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DOSTOPNOST INOVATIVNIH ZDRAVIL, KI SO BILA UVEDENA NA TRGE IZBRANIH EVROPSKIH DRŽAV MED LETOMA 2004 IN 2009

PATIENT ACCESS TO NOVEL PHARMACEUTICALS LAUNCHED IN SELECTED EUROPEAN COUNTRIES BETWEEN 2004 AND 2009

DIPLOMSKA NALOGA

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This diploma thesis was conducted at the headquarters of GlaxoSmithKline Services Unlimited in Brentford, United Kingdom and at the chair of Social Pharmacy at the Faculty of Pharmacy, University of Ljubljana under the mentorship of Assist. Prof. Dr. Mitja Kos, M. Pharm. and co-mentorship of Prof. Dr. David Taylor from The School of Pharmacy, University of London.

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Izjava

Izjavljam, da sem diplomsko nalogo izdelal samostojno pod mentorstvom doc. dr. Mitje Kosa, mag. farm. ter pod somentorstvom prof. dr. Davida Taylorja

Statement

I hereby declare that I have conducted the research and written this diploma thesis by myself under the mentorship of Assist. Prof. Dr. Mitja Kos, M. Pharm. and co-mentorship of Prof. Dr. David Taylor

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Disclosure statement

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Ljubljana, 13.6.2011

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POVZETEK

Nezadosten dostop do potencialno življenjsko pomembnih inovativnih zdravil lahko zmanjša bolnikovo kakovost življenja in pomembno vpliva na bolnikove možnosti za preživetje. Hkrati pa zakasnelo trženje inovativnih zdravil farmacevtski industriji onemogoča priliv prihodkov, s katerimi bi pokrili pomemben del naložb za tekoč razvoj in raziskave številnih novih zdravil. Namen študije je analizirati ter primerjati obseg dostopnosti do inovativnih zdravil, ki so bila uvedena na trge 27 izbranih Evropskih držav (E-27) med letoma 2004 in 2009.

Analizirali smo regulatorne postopke, po katerih se za inovativna zdravila najpogosteje pridobijo dovoljenja za promet z zdravili, ter določili trend časovnega zaostanka v petih fazah centraliziranega postopka (CP), ki ga izvaja Evropska agencija za zdravila ("čas EMA"). Določili smo število inovativnih zdravil dostopnih v E-27, analizirali kolikokrat je posamezna država prva pričela s trženjem zdravila v Evropi ter primerjali srednje čase do uvedbe novih zdravil v posamezni državi. Analizirali smo tudi privzem oziroma uvajanje ter prodajo inovativnih zdravil v posamezni državi in poskušali raziskati vzroke za razhajanje med povprečnimi odstopanji cen zdravil in kupno močjo posameznih evropskih držav.

85.6 % vseh inovativnih zdravil, uvedenih na trge E-27 med letoma 2004 in 2009, je bilo odobrenih po CP pri EMA. Srednji »čas EMA« se je med letoma 2004 (518 dni) ter 2007 (423 dni) opazno skrajšal, vendar je bil do leta 2009 (455 dni) ponovno v porastu. Povprečje ter mediana »časa EMA«, porabljenega za aktivno preučitev predane dokumentacije v vseh šestih letih, razen v 2005, ni presegla regulatorne omejitve 210 dni. Čas, ki ga med CP porabi podjetje za predložitev dodatno zahtevane dokumentacije, predstavlja kar 30 % delež "časa EMA" ter tako pomembno vpliva na podaljšanje časa dostopa do zdravil v E-27. V zahodnoevropskih državah (z izjemo Grčije, Portugalske in Luksemburga) je bil čas dostopa do inovativnih zdravil med E-27 najkrajši. V državah vzhodne in centralne Evrope (CEE), z izjemo Slovaške in Poljske, je bil dostop omogočen le 65 % vseh inovativnih zdravil, uvedenih med 2004 in 2009. Zahodno evropske države so ekonomsko bolj razvite ter bistveno hitrejše pri uvajanju novih zdravil za tem, ko je bilo zdravilo že uvedeno v prvi izmed držav E-27. Francija, Španija, Danska in Nemčija so med članicami E-27 vodilne v privzemu ter uvajanju inovativnih zdravil. Cene inovativnih zdravil se v državah E-27 bistveno ne razhajajo in so zato diskriminatorske do držav vzhodne in centralne Evrope z nižjimi dohodki na prebivalca.

Ugotovili smo, da regulatorni postopek predstavlja relativno hitro, dobro nadzorovano ter, z vidika EU, uravnoteženo fazo poti k dostopu do inovativnih zdravil. Večina držav CEE je bistveno počasnejših pri uvajanju in privzemu inovativnih zdravil od preostalih držav E-27. Po naših ugotovitvah je to predvsem posledica razlik v nacionalnih kriterijih za odločitev o financiranju zdravstvenih programov ter tudi razlik v razvitosti in velikosti posameznih držav.

ABSTRACT

Poor patient access to potentially life-saving novel pharmaceuticals reduces patients' quality of life and impacts patients' chances of survival. Delayed access and poor access performance prevent the pharmaceutical industry from generating significant returns to cover research and development costs of a number of innovative medicines in the pipeline. The aim of our study was to measure and compare the extent of patient access to novel pharmaceuticals first launched between 2004 and 2009 in any of the 27 selected European countries (E-27).

We analysed regulatory procedures most frequently applied in approval of new innovative drugs and measured the trend in duration of five stages of the 'EMA time lag'. We measured the number of new innovative drugs made available in each country, the number of times countries were first or among the first to launch new drugs and compared the mean times to launch in each country after drug was first made available in E-27. We analysed monetary uptake and sales of new drugs in each country as well as the affordability gap existing in some European countries.

85.6% of all novel pharmaceuticals launched between 2004 and 2009 have been granted marketing authorisation through centralised procedure. The overall 'EMA time lag' reduced noticeably between 2004 (518 days) and 2007 (423 days), but rose again until 2009 (455 days). Mean and median EMA 'active times' were kept below the prescribed limit of 210 throughout the 6-year period, but surpassed the limit in 2005. Except in 2005, company time accounted for more than 30% of the total 'EMA time lag', thus having the biggest impact on prolongation of time to access in E-27 during regulatory approval. Western European countries (with exception of Greece, Portugal and Luxembourg) have used the least time to access new innovative treatments among E-27. In Central and Eastern European (CEE) countries (with the exception of Slovakia and Poland) only 65% or less of all novel pharmaceuticals introduced between 2004 and 2009 were made available. Western European countries are economically more developed and much faster, taking no longer than 26.6 (the slowest being Belgium) months in introducing new drugs to their patients after a drug was first made available in E-27. CEE countries take at least 21.9 months (the fastest being Poland). France, Spain, Denmark and Germany are leading the uptake of new medicines among E-27. Prices of new innovative drugs across E-27 are comparable and thus discriminatory towards CEE countries with significantly lower income per capita.

We can conclude that regulatory approval represents a relatively timely and well regulated phase, enabling all EU countries to simultaneously move a step further to enabling patient access to novel pharmaceuticals. Nevertheless, the CEE countries are significantly slower in the introduction of new drugs to their patients as well as in the uptake of these drugs as compared to the rest of the E-27. This may well be related to cross-country economic and demographic differences and also to country-specific pricing and reimbursement regulations.

LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AIFA	*Agenzia Italiana del Farmaco*
ATC classification	Anatomical Therapeutic Chemical classification system
CEE	Central and Eastern Europe
CEPS	*Comité Economique des Produits de la Santé*
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Centralised Marketing Authorisation
CMS	Concerned Member State
CP	Centralised Procedure
CT	*Commission de la Transparence*
DcP	Decentralised Procedure
DDD	Defined Daily Dose
E-21	21 European study countries (Estonia, Greece, Ireland, Luxembourg, Portugal and Romania are excluded)
E-27	All 27 European study countries
EC	European Commission
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EMA	European Medicines Agency
EMU	Economic and Monetary Union
EPAR	European Public Assessment Report
EU	European Union
EU-5	5 biggest European countries: France, Germany, Italy, Spain, United Kingdom
EUnetHTA	European network for Health Technology Assessment
EUR	Euro
FDA	Food and Drug Administration
GBP	British Pound Sterling
GDP	Gross Domestic Product

GHO	Global Health Observatory
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline Services Unlimited
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
IMS	Intercontinental Medical Statistics
MA	Marketing Authorisation
MIDAS	Multi-International Integrated Data Analysis System
MRP	Mutual Recognition Procedure
NBE	New Biological Entity
NCE	New Chemical Entity
NME	New Medical Entity, either a NBE or a NCE
No./N	Number
NP	National Procedure
OECD	Organisation for Economic Cooperation and Development
OTC	Over-the-counter (drug)
P&R	Pricing and Reimbursement
PPP	Purchasing Power Parity
PPRS	Pharmaceutical Price Regulation Scheme
PPS	Purchasing Power Standard
R&D	Research and Development
RMS	Reference Member State
SEM	Standard Error of Mean
SPC	Summary of Product Characteristics
SU	Standard Units - smallest common dose of a product form as defined by IMS Health, for example a standard unit could be 1 tablet or capsule, 5 millilitres of syrup, 1 ampoule
UK	United Kingdom
USA or US	United States of America
VAT	Value Added Tax
WHO	World Health Organization

1 INTRODUCTION

New innovative medicines may represent an essential part of new therapeutic solutions and are potentially indispensible in tackling pathologies and conditions that to date remain either untreatable or insufficiently controlled, thus representing a significant burden of mortality and morbidity for patient populations.

It is not only vital that research focus on discovering new chemical entities (NCE) and new biological entities (NBE) is being incentivised, but at least equally important that once developed, produced, pre-clinically and clinically tested, new medicinal products soon reach their end user. In order to provide an immediate benefit to an individual patient in improving their health related quality of life or prolonging their life - consequently also raising the level of public health - it is vital that new therapies reach patients as soon as their safety and efficacy are assured and their benefits over risks are confirmed. However increasingly stringent regulations and numerous hurdles stand in the way of bringing new new medical entities (NME) to patients once research and development (R&D) activities have been concluded. As previously exposed by Russo et al. [1] according to OECD, R&D is a term covering three activities: basic research, applied research and experimental development [2]. Accordingly, the date when an application dossier of a novel pharmaceutical is submitted to the regulatory agency for assessment of eligibility for Marketing Authorisation (MA), could to some extent be considered as a final step of R&D, and a first step to patient access.

