiotensin-converting enzyme

Country	Beta-blocking agents, C07A	ACE inhibitors, plain, C09AA	Peripheral vasodilators, C04	Psychostimulants and nootropics, N06BX
Austria	54/21	29/13	44/23	10/3
Belgium	28/17	11/9	12/10	7/3
Denmark	39/15	22/10	2/2	0/0
Finland	38/16	26/12	6/3	1/1
France	27/17	15/10	38/17	12/7
Germany	94/21	56/13	96/24	58/7
Ireland	32/14	14/9	9/8	2/2
Italy	25/15	29/13	50/17	48/11
Luxembourg	34/20	15/12	34/16	15/7
Netherlands	92/18	20/10	21/8	6/2
Portugal	41/17	48/12	51/22	52/9
Spain	26/13	58/10	22/10	25/8
Sweden	24/13	15/9	4/4	1/1
UK	39/15	14/10	11/9	2/1

The range of drugs available in each country represents differences in regulatory and market policies, as well as cultural and historic differences [2]. This is not to necessarily imply that a decision in one country is better than another but to raise questions that require explanation. In the UK, for instance, the government has encouraged generic prescribing that in turn promotes the production of more preparations of widely used medicines, often unbranded, that are less expensive than the major-branded forms. Such generic or unbranded forms are not well documented in standard reference sources but were all included in our directory. There may also be differences in medical culture and diagnosis, for instance the wide differences in rates of prescribing with higher rates in Mediterranean countries and lower in Scandinavia [2, 11] or a diagnosis of systemic hypotension in Germany which is rarely made in the UK [2]. Garattini [3, 4] attributes the differing patterns of use of medicines in major European markets to the influence of promotion by national pharmaceutical companies, the lack of adequate training of physicians in clinical pharmacology and the lack of reliable comparative clinical data to allow clinicians to distinguish between more expensive 'me-too' drugs and their prototypes. This has resulted in the past in 20% of expenditure in Italy or France going for drugs considered to be of little or no proven therapeutic benefit [12, 13]. Both countries have since taken drastic action to redress this situation, but discrepancies still exist [14].

The discrepancies in the market originate at least in part with discrepancies in the medicines available in each country. These discrepancies may take a number of forms. Medicines may be licensed in some countries but not in others, as shown in this article. Others may be withdrawn for safety reasons from some countries, but may be among the best-selling and most widely used drugs in other countries (e.g. dipyrone was withdrawn in many countries but is widely used in Spain). There may also be differences in the indications for older drugs across national boundaries (e.g. trimetazidine is used for angina in France and for Meniere's disease in Denmark). It is difficult to keep track of new products, indications, contraindications and adverse drug reactions within one country, but with such wide variations in medicines licensed and the terms of the licence, the increasing movement of patients or health care profes-

sionals across national boundaries will cause many problems. The lack of a comprehensive database of available products compounds this.

The difficulties of creating this database were greater than initially anticipated. An important weakness in our data is the lack of uniformity between countries in the assignment of ATC code, particularly for the active ingredients with more or many ATC codes. To explore this problem, a comparative analysis of ATC assignment in European countries has been planned in co-operation with the WHO-Oslo Centre. Another weakness in the data is the difficulties of defining numbers of OTC or general-sales-list preparations, and this may explain a small amount of the variation in number of preparations between countries.

Some countries had only an incomplete or even no national list available from government sources, despite a European Union (EU) directive [9]. The EU recognises the need for product information of the type in our database. An initiative of the European Medicines Evaluation Agency, the Medicines Information Network for Europe [15], is attempting to improve market transparency within the EU by harmonising the product information available in the EU. Its aims are to make available all SPCs and any Patient Information Leaflets in all EU official languages in an electronic database, regularly updated. It does not attempt to harmonise medical practice, nor to move too quickly to a single European pharmaceutical market [16]. A pilot project is to be undertaken by the European Joint Research Centre between 2000–2002, initially only for those products approved by the European Commission under the centralised and mutual recognition procedures. It will be some years before any results are seen. Its content and coverage differ from that in our database. As mentioned earlier, a previous attempt to establish a directory similar to EURO-Medicines as part of the European Union Drug Regulatory Agencies Network was unsuccessful.

A further advantage of our database is that it was developed in parallel with another database covering most of the countries of central and eastern Europe preparing to join the EU in another project funded by the European Commission (CEE-Medicines, Folino P). This will allow EURO-Medicines to be rapidly expanded to keep pace with the future expansion of the EU.

The advantages of such databases extend beyond supporting clinicians and promoting harmonisation of information and availability of medicines. Better knowledge of the current situation in other countries can be the foundation for new policy decisions constructed in the best interest of the patient. Such databases are therefore of interest to both European and national policy makers as well as to regulatory agencies, the WHO, consumer groups and pharmaceutical industry associations. Our database may allow countries to identify and address concerns about availability of medicines or to identify where and how they can improve their work, especially where benchmarking against other states suggests that patients are being exposed to dangerous or ineffective therapies. This may lead to a substantial improvement in the quality of care and therapeutic outcome and a significant improvement in the efficiency of the health systems.

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