1.1 Hurdles of patient access

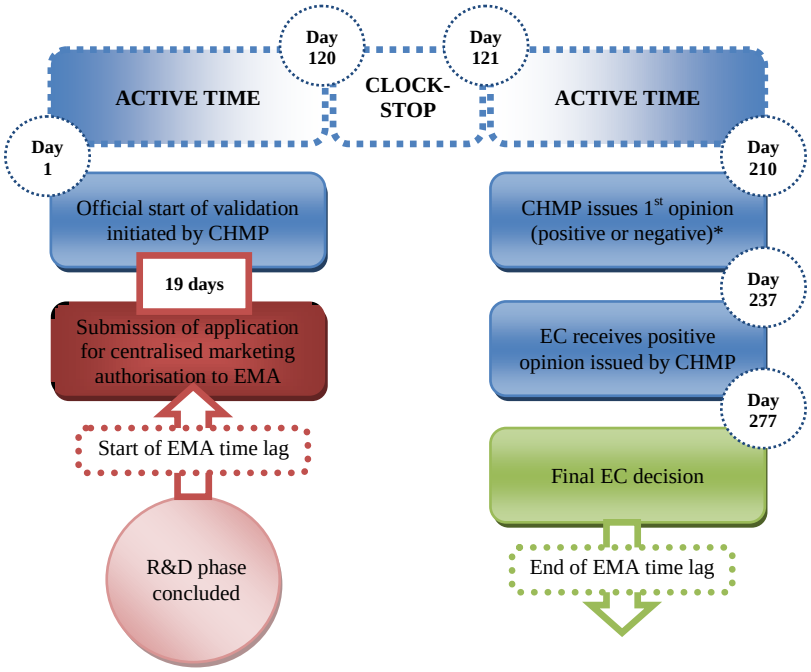
1.1.1 Regulatory approval

In the 1980s and 1990s, discussions about access to newly approved drugs focused mainly on delay between application for approval and granting of MA [3; 4]. This was considered the first barrier to patient access. With the establishment of the European Medicines Agency (EMA) on the 1st January 1995, receiving its present name only in 2004, the old Member States of the European Union (EU) made an important step towards harmonisation of legislation and rules governing regulatory activities in 15 EU Member States at the time. EMA's introduction of the Centralised Procedure (CP) in 1995 enabled simultaneous approval of new medicines in all member states and reduced potential inequalities in the availability of new pharmaceuticals from the patient's viewpoint [5].

Even though for the innovative pharmaceutical industry the CP remains the most popular and most frequently employed procedure, enabling simultaneous EU-wide approval with common branding strategy, the European legislation foresees the possibility that pharmaceutical companies may wish to market their products in a limited number of countries. With this aim the Mutual Recognition Procedure (MRP) was established on 1st January 1998. This type of community procedure is compulsory for all medicinal products to be marketed in a Member State other than that in which they were first authorised. Any national MA granted by an EU Member State's national authority can be used to support an application for its mutual recognition by other Member States [6]. Basic arrangements for implementing the MRP in Member States have been laid down in Directive 2001/83/EC [7]. Later on a Decentralised Procedure (DcP) was also implemented on 30th October 2005 with its legal basis introduced by Directive 2004/27/EC [8] of the European Parliament and of the Council of 31st March 2004 amending Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use. As the MRP, also DcP is based on recognition by national authorities of a first assessment performed by one Member State. The difference is that it applies to medicinal products which have not yet received a MA in an EU country. In DcP an identical application for MA is submitted simultaneously to the competent authorities of the Reference Member State (RMS) and of the Concerned Member States (CMS). At the end of the procedure, the draft assessment report, summary of product characteristics (SPC), labelling and package leaflet, as proposed by the RMS, are approved. For both the MRP and DcP, the subsequent steps are identical [9]. Where the CP is not a viable nor possible route, the DcP certainly presents an attractive and more affordable regulatory pathway to bring new medicines to patients in the EU [10]. The oldest regulatory path to obtain MA in only one Member State is the National Procedure (NP). This procedure is nowadays seldom used by the innovative pharmaceutical industry. However for MA sought in non-EU countries such as Switzerland, where community procedures do not apply, this procedure remains the only possible option.

With rare exceptions, the CP is usually the choice for all new innovative medicines seeking EU-wide MA, therefore it is of great importance that approvals are achieved timely and efficiently. Even though the duration of the CP and its interim milestones are legally prescribed, there still exists a potential problem for access delay due to the ‘EMA time lag’. Such delays were exposed also by Netzer T. [11], concluding that the accelerated evaluation of new medicines for serious diseases is not working efficiently and the administrative time

needed to support rapid authorisation of oncology drugs should be reduced. As illustrated on Figure 1, 'EMA time lag' is defined as the time span stretching from the end of R&D phase to first MA granted by EMA through CP.



CHMP, Committee for Medicinal Products for Human Use; CP, Centralised Procedure; EMA, European Medicines Agency; EC, European Commission; R&D, Research and Development

Red - marks the initial point of the centralised procedure; Green – marks the end point of the centralised procedure; Full boxes – denote the interim milestones during the EMA centralised procedure; Blue shaded boxes with dotted lines - denote the assessment phase conducted by CHMP.

* only positive opinions are mediated to EC

Figure 1. Visual presentation of procedural steps that account for the EMA time lag during the CP

During the conclusive phase of R&D the manufacturer applies for the MA through EMA. In case of CP, the applicant is required to submit the MA application to EMA together with a copy of a full dossier and additional validation information (if requested) to both Rapporteur and Co-Rapporteur by the day when the dossier is validated by EMA. If the applicant has not done so, the start of the procedure may be delayed because of the time laps between the validation by EMA and the confirmation that the Rapporteur and Co-Rapporteur have received the dossiers [12]. As a result the procedural starting date may even be postponed to the next month [13] thus further delaying market access. Monthly submission deadlines as well as the predefined 19-day duration of period between submission and start of validation (pre-assessment phase) are both set and published by EMA [14].

Once the assessment phase has started (day 1 of the CP), EMA commences to track the so called 'active time' – time used for validation and assessment of the application. According to the first subparagraph of Article 6 (3) of the REGULATION (EC) No. 726/2004 [15] the

‘active time’ of the assessment phase shall not exceed the timeline of 210 days which is the defined time-limit for the assessment conducted by Committee for Medicinal Products for Human Use (CHMP). At this point we have to mention that Article 14 (9) of the REGULATION (EC) No. 726/2004 enables the assessment time of MA application to be reduced to 150 days if the medicinal product proves to be of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation [15]. This so called ‘accelerated assessment procedure’ was introduced by the revised EU pharmaceutical legislation already in November 2005 [16].

According to the timetable of the CP the ‘company phase’ or so called ‘clock-stop’ phase is usually scheduled to commence around day 120 of the assessment phase, when CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the Applicant by the EMA [12]. This phase actually accounts for the time during which EMA halts the actual assessment and waits for the applicant to provide further information, data or explanation towards outstanding questions posed by CHMP during the evaluation procedure. It may also account for the time spent during the possible inspection of manufacturer’s production sites or importing sites to confirm their good manufacturing practice (GMP) compliance status. Such inspections are conducted by the Inspection Team and do not fall within immediate competence of CHMP. They usually take place in parallel with the 'clock-stop' period and will approximately be conducted within two months from the adoption of the inspection request [12].

Once required data and explanations have been provided, the clock for ‘active time’ resumes at day 121. After adoption of a CHMP opinion (anticipated at day 210 of the CP), the preparation of the annexes to the Commission Decision are carried out whereby the applicant has at most 5 days (at day 215) to provide the EMA with product information and Annex A in all EU languages, including Norwegian, for review by member states [12]. While member states review product information and send linguistic comments back to EMA, the applicant has to provide EMA with final translations of the Summary of Product Characteristics (SPC), Annex II, labelling and package leaflet in all EU languages no later than until day 22 after the opinion is issued by CHMP (day 232 of the CP). Opinion and Annexes in all EU languages are then transmitted to applicant, European Commission (EC), and Members of the Standing Committee, Norway and Iceland by day 237 according to the EMA timetable [12]. If Members of the Standing Committee are in favour of the decision drafted by EC and do not address further questions of scientific or technical nature then the final EC decision should be

issued no later than day 277 of the CP. Thus EC has 40 days to issue the final decision by either granting or rejecting MA for a new drug.

CP is compulsory for any medicine manufactured using biotechnological processes[1], for orphan medicines and for human products containing a new active substance which was not authorised in the Community before 20th May 2004 (date of entry into force of Regulation (EC) No. 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes [15]. As of May 2008 the CP has also become mandatory for medicinal products containing new active substances for the treatment of auto-immune diseases and other immune dysfunctions and viral diseases [17].

1.1.2 Health Technology Assessment (HTA)

Increasing aging population, discovery of new mechanisms of diseases, vast development with introduction of countless new technologies and an increasing importance of preventive treatment resulted in rising expenditures for healthcare, posing new challenges for healthcare providers across Europe.

This phenomena had been largely responsible for the rise of technology assessment activities that lead to development of national and regional public HTA agencies and programmes in almost all Member States of the European Union (EU) in the 1990s [18]. Thus in some of the more developed older EU member countries (i.e. Netherlands, Spain, Sweden, United Kingdom) during the past two decades there has been a strong tendency for evolution of HTA and health economic evaluations put in place by healthcare purchasers and budget holders. Since then, demonstrating to regulatory agencies a product's safety, efficacy, and quality (the first three hurdles) is no longer sufficient [19]. Instead, manufacturers in certain countries today often come across the so called ‘fourth hurdle’. The ‘fourth hurdle’ is a common expression used for an additional step in drug evaluation processes whereby healthcare providers or third-party payers consider the clinical effectiveness and cost-effectiveness of interventions in addition to mandatory evaluation of safety, efficacy and quality conducted by responsible regulatory agencies (i.e. EMA, FDA, National regulatory agencies, etc.) [19]. Among European countries, such additional type of evaluation is often required from the pharmaceutical companies in order to secure reimbursement of a newly launched product or even to allow for the actual launch to take place. Therefore,

[1] Medicinal products developed by means of one of the following biotechnological processes: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods.

reimbursement procedures could as such be considered as a ‘fourth hurdle’ by some authors, as discussed below in part 1.1.3.

It should be mentioned that the recommendations and initiatives for harmonisation of evidence requirements for HTA in reimbursement decision making are currently being implemented through EUnetHTA project in Europe. However Hutton et al. explain that harmonisation of HTA across jurisdictions should not aim to produce a single decision on reimbursement and utilisation of a technology. Due to inherent differences between economies, societies, and health systems such an outcome would be neither feasible nor desirable [20].

Thus, to date HTA remains in domain of individual countries and their health care systems. However, as it has been shown before, the leading countries in HTA development (Netherlands, Spain, Sweden and the United Kingdom) may not be among those leading with regard to patient access (Austria, France, Spain and Switzerland) with the exception of Spain [4]. In the United Kingdom (UK) alone, there are three HTA bodies to be considered by the pharmaceutical companies when securing market access and enabling optimal uptake of medicines: Scottish Medicines Consortium (SMC) issues guidance for Scotland, All Wales Medicines Strategy Group issues guidance for Wales and National Institute for Health and Clinical Excellence (NICE) for England and Republic of Ireland. In particular, the impact of review and issuance of NICE guidance regarding a product or class of product is quite significant; positive NICE review may lead to a rapid uptake and faster patient access. Therefore NICE has previously been referred as the possible cause for delaying or even obstructing access to new innovative drugs and additionally delaying the optimal uptake of innovative therapies in the UK as NICE does not manage to undertake such reviews in a timely fashion [4]. Also in the CEE almost all of the 10 countries (Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia) have dedicated HTA bodies that are currently under development or discussion. These bodies have mostly advisory roles and thus make recommendations on reimbursement and/or pricing to decision-making bodies or payers [21].

While a great deal of harmonisation among European countries may have been achieved with common regulatory policies and with establishment of community procedures (CP, MRP and DcP), there is an evident harmonisation gap in the area of pricing and reimbursement (P&R). These activities have somewhat much more significant effect on patient access and availability of medicines, but still remain in domain of each individual member state to consider according to their health resources and priorities of their public health systems. Drs

Jönsson and Wilking warned that budgetary limitations of health care providers most probably pose the most serious treat to the optimal uptake and it is due to budgetary costs of some more expensive and most needed drugs that health care policy and decision makers may seek to delay or even restrict patient access to new innovative drugs, which can have unintended consequences for patients [4].

1.1.3 Pharmaceutical Pricing and Reimbursement

It has been shown before that price regulation may impact the launch of new drugs and thus access to new innovative therapies on different levels. This is also why reimbursement and pricing of approved drugs have been addressed before as the fourth and fifth hurdles of patient access [22]. Barros concluded that majority of EU countries regulate prices of pharmaceuticals through either international referencing (using as benchmark countries that have set lower prices), internal reference pricing systems put in place to promote price competition in domestic markets, and through so called positive lists for reimbursement to promote consumption of generics (including in some cases substitution by pharmacists of drugs prescribed by physicians) [23].

National regulators apply different pricing policies with the aim of limiting the expenditure of scarce resources. As reported until 2009, in countries such as Denmark and Germany, "free-pricing" policy was in place, whereby the manufacturer may freely set the prices of pharmaceuticals; however in both countries the authorities made sure that the prices of reimbursable pharmaceuticals (in particular the reimbursement prices) are indirectly influenced by the reimbursement system [24; 25]. In Germany a new system for determining drug prices was adopted on 1st of January 2011: manufacturers will still be able to freely set a price for a new drug, however during the first twelve months of the drug's introduction on the market, the manufacturer must prove that the drug offers some form of added clinical benefit over existing drugs, otherwise the product will be added to the reference pricing system [26]. Thus in Germany physicians bear a greater responsibility for the use of drugs as they are accountable for their own office budget [4]. In other European countries prices are controlled for outpatient pharmaceuticals. In the majority of these countries (e.g., in Finland, Italy and Poland), price control is limited to reimbursable pharmaceuticals, however some countries (amongst which are Greece and Luxembourg) regulate the prices of all pharmaceuticals, and in three countries (Netherlands, Norway and Portugal) price controls are applied for prescription-only pharmaceuticals [24]. An exception is the UK where no direct price control is in place, however the Pharmaceutical Price Regulation Scheme (PPRS) of the Department

of Health controls company profits and can demand price cuts or paybacks from companies [24; 4].

Individual European countries usually employ one, or a combination of two existing pricing policies. The one employed by most European countries is statutory pricing, where the price is being set on a regulatory basis often based on external price referencing procedures (i.e. international price comparison) with the reference countries and other methodological issues defined by statutory rules. The second are price negotiations, very common in Italy where prices are negotiated between the manufacturer and the government authority (like the Medicines Agency in Italy). In some countries, like Estonia, Latvia and Poland, statutory pricing is combined with price negotiations (so that statutory pricing follows price negotiations), whilst in others, like France, it is used as a back-up in case of the failure of negotiations [24].

Majority of European countries first set the price at the manufacturer level and then further control through margins. In some countries (Denmark, Finland, Latvia, Netherlands, Norway, Poland, Sweden and UK) prices are set at wholesale level. In seven of these countries, the ex-factory price is freely negotiated by the manufacturer and the wholesaler. In Luxembourg and in Slovakia prices are, in the first place, set at pharmacy retail level, but because of statutory wholesale and pharmacy margins the ex-factory and the pharmacy purchasing prices are indirectly fixed [24].

The most common pricing procedures among European countries are external price referencing, internal price referencing, and, to a less extent, cost-plus pricing [24]. External price referencing - i.e. international price comparisons - with various country "baskets" is used in majority of the European countries, except in Sweden, Switzerland [27], UK and in the free pricing countries, Germany and Denmark. Usually, external price referencing is undertaken for reimbursable pharmaceuticals since these prices are usually controlled. Lower income countries tend to refer to other low-price countries, while wealthier countries might define high-price states as reference countries. Some countries employ mixed baskets of low- and high-price countries [24]. Danzon and Epstein have shown that, particularly within the EU, regulatory price referencing by high-price countries (i.e. Germany, UK, Netherlands, Sweden) to lower-price countries (i.e. France, Greece, Italy, Portugal, Spain) incites manufacturers to delay launch in low-price countries until higher prices have been secured in other countries [28]. Moreover launch prices in low-price EU countries are directly related to prior launch prices in high-price EU markets. Whilst some authors suggest that lower prices in low-income countries could lead to a more equal access if only the parallel export to high-

price countries could be contained [4], the others confirm that regulating low prices may indirectly lead to launch delays [28].

Mostly as part of their reimbursement systems, European countries use different approaches to rationalise the use of medicines and contain expenditure on pharmaceuticals. For example, several European countries introduced ‘prescription guidelines’. In most cases these guidelines are only indicative; obligatory prescription guidelines are in place in Austria, Germany, Hungary, Norway and Slovakia. In most of the European countries ‘prescription monitoring’ is in place. In Belgium, for instance, each doctor has to prescribe a specific minimum amount of “cheap pharmaceuticals”: If they do not comply, they are asked to explain their actions and can also be fined or even lose their accreditation. Rarely, however still in place, are so called ‘pharmaceutical budgets for doctors’, mandatory in Germany, Latvia (with sanctions against prescribers for unjustified prescribing), Sweden (in some regions only) and Slovakia. They are also implemented in Czech Republic and in the UK [24].

1.2 Determinants and measures of patient access

In related peer-reviewed literature, the term ‘patient access’ is sometime used in combination with the term ‘market access’ [1; 4; 29]. Even though no clear distinction could be found between these two terms, it could be understood that ‘patient access’, in its meaning, can be considered superior to ‘market access’. The term ‘market access’ might refer only to the interim “destination”, whereas the ultimate benefit from the new treatments is actually destined for the patient.

Additionally there seems to be no distinct definition around the measures and hurdles standing in the way of patient access, thus different authors seemed to have used most distinct approaches to measure its extent and cross-compare it between different countries. The choice and methodology to measure its effect depend very much on the author and the scope of data available. In an international comparison of patients access to 100 best-selling pharmaceuticals, Cohen et al. observed patient access in France, Netherlands, UK and in the United States of America (US) through eight sub-dimensions: number of drug approvals, time of MA for approved drugs, coverage by third-party payers, cost sharing, percentage of covered drugs with conditions of reimbursement, speed from marketing approval to reimbursement, flexibility and evenness of drug availability to the population [3]. Interestingly, though not surprisingly, most authors focused on studying patient access in regard to oncology products. In fact, cancer patients experience among the highest morbidity and mortality rates of any other diseases in the developed world [30], thus making the need

for timely and equal access even more important. In a global report entitled "A pan-European comparison regarding patients access to cancer drugs", Drs Jönsson and Wilking addressed the issue of access by observing and describing possible hurdles that stand in the way of timely and equal access to oncology drugs across some European and non-European countries [4]. They also measured accessibility to oncology drugs through market uptake, concluding that some lower-income countries of CEE (i.e. Poland, Hungary and Czech Republic) - despite the fact that drug expenditure in these countries accounts for a large part of health care spending - have a slower uptake of oncology drugs compared to high-income countries (i.e. Austria, France and Switzerland) [31]. Russo and colleagues focused on measuring the duration of four sequential phases from European assessment until patient access in Italy [1]. Measuring the accessibility to targeted oncology drugs in Slovenia and selected European countries, Kos et al. observed the utilisation (volume uptake expressed in mg per individual dying of cancer type) of selected individual oncology drugs and concluded that low utilisation of most of the targeted oncology drugs in Slovenia, compared to selected European countries, limits the possibility for the high quality care of cancer patients [32]. On the other hand Obradović et al. [33] assessed the market uptake of biologic and small-molecule-targeted oncology drugs in selected European countries from the point of view of expenditures for specific drugs and in tracking market shares from 1997 – 2007. They concluded that expenditures on targeted oncology drugs have been increasing exponentially reaching a 40% share of the oncology drug market by 2007 and surpassed the market share of small-molecule-targeted oncology drugs as of 2007 [33].

All things concluded, there is probably no one-way of measuring patient access as the extent of all aforementioned hurdles varies greatly across countries. It is obvious that rapidly changing pharmaceutical markets together with constantly adapting healthcare systems form a very dynamic and complex European environment governed by a number of stakeholders (i.e. pharmaceutical industry, regulatory bodies, payers, policy makers and prescribers). All these stakeholders need to work together to improve the efficiency of drug evaluation processes to ensure that patients have timely access to safe and effective medicines at the price they and their nations can afford [34].

Restrictive conditions and high cost sharing may as well limit access to patients. As mentioned before, a delay in access may occur during the time it takes a payer to make its reimbursement decision after marketing approval [3], during marketing approval itself, but also due to delays in reimbursement dossier submission by the pharmaceutical company. Poor patient access to potentially life-saving novel pharmaceuticals reduces patients' quality of life

and may ultimately impact patients' chances for survival. Every delay in access and poor access performance also prevents the pharmaceutical industry from generating significant returns to cover the cost of research and development of a number of novel pharmaceuticals in their pipeline. Therefore, the pharmaceutical industry is constantly working on improving strategies and looking for new ways to satisfy the needs of regulators and payers with the aim of providing patient populations with rapid access and high uptake of their novel pharmaceuticals; while payers are gradually adapting their regulations and improving HTA strategies with the purpose of assuring optimal access to pharmaceuticals.

1.3 IMS MIDAS Quantum

Majority of the aforementioned authors employed Intercontinental Medical Statistics (IMS) data for purpose of defining the panel of study drugs, measuring the extent of patient access and market uptake of pharmaceuticals. IMS sales data are payable and can be obtained from IMS Health on demand. For purposes of our study IMS data has been kindly provided by *GlaxoSmithKline Services Unlimited, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom* (hereinafter referred as: GSK) with a prior written consent obtained from IMS Health.

IMS is short for IMS Health - the company who collects the MIDAS data. MIDAS is IMS Health's international system of integrated databases covering pharmaceutical sales information. The acronym stands for Multi-International Integrated Data Analysis System.[2]

IMS MIDAS Quantum is an on-line system which contains worldwide sales of pharmaceutical products. MIDAS Quantum consolidates data from IMS Health local country audits. Each audit gives an overview of how drugs are being distributed, sold and marketed by pharmaceutical companies in that country. In most major countries there are separate audits for retail and hospital channels, except for the USA which has additional channels. For each individual audit, IMS Health collects sample data from manufacturers, wholesalers or retailers (or a combination of these) at pack level. An estimate is made of the 'missing' proportion of data and a projection factor is calculated, which is then applied to the sample data to project it to national level. IMS Health audits both ethical and over-the-counter (OTC) sales data. In some audits these data are separated out and in others they are combined. All these audits feed into MIDAS Quantum.[3]

[2] *Sourced from internal website of GlaxoSmithKline Services Unlimited*

[3] *Sourced from Global Decision Support: Reference Guide to Secondary Data by IMS Health*

2 AIMS and OBJECTIVES

The study aim is to measure the differences and delay in patient access to novel pharmaceuticals launched in 27 selected European countries during a 6 year period between beginning of 2004 and the end of 2009. The study will focus on observing the causes of delay and inequality in patient access across study countries once the R&D activities have concluded.

The study objectives are to:

- Analyse the types of regulatory procedures employed in approval of new innovative drugs and measure annual trend in potential delay occurring during every stage of the centralised procedure;
- Examine the number of new innovative drugs made available in each country, the number of times countries were the first to launch in Europe and compare the time each country needed to introduce a novel pharmaceutical to their patients;
- Observe the annual rise in sales of novel pharmaceuticals as well as analyse cumulative sales and the uptake of novel pharmaceuticals in each country between 2004 and 2009;
- Compare the level of affordability to the level of average prices of novel pharmaceuticals in each country and thus indentify affordability gaps existing among selected countries.

This study will enable us to retrospectively assess whether patients gain equal and timely access to new innovative drugs in selected European countries and whether discrepancies in provision of such access are minor or otherwise. Any conclusions drawn from such a study could be of benefit to principle stakeholders who are either developing access strategies or aiming to create an optimal regulatory environment to facilitate patient access to novel pharmaceuticals entering the European markets in the future.

3 METHODS

3.1 Study design

We defined the panel of our study drugs using the sales data extracted from IMS MIDAS Quantum database. Drugs were sorted according to corresponding therapeutic areas and the selected European study countries described according to their economic and demographic indicators. In line with our objective to deliver a comprehensive and well structured study we then analysed patient access by applying four major measures: **1. Regulatory approval and 'EMA time lag'; 2. Launch delays; 3. Market and patient uptake to novel pharmaceuticals; 4. Affordability gap**.

3.2 Data collection

The main source of data for this study was IMS MIDAS Quantum. For this study we obtained IMS quarterly sales data in the period between the 1st quarter of 2004 and 2nd quarter of 2010, expressed in 3 different measurement units (value sales expressed in Euros, volume sales expressed in Standard Units (SUs) and weight measured sales expressed in KGs of active ingredient sold). Additionally we obtained IMS launch dates, country of launch and Anatomical Therapeutic Chemical (ATC) classification code reported by IMS for every molecule included in the study. For purpose of selecting a range of novel pharmaceuticals, with defined inclusion and exclusion criteria corresponding to the above described aims and objectives, IMS data were used.

Originally the IMS data were gathered on a regional level, characterised as 'Europe' in the IMS MIDAS Quantum, including 25 EU Member States (Malta and Cyprus are not available on IMS MIDAS database), Switzerland, Norway and Croatia. The market type defined by IMS was 'Ethical' including medicines that are available on prescription or are prescription bound and products that can be prescribed and purchased (OTC).

We excluded Croatia from our data collection and from the study since it is not a member state of the EU, EEA (European Economic Area) or EFTA (European Free Trade Association) and does not fall under the jurisdiction of the Centralised Marketing Authorisation (CMA) procedure conducted by the European Medicines Agency (EMA). Additionally hospital audits for Croatia are practically non-existent in our study and thereby the sales data provided does not include sales to hospitals. IMS sales data for hospitals markets in Greece, Portugal and Luxembourg are also not available in IMS MIDAS, therefore

these markets have been formally excluded from analysis of "Market and patient uptake of novel pharmaceuticals" as described on page 21. As for Estonia, Romania and Ireland, sales data are incomplete for the period between 2004 and 2010, thus data from these countries have also been excluded from analysis of "Market and patient uptake of novel pharmaceuticals" later on.

3.2.1 Exchange Rates and Currency Conversion on IMS MIDAS

Sales values (in any currency) are reported at ex-manufacturer price level. The MIDAS exchange rates are held by quarter and are at the average 'selling price' level for each period, compiled from the daily rates published in the Wall Street Journal. In our model the original currency used was British Pound Sterling (GBP) converted to Euros (EUR) at constant exchange rate: Sales in EUR = 1.137413 times sales in GBP.

3.3 Novel pharmaceuticals included into scope of our research

Using IMS data, in our study we included all novel pharmaceuticals – NCE and NBE – (hereinafter also as NMEs or new innovative drugs) launched for the 1st time in any of the 25 EU member states (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom) with addition of Switzerland and Norway (hereinafter as E-27) between January 1st, 2004 and December 31st, 2009.

First European launch of any panel drug was denoted by date (quarter and year) and country of first IMS reported sales of an active ingredient within E-27. The specified time span (study period) - January 1st, 2004 to December 31st, 2009 - during which all launches of our novel pharmaceuticals occurred for the first time in E-27, was chosen for 2 reasons:

- In 2004 eight European countries from Central and Eastern Europe (CEE) - Estonia, Czech Republic, Hungary, Slovakia, Slovenia, Latvia, Lithuania, Poland - joined the EU, followed by Romania and Bulgaria in 2007. The problem of equal access thus became a much broader issue within the enlarged EU after 2004;
- Considering novel pharmaceuticals first launched in 2004 as the oldest new drugs in the scope of our research, we still managed to largely avoid the impact of generic competition on reported sales.

Novel pharmaceuticals included into the scope of our research had to be 'new' – having not been used previously in any human application. We have not considered novel

pharmaceuticals that have been awarded MA in the EU, but have never been launched and thereby prescribed. We have included only active pharmacological agents and excluded diagnostics or medical devices. Vaccines were excluded from the scope of our research as they need to be considered separately from the regulatory, as well as pricing and reimbursement perspective. Additionally some vaccines, such as those used to protect the population against pandemic influenza, follow distinct authorisation procedure in the EU, allowing them to be authorised quicker than the 18 to 24 months usually required for the authorisation of a medicine in the EU.[4]

Using the ATC classification system, as described in Guidelines for ATC classification and Defined Daily Dose (DDD) assignment by WHO [35], we sorted all drugs in the scope of our research by 2nd level of ATC classification system. ATC codes for all panel drugs were extracted from the WHO website [36]. Using ATC codes we then analysed the availability of new innovative drugs according to their therapeutic subgroup.

3.4 Selected European study countries

The above mentioned 25 EU member states along with Norway as an additional member state of EEA and the EFTA, as well as Switzerland - an EFTA member state - had been selected as 27 European study countries (E-27). All countries apart from Switzerland adopted the complete *Community acquis* on medicinal products and are consequently parties to the 3 different marketing authorisation Community procedures: Mutual Recognition Procedure (MRP), Decentralised Procedure (DcP) and Centralised Procedure (CP), whilst in Switzerland National Procedure (NP) is required to gain marketing authorisation. The EEA agreement, together with the EEA Joint Committee Decisions, implies that regulation of pharmaceuticals in Norway is harmonised with the EU regulation. Thus, the requirement specifications in Norway are identical to those of the EU. Additionally we added Switzerland to the scope of our research, as a country often analysed in corresponding peer-reviewed literature [31; 32] as well as one of the countries to be noticeably specific in providing early and also first access to novel pharmaceuticals in Europe. To illustrate the differences amongst the chosen countries, E-27 were characterised by their economic and demographic parameters:

- Gross Domestic Product (GDP) per capita at market prices expressed in Purchasing Power Standards (PPS) obtained from Eurostat of the EC [37] for 2008;

[4] *From EMA webpage at www.emea.europa.eu*

- Total expenditure on health as percentage of GDP obtained from Global Health Observatory (GHO) at WHO website [38] for 2008;
- Country population expressed in number of residents reported for 2008 obtained from Eurostat [39] and
- Pharmaceutical expenditure as percentage of total expenditure on health extracted from OECD website [40] reported for 2008 or earlier years if not available.

Some of the described parameters were used in further analyses of time to access, uptake of new innovative drugs and affordability gap split by country.

3.5 Regulatory approval and 'EMA time lag'

To carefully examine all phases preceding the actual introduction of new innovative medicines to patients in E-27 we looked at some significant sub-dimensions and sets of activities taking place before the actual launch of the new medicine occurs. Thus we mainly examined the regulatory procedures applied in approval of some of our study drugs and focused on measuring the time lag occurring during the EMA centralised procedure.

3.5.1 Marketing authorisation of panel drugs

All novel pharmaceuticals extracted from IMS MIDAS database according to above described inclusion criteria have first been sorted by type of marketing authorisation procedure through which their first regulatory approval would have been obtained:

- Centralised Procedure (CP);
- Mutual Recognition Procedure (MRP);
- Decentralised Procedure (DcP);
- National authorisation Procedure (NP).

Thus we determined the exact number of novel pharmaceuticals approved through different marketing authorisation (MA) procedures. Drugs that never applied for MA or had never been registered in any of the study countries during the time span of recorded sales were mentioned or emphasized separately. Accessing the 'MRI product index' on Head of Medicines Agencies (HMA) webpage we obtained dates of first approval for all our study drugs approved through either MRP or DcP and information about Reference Member States (RMS) and Concerned Member States (CMS) for every approved pharmaceutical [41].

3.5.2 Time lag during EMA centralised marketing authorisation procedure

Time lag during CMA procedure conducted by EMA was fragmented into 5 distinct time phases (Figure 1), thus enabling to analyse possible trends of mean and median times spent during every stage of the CP. When analysing all five phases of assessment conducted by EMA during CP, evidently only the collated times of those novel pharmaceuticals that had undergone CP between 2004 and 2009, were considered. Thus a drug must have received its first opinion issued by CHMP between 2004 and 2009 to be included into further analyses of 'EMA time lag' described below.

For each novel pharmaceutical we calculated the duration of each phase using relevant interim dates obtained from European Public Assessment Reports (EPAR) [42] and EMA Annual Reports for years 2004 to 2009 [43]: (i) Date of submission of the application for a CMA, (ii) Date of official start of assessment process conducted by CHMP, (iii) Date of 1st opinion issued by CHMP, (iv) Date of opinion received by EC, (v) Date of issue of MA valid throughout the EU. Durations of 'active time' and 'clock-stop time' (or 'clock-stop'), spent during the assessment phase of every drug undergoing CP, were also obtained from these sources. Analysing these five steps using Box and Whisker plot chart, we demonstrated median times as well as examined the distribution of times spent during every stage of review of novel pharmaceuticals conducted by EMA:

1. **Pre-assessment phase: Time lag between Submission of application to EMA – Official start of assessment**

   Calculated as a difference between the date of official start of assessment process conducted by CHMP and the date of application submitted for a CMA procedure (expressed in number of days).

2. **Assessment phase (ACTIVE TIME): Time lag between Official start of assessment – first opinion issued by CHMP**

   It accounts for the time spent by EMA and CHMP during the actual effective assessment of the dossier submitted for CMA by the applicant. It is reported by EMA in its Annual Reports as 'active time' used between the day of the official start of assessment conducted by EMA/CHMP and the day of first opinion issued by CHMP.

3. **Company phase (CLOCK-STOP): Time lag between Official start of assessment – first opinion issued by CHMP**

'Clock-stop' accounts for the remaining time (other than the 'active time') used between the day of the official start of assessment conducted by EMA/CHMP and the day of first opinion issued by CHMP. It is also reported in EMA Annual reports.

4. **EMA post-opinion phase: Time lag between 1st positive issued opinion by CHMP – Opinion received by European Commission (EC)**

Once the CHMP reaches a final decision and issues a positive opinion, the opinion must be mediated to the EC for official European-wide approval of marketing authorisation in EU and EEA member states. Time lag during this phase is therefore calculated as number of days spent for the CHMP's opinion to reach the EC.

5. **EC decision process: Time lag between Opinion received by European Commission (EC) – Marketing Authorisation granted by EC**

Once the EC receives the final positive opinion issued by CHMP together with all documentation translated into official languages of all EU and EEA member states, it then adopts the positive opinion issuing a marketing authorisation valid throughout the European Union and European Economic Area (EU approval). EC decision process therefore accounts for the time passed from the date when opinion is received by EC to the date of official marketing authorisation adopted by EC.

3.5.2.1 Median and average days spent during every stage of the centralised procedure

To observe trends of shortening or prolongation of 'EMA time lag' and for the sake of possible comparison with the analyses of similar times and stages published by EMA in its Annual reports, the analysed median and mean times used for approval of panel drugs within each of the five phases have been split by year of first opinion issued from CHMP. We performed the analyses of mean and median times spent during every phase of the CP in two separated stacked column charts. In both analyses times spent during every phase have been first sorted by year in which novel pharmaceuticals received first opinion issued by CHMP. Mean and median times spent during every phase of the CP for every year between 2004 and 2009 have been calculated and marked to be clearly distinguished. We calculated also cumulative time presenting the sum of median and mean times of all phases between 2004 and 2009. Column showing 'clock-stop' days (usually occurring due to requests for additional explanations and documentation by EMA experts to the company) have been shown separately for illustrative purposes, but included into cumulative value.

3.6 Launch delays

We analysed the countries in which novel pharmaceuticals had first been launched and the number of first launches occurring in every country. We also looked at the mean time from first launch of drug in Europe to introduction in individual countries and additionally observed the relation of such calculated mean times to country specific demographic and economic indicators.

3.6.1 Novel Pharmaceuticals introduced in E-27

We analysed how many of all drugs included in the scope of our study have actually been introduced to patients in each of the 27 European study countries (E-27) between 1st January 2004 and 1st July 2010, the end date of our sales data collection. Using country-specific launch date - defined as the quarter of first recorded sales in the country - we separately examined every novel pharmaceutical in the scope of our research and reviewed 27 European countries to conclude where and in how many of the E-27 had each of the panel drugs been introduced to date.

3.6.2 Number of first European launches recorded in each country

Using IMS MIDAS Quantum quarterly sales data for every drug in the scope of our research, we were able to identify the quarter and year when sales of that particular medicine first accrued and also the exact country where sales of such novel pharmaceutical was first detected among all E-27 study countries. According to the definition by IMS Health, a year and quarter of first sales recorded in a particular country can be identified as a date when product or a pack had first been sold to either wholesaler, hospital or even directly to pharmacy.[5,6] Based on such definition we assumed the date when the sales first occur in a country, to be approximately equal to the date when the drug is being prescribed or dispensed to the patient for the first time. Sorting the innovative molecules launched between 2004 and 2009 by country and by year of their first launch, we were able to analyse the number of first European launches (within E-27) that occurred in each of the study countries and determine the number of first recorded launches per year of launch for each country.

[5] *Global Decision Support prepared by IMS Health; Reference guide to Secondary data (GSK internal source)*

[6] *Retail and Hospital Audit Synopsis by IMS Health (GSK internal data source)*

3.6.3 Time from the first European launch to the first use following in each country

To most accurately estimate the mean time it took for each of the study countries to introduce a new innovative drug to their patients after it had been first launched in E-27 we decided to apply Kaplan-Meier survival curve. After counting the number of novel pharmaceuticals launched in each of our study countries (as shown in Table V) by the end of our observation period in 2nd quarter of 2010, it was clear that not all new drugs have been made available in each of the E-27 during time scope of our research. This is because some of these drugs may have been registered only through NP and were not successful in obtaining CMA, but also because some drugs may have been introduced in a country even after our observation of the sales data ended. Thus we assumed that only in the case of drugs approved by either CP, MRP or DcP during the time scope of our research, we could reasonably allow for the prospect of these particular drugs to be introduced in any E-27 during our time of observation and also after the 2nd quarter of 2010, when our observation of the sales data ended. Drugs launched in E-27 that have not yet been introduced in particular countries by the end of our observation period have been considered 'censored' events. In cases where a marketing authorisation for a particular drug would have been removed during the observation period between the first quarter of 2004 and 2nd quarter of 2010 - thus preventing this drug from being introduced in any further countries - such drug would be considered a 'right censored' event.

Using Kaplan-Meier curve, our analysis of comparing countries according to their speed of launch considered both the number of times a country was first to launch among E-27 as well as the time it took the country to launch the medicine after the first recorded European launch. Kaplan-Meier curve was fed with time span calculated for every drug approved in each country separately either by CP, MRP or DcP counted from the first European launch to the first use in each country. Using IMS sales data to identify quarter and year when sales of a particular medicine first accrued, for every molecule in every country in the scope of our research, we calculated the time gone by from date of first launch to the launch date in the country. For every country, the calculated time lag was expressed as a mean number of months needed to introduce a new innovative drug after first European launch. As sales data, and thereby dates of launch, were reported quarterly – with 3-month accuracy – the mean time span calculated using Kaplan-Meier method was presented with a 3-month accuracy. Germany was used as a comparator (index) country on all four charts.

3.6.3.1 Relation of calculated mean times to country specific demographic and economic indicators

Using the bubble chart we examined possible relation between:

- abscissa – calculated mean times (using Kaplan-Meier curve) spent from the first European launch to the first subsequent use in each country,
- ordinate – the PPP-adjusted GDP per capita (expressed in PPS) and
- bubble size – the size of total number of residents in the country.

Making such a comparison we tried to indentify if disparities in patient access could possibly be related to the size of different healthcare systems in Europe and at the same time also to the affordability of each country. We expressed the size of every country's healthcare system through its number of inhabitants in 2008 and country's affordability through GDP per capita in 2008 adjusted by purchasing power parity (PPP) to abolish the price differences.

3.7 Market and patient uptake of novel pharmaceuticals

Overall we observed the uptake using quarterly cumulative sales from the time of first detected use of new drugs in the 1st quarter of 2004 up to the end of our recorded sales data in 2nd quarter of 2010. Due to either incomplete or missing sales data – reasons are more accurately described in chapter 3.2 above - countries such as Estonia, Greece, Ireland, Luxembourg, Portugal, Romania are formally excluded from this analysis, but are still presented on the charts for arbitrary interpretation. However, for possibility of interpretation and possible comparison of uptake, we decided to present also the aforementioned countries, although with notice of caution in their interpretation considering the reasons why these countries were excluded from such analysis. Accordingly, lines marking the utilisation of novel pharmaceuticals in Estonia, Greece, Ireland, Luxembourg, Portugal, Romania are therefore slightly shadowed in the colour (and reduced in the width of the line).

3.7.1 Sales of novel pharmaceuticals

We analysed the increasing annual trends in total monetary sales of all novel pharmaceuticals launched between 2004 and 2009 as well as the portion of sales presented by groups of pharmaceuticals split by year of first launch in E-27. We compared the absolute total monetary sales per capita of all novel pharmaceuticals in each country with the number of volume units of new drugs sold per capita in each country and performed a cross-country comparative analysis of portions of sales attributed to groups of new drugs split by year of first launch in E-27.

3.7.2 Absolute cumulative uptake of novel pharmaceuticals

We examined the uptake of a set of specific drugs launched in 21 European countries (E-21) for which we obtained consistent and complete IMS data. Formally, however not visually, Estonia, Greece, Luxembourg, Portugal, Ireland and Romania have been excluded from this analysis and its argumentation. Uptake was analysed using IMS sales data as approximate indicator of actual cumulative utilisation. Sales data expressed in EUR of a specific drug sold in individual country by quarter of each year, were divided by number of residents in the respective country recorded in 2008 obtained from Eurostat database of European population [44]. Absolute cumulative uptake was calculated as cumulative sales (expressed in EUR/inhabitant) of all novel pharmaceuticals introduced in each of the E-27 countries anytime between 1st quarter of 2004 and 2nd quarter 2010, when the time scope of our study ended. To improve the graphic presentation of uptake the total sales was projected in four different line charts illustrating market uptake for countries divided by segments of:

A. five largest European markets of pharmaceuticals (thereinafter referred as: EU-5),

B. countries that joined the EU before 2004, excluding the EU-5 (thereinafter referred as: EU before 2004) and additional 2 non-EU countries (Norway and Switzerland)

C. countries that joined the EU during or after 2004 (thereinafter referred as: EU after 2004),

D. a line chart representing average uptake of all 3 aforementioned groups of countries for the sake of easier regional comparison.

In all four charts representing different groups of countries we used average uptake of E-21 and EU-5 as comparator lines between separate charts.

3.7.3 Absolute cumulative uptake valued against affordability of each country

To analyse the impact of economic affordability of every country to uptake new innovative drugs launched between 2004 and 2009, we adjusted the cumulative market uptake using the measure of affordability of country's economy expressed as income per capita. Thus monetary sales per capita (EUR/inhabitant) representing the absolute cumulative market uptake of novel pharmaceuticals was divided by PPP-adjusted GDP per capita (expressed in PPS) in 2008 [37] representing country's affordability. To maintain a comparable scale - for the sake of easier comparison - between charts displaying adjusted and unadjusted absolute cumulative uptake, PPP-adjusted GDP per capita was indexed on Germany (as a reference country).

3.7.4 Absolute cumulative uptake valued against countries' total expenditure in health care

In order to assess the capability of different healthcare systems in enabling rapid uptake of novel pharmaceuticals, we valued the absolute cumulative market uptake also against affordability of healthcare systems in individual countries. Thus market uptake, expressed as cumulative value spent for novel pharmaceuticals in EUR per capita, had to be divided by health expenditure per capita expressed in PPS for respective country included in this analysis. Health expenditure per capita expressed in PPS was calculated by multiplying the PPP-adjusted GDP per capita (expressed in PPS) [37] by total expenditure on health (expressed in % of gross domestic product) [38]. To maintain a comparable scale - for the sake of easier comparison - between charts displaying affordability-adjusted and unadjusted absolute cumulative uptake, also in this case health expenditure per capita expressed in PPS was indexed on Germany.

3.8 Affordability gap

To uncover possible affordability gaps we indirectly compared the SU prices of novel pharmaceuticals expressed at ex-manufacturer level to GDP per capita in each of the E-27 study countries. This said, for every individual drug in each country we first calculated the mean value of SU prices reported in the first two consecutive quarters after launch. Using this mean SU price for every individual drug we then calculated the relative difference from the mean SU price reported for Germany (index country with index price of 100%). For each country of the E-27 we then used the calculated relative differences in prices of individual drugs (expressed in %) to calculate the mean deviation in price of all pharmaceuticals launched in that country. Such mean of relative deviation in price was then plotted as a column for every individual country. We then also calculated the relative deviation of GDP per capita (expressed in PPS) reported for each country from the one reported for Germany (index country with index GDP per capita of 100%) and plotted them onto the chart in descending order for easier interpretation.

For easier comparison and to keep it consistent with previous methods (i.e. comparison of times analysed using Kaplan-Meier curve method, absolute cumulative uptake) we again used Germany as a reference (index) country. Thus Germany automatically accounted for 100% in both parameters observed.

4 RESULTS

4.1 Novel pharmaceuticals included into scope of our research

A total of 125 novel active ingredients used for the first time in any human application, launched in E-27 between January 2004 and December 2009, have been extracted from IMS MIDAS Quantum. They were grouped into 38 therapeutic subgroups according to ATC classification system (Table III in Appendix 1). 15.2% (19 molecules in total) and thereby far the most of new molecules are from the ATC class of antineoplastic agents (L01), followed by almost 9% (11 molecules) of agents with immunosuppressant (L04) properties and 6.4% (8 molecules) of antiviral agents for systemic use (J05). There were 7 new active molecules made available in each of two other therapeutic subgroups: anti-diabetic agents (A10) and antithrombotic agents (B01), both accounted for little more than 11%. At the 6th place in line by number of new active ingredients launched are agents designated for cardiac therapy (C01) and anti-bacterial agents for systemic use (J01), with 6 NMEs in each class. Other therapeutic subgroups follow accordingly. 25 of all drugs have been designated an orphan drug status. 31 of all drugs are of biologic origin thus considered new biological entities (NBEs).

A complete list of all novel pharmaceuticals included in our research can be found in the "Appendix 5: List of all novel pharmaceuticals included in the scope of our research".

4.2 Selected European study countries

As shown in Table I, the biggest 5 EU countries (EU-5), considering their population size in descending order are Germany, France, UK, Italy and Spain, whilst the five countries with the highest income per capita are Luxembourg, Norway, Switzerland, Netherlands and Ireland. Countries spending the most of their national GDP on health care are France, Switzerland, Germany, Austria and Portugal. Five countries with the highest portion of expenditure on pharmaceuticals leading by far are Hungary, Greece, Slovakia, Poland and Portugal.

Table I. Relevant country specific demographic and economic indicators

COUNTRY	PPP-adjusted GDP per capita at market prices (in PPS) in 2008 [37]	PPP-adjusted GDP per capita at market prices (indexed on Germany)	Total population in 2008 [39]	Total Expenditure on Health (% of GDP) in 2008 [38]	Pharmaceutical Expenditure (% of Total Expenditure on Health) in 2008 [40]	
Austria	31,100	107	8,318,592	**10.1**	13.3	
Belgium	28,800	99	10,666,866	9.7	15.1	Estimate

COUNTRY	PPP-adjusted GDP per capita at market prices (in PPS) in 2008 [37]	PPP-adjusted GDP per capita at market prices (indexed on Germany)	Total population in 2008 [39]	Total Expenditure on Health (% of GDP) in 2008 [38]	Pharmaceutical Expenditure (% of Total Expenditure on Health) in 2008 [40]	
Bulgaria	10,900	38	7,640,238	7.3	N/A	
Czech republic	20,200	70	10,381,130	6.8	20.4	
Denmark	30,800	106	5,475,791	9.9	8.6	2007 data
Estonia	17,000	59	1,340,935	5.3	20.7	
Finland	29,500	102	5,300,484	8.4	14.4	
France	26,700	92	**64,004,333**	**11.1**	16.4	
Germany	29,000	100 (index)	**82,217,837**	**10.4**	15.1	
Greece	23,500	81	11,213,785	9.7	**24.8**	2007 data
Hungary	16,200	56	10,045,401	7.4	**31.6**	
Ireland	**33,300**	**115**	4,401,335	8.7	17.3	
Italy	26,000	90	**59,619,290**	9.0	18.4	
Latvia	14,100	49	2,270,894	6.5	N/A	
Lithuania	15,300	53	3,366,357	6.2	N/A	
Luxembourg	**70,000**	**241**	483,799	7.2	9.1	
Netherlands	**33,500**	**116**	16,405,399	9.1	N/A	
Norway	**47,300**	**163**	4,737,171	8.6	7.5	
Poland	14,100	49	38,115,641	6.6	**22.6**	
Portugal	19,500	67	10,617,575	**10.1**	**21.8**	2006 data
Romania	11,700	40	21,528,627	4.7	N/A	
Slovakia	18,100	62	5,400,998	7.8	**27.6**	
Slovenia	22,800	79	2,010,269	7.8	18.7	
Spain	25,900	89	**45,283,259**	8.7	20.5	
Sweden	30,800	106	9,182,927	9.1	13.2	
Switzerland	**35,800**	**123**	7,593,494	**10.5**	10.3	2007 data
United Kingdom	28,700	99	**61,191,951**	9.0	11.8	

GDP = Gross Domestic Product; PPP = Purchasing Power Parity; PPS = Purchasing Power Standards (unit); N/A = Not available
The leading five values it its category are displayed in **bold letters.**

4.3 Regulatory approval and 'EMA time lag'

4.3.1 Marketing authorisation of panel drugs

Between January 2004 and December 2009, 125 novel pharmaceuticals used for the first time in any human application have been first registered and made available in Europe. One NME (picibanil), even though it was made available, was never really authorised for human use in Europe. As shown in Table II, 85.6% of these new innovative drugs (107 drugs) have been granted marketing authorisation through CP conducted by CHMP at the EMA. 12 drugs, representing only 9.6% of all panel drugs, have been approved through MRP in selected EU member states. Only 2 drugs were approved by DcP in 2008 and 3 novel pharmaceutical of all 125 drugs have been successfully approved only in Switzerland through NP.

Table II. All 125 panel drugs split by type of marketing authorisation procedure and by year of 1st authorisation granted

Marketing authorisation procedure	Year of first authorisation granted							Overall approved in Europe
	> 2004	2004	2005	2006	2007	2008	2009	
Centralised procedure	2	16	10	19	25	16	19	107
Decentralised procedure						2		2
Mutual recognition procedure	6	5	1					12
National procedure*	1					1	1	3
Never authorised for HU in E-27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(1)
Total of panel drugs	**9**	**21**	**11**	**19**	**25**	**19**	**20**	**124 + (1)**

* = marketing authorisation granted only in Switzerland
HU = human use; N/A = Not applicable

4.3.1.1 Centralised Procedure

For 109 of our study drugs, the licence holder submitted their first application for a CMA to EMA, however in 2 cases Ixempra® (ixabepilone) and Zeftera® (ceftobiprole medocaril) have been issued a final negative opinion by CHMP and have not been granted a CMA. Finally, in total 107 novel pharmaceuticals introduced to E-27 had been successfully approved by EMA, even though Dynepo® (epoetin delta) received CMA already in March 2002 and Tikosyn® (dofetilide) even before, in November 1999. Both were later voluntarily withdrawn by MA holder for commercial reasons – Tikosyn® in January 2004 and Dynepo® in March 2009. Thus, effectively 105 novel pharmaceuticals, representing 96.3% of 109 medicines submitted for CMA and 84.0 % of all 125 panel drugs, were first successfully authorised by EMA through CP sometime between 2004 and 2009 (Table II and Table IV in Appendix 2).

4.3.1.2 Decentralised Procedure and Mutual Recognition Procedure

Looking at Table IV in Appendix 2 and Table II we can see that only two pharmaceuticals - Taflotan® (tafluprost), with Sweden as a reference member state (RMS) in DcP and Priligy® (dapoxetine) registered in Germany as RMS - received MA through DcP. 12 other drugs had been authorised by MRP after being first approved in RMS. For two of the 12 medicines, first authorised by MRP, the licence holder later submitted an application for CMA to EMA. Thus Remodulin® (treprostinil sodium), first registered by MRP, had been added a different preservative (metacresol) and applied for CMA under branded name Tyvaso® (treprostinil sodium) in December 2008. However whilst being reviewed by CHMP, the applicant decided to withdraw the application stating that decision to do so was based on a major objection of the CHMP that findings of non-compliance with good clinical practice (GCP) at two sites would preclude a recommendation for approval [45]. In another case, medicine Afinitor®

(everolimus) indicated for patients with advanced renal carcinoma was granted CMA with an orphan drug status only after being first registered through MRP as Certican® (everolimus) for prophylaxis of organ rejection in adult patients at low to moderate risk of receiving an allogenic renal or cardiac transplant.

4.3.1.3 National Authorisation Procedure

As per Table IV in Appendix 2, three of our panel drugs, Norataka® (nesiritide), Zevtera® (ceftobiprole medocaril), Ixempra® (ixabepilone) had only been successfully authorised by Swissmedic - Swiss Agency for Therapeutic Products - through NP in Switzerland. Zevtera® (ceftobiprole medocaril) and Ixempra® (ixabepilone) were both rejected by CHMP.

4.3.1.4 Drugs without marketing authorisation during the time of recorded sales

For OK-432 (picibanil) and Tikosyn® (dofetilide) IMS reported minor sales only in Poland. Picibanil is a lyophilised preparation of a low-virulence strain (*Su*) of Streptococcus Pyogenes (*S. Hemolyticus*) incubated with benzylpenicillin that has been used as immunotherapy for malignant tumours [46]. As per Table IV, picibanil has not been approved in any European country to date. In fact it has only been approved in Japan as an anticancer agent in 1975 [47] and later also in South Korea and Taiwan [48]. Tikosyn® (dofetilide) had been authorised by EMA already in November 1999 (Table IV in Appendix 2), but was voluntarily withdrawn by MA holder for commercial reasons in January 2004 [49].

4.3.2 Time lag during EMA centralised marketing authorisation procedure

Having sorted 105 novel pharmaceuticals successfully authorised through CP by year of their first positive opinion granted by CHMP, we observed the annual trends (from 2004 to 2009) of median and mean times spent for every stage of the evaluation process during the CP as described in paragraphs below. Box and Whisker plot chart, as shown on Figure 2, was used to illustrate median times as well as the range in distribution of those times spent during every stage of review of novel pharmaceuticals conducted by EMA:

1. Pre-assessment phase

It turns out the median time used to officially commence the evaluation process, once the dossier had been submitted (Figure 2), appears to have been steadily increasing from 2004 to 2009. While in 2004 and in 2005 the median time appeared to be around 19.5 and 18.5 days respectively, in 2006 the median time passed to start the assessment reached 21.0 days, with

more than 50% of all times calculated for medicines approved in 2007, 2008 and 2009 remaining above the 19-day margin.

2. Assessment phase (ACTIVE TIME)

Observing the distribution and median times actively spent for the actual assessment of the dossier submitted for CMA on Figure 2, from 2004 to 2005, we can clearly observe an evident 8.9% increase in the number of days it took EMA to actively assess the application rising from median of 196 days to 213.5 days. By dropping back to 197 in 2006, there was again a decline in the number of days spent for EMA 'active time'. Since then the 'active time' used during assessment of all drugs approved until 2009 remained more or less steady with a relatively small interquartile range in times observed between different years.

3. Company phase (CLOCK-STOP)

On Figure 2 we can observe the median 'clock-stop' times used by the applicant during the evaluation procedure of novel pharmaceuticals to be in a relatively steep decline between 2004 and 2006, when the median time dropped from to 173.0 days to 112.0 days respectively. In 2007, 2008 and 2009 the median 'clock-stop' time was kept constant at 132.0 days.

4. EMA post-opinion phase

From 2004 to 2009 there appears to be no steady trend in time spent for the EC to receive the positive opinion once granted by the CHMP. Thus we can observe a significant variation in median times and distribution of times between 2004, when the median time of only 6.0 days was needed for the opinion to be sent to EC, and 2005, when the longest median time at 48.0 days was reached. From 2006 to 2009 the median time remained more or less constant at around 28.0 days needed for the final positive opinion to reach the EC. For Nagalzyme® (galsulfase), approved in 2006, we can observe also the longest time of 98.0 days for the CHMP's opinion to reach the EC. Three outliers, with times of 99.0 days and 129.0 days recorded in 2006 for Macugen® (pegaptanib) and Atryn® (antithrombin alfa) respectively and time of 173.0 days for Vectibix® (panitumumab) authorised in 2007, have been excluded from this analysis as in this three cases the times were prolonged either due to re-examination procedure after CHMP first issued a negative opinion or due to CHMP's request for new safety information after the medicine had already been granted a positive opinion.

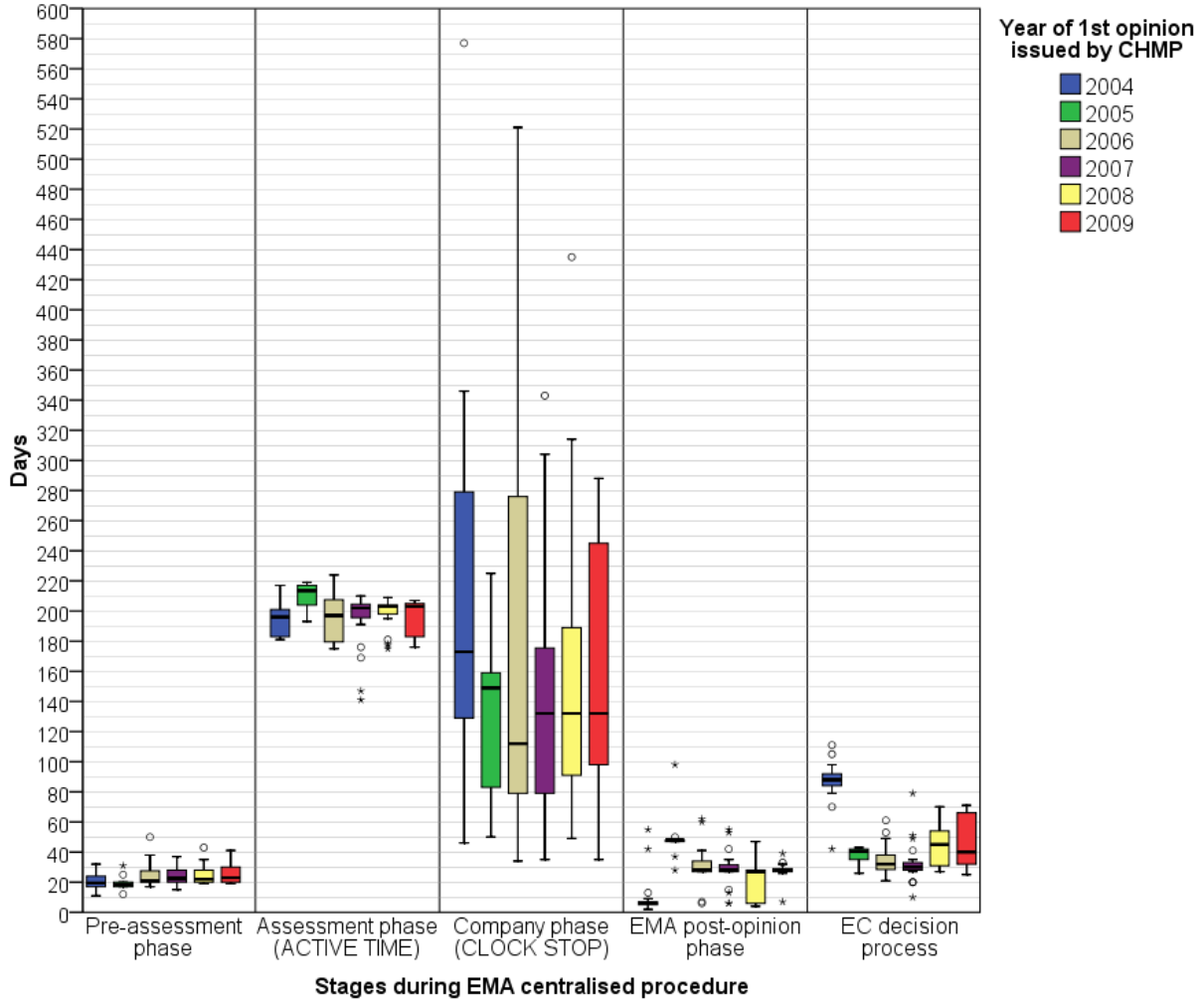


Figure 2. Box and Whisker plot of time spent during every stage of the EMA centralised authorisation procedure for new innovative drugs. Split by year of 1st CHMP opinion issued.

5. EC decision process

From 88 days in 2004, we can observe a significant drop for more than 50% in a median number of days used by the EC to adopt the CHMP's positive opinion in 2005 – reaching only a median of 40.5 days (Figure 2). In 2006 and 2007 the decline in time continues thus reaching the bottom at the median time of 30.0 days. However, in 2008 and 2009 we can again observe a relatively significant increase in the number of days used by the EC to adopt the positive opinion, therefore reaching the median value of 45 days in 2008 with 50% of times (between the 25th and 75th percentile) being stretched between 30.0 and 58.0 days. For novel pharmaceuticals approved in 2009 the times observed between the 25th and 75th percentile of all times analysed stretch between 32.0 and 68.5 days, however median time for the EC to adopt the CHMP's positive opinion drops slightly reaching 40.0 days. Analysing the times of medicines approved in 2008 we excluded the outlaying time of 149 days observed for Tykverb® (lapatinib), since in this case the dossier and new clinical data received just after

CHMP issued their first positive opinion in 2007 had to be reviewed by CHMP for the second time and therefore substantially delayed the process of final approval by EC.

4.3.2.1 Median and average days spent during every stage of the centralised procedure

Looking at the column chart on Figure 3, we are able to observe and compare the changing trends in median number of days spent for every stage during the CP. In the following chart (Figure 3), we can observe a significant decline in the overall number of median days spend during every stage of the CP in 2005 and then in 2006. Afterwards, the overall number of median days spent for every stage of the procedure remains practically constant with minor fluctuations between 2006 and 2009. Separately for every year, we can also observe a slight but almost constant decline in the median time spent for 'clock-stops'.

For purposes of comparison of our analysis with analysis annually conducted by EMA, we have prepared a similar chart on Figure 4 analysing also the mean times spent during every stage of the CP. Even though with slight differences in values, the overall annual trend of mean times spent during CP was similar, however the decrease in cumulative mean time used from 2004 to 2007 and increase from 2007 to 2009 was more gradual from that of the total of median times shown in Figure 3.

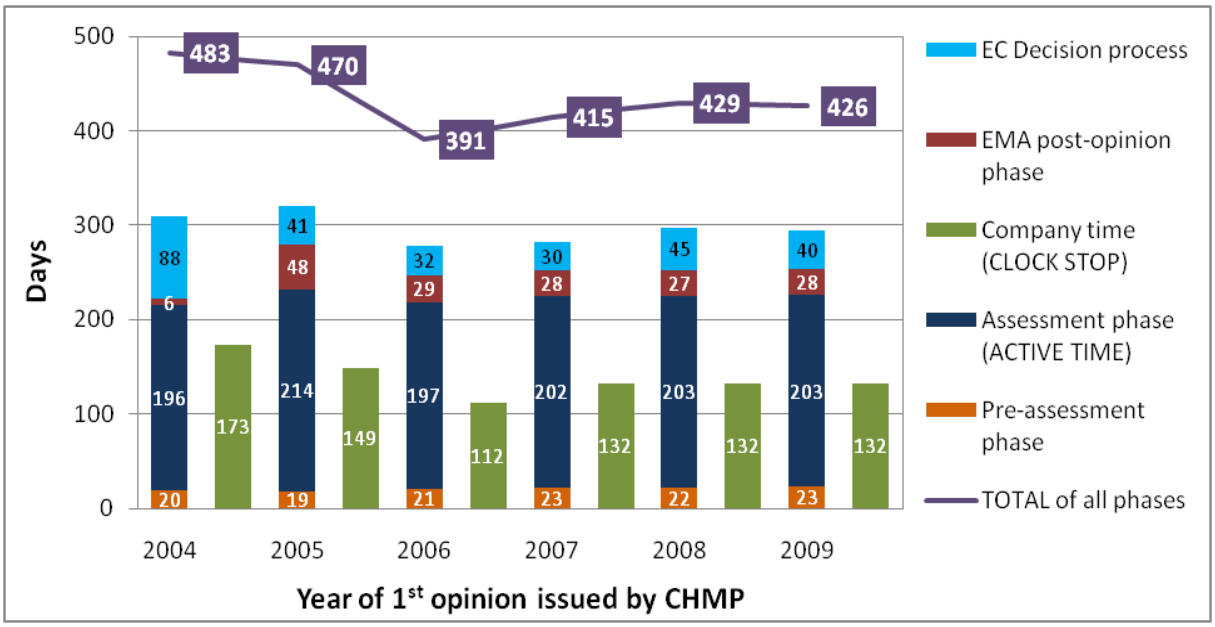


Figure 3. Median times used by EMA during each phase of centralised procedure for 105 novel pharmaceuticals split by year of 1st opinion issued by CHMP.

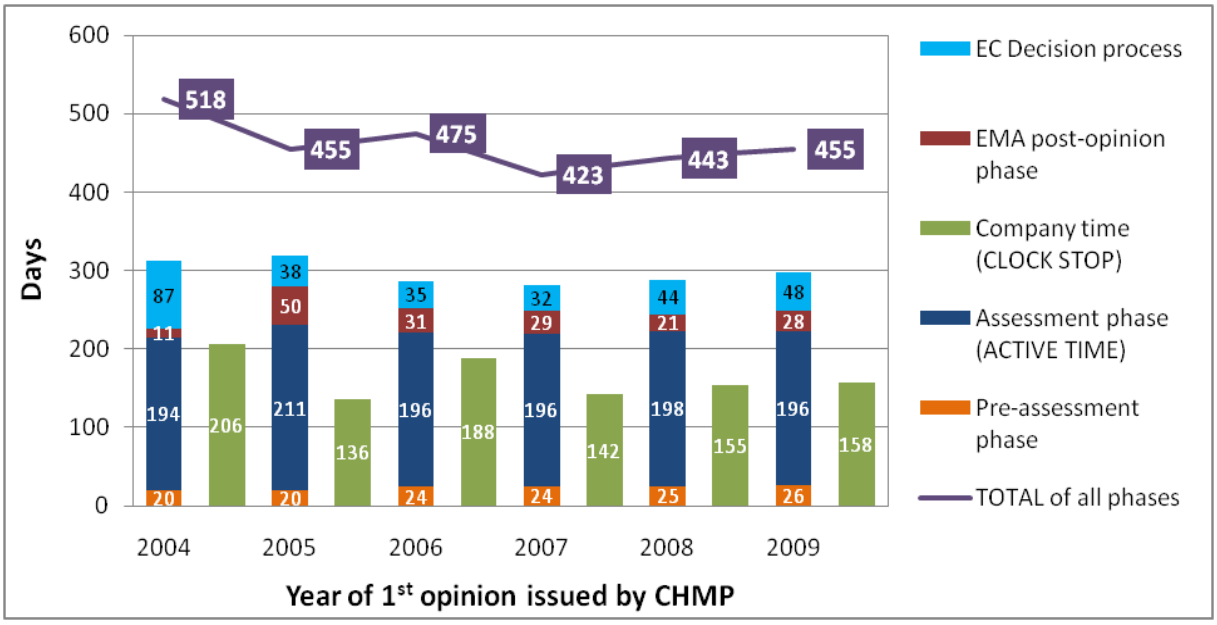


Figure 4. Mean times used by EMA during each phase of centralised procedure for 105 novel pharmaceuticals split by year of 1st opinion issued by CHMP.

4.4 Launch delays

4.4.1 Novel pharmaceuticals introduced in E-27

Germany, UK, Austria, Norway, Sweden and Denmark appear to be leading, having made available more than 100 novel pharmaceuticals (out of all 125) to its patients. Spain, Finland, Italy and Poland appear to have launched somewhere between 73% and 79 % of all novel pharmaceuticals launched in Europe between 2004 and 2009, while countries such as France, the Netherlands, Switzerland, Ireland and Greece fall into a group with less than 71% of all new molecules launched between 2004 – 2009 introduced to their patients until June 2010. With less than 61% of all novel pharmaceuticals made available to their patients are predominantly countries of the CEE that joined the EU after 2004. Nevertheless, two exceptions are Poland with 92 and Slovakia with 88 novel drugs introduced during the specified 6.5-year period, following all other new western EU member states. Portugal, has managed to introduce merely 27.2% of all new drugs launched between 2004 and 2009 to their patients until the end of our sales tracking period in June 2010.

In Table V in Appendix 3 a full list of E-27 can be seen, arranged according to total number of new innovative drugs made available to their patients at any time over a 6.5 year tracking period between January 2004 and June 2010 as per time interval of the sales data provided by IMS MIDAS Quantum.

Looking at the trend of total number of launches recorded over the past 6 years at the last row in Table V in Appendix 3, we are able to observe an average launch rate of approximately 20.8 new molecules a year. During 2005 the number of new launches detected in European countries was well below the average, whilst in 2004, 2007 and 2009 the launch rate was just above the average number of annual launches of novel pharmaceuticals.

4.4.2 Number of first European launches recorded in each country

In Figure 5 we can observe the number of time each country was the first country to use novel pharmaceuticals in E-27 and make them available to patients.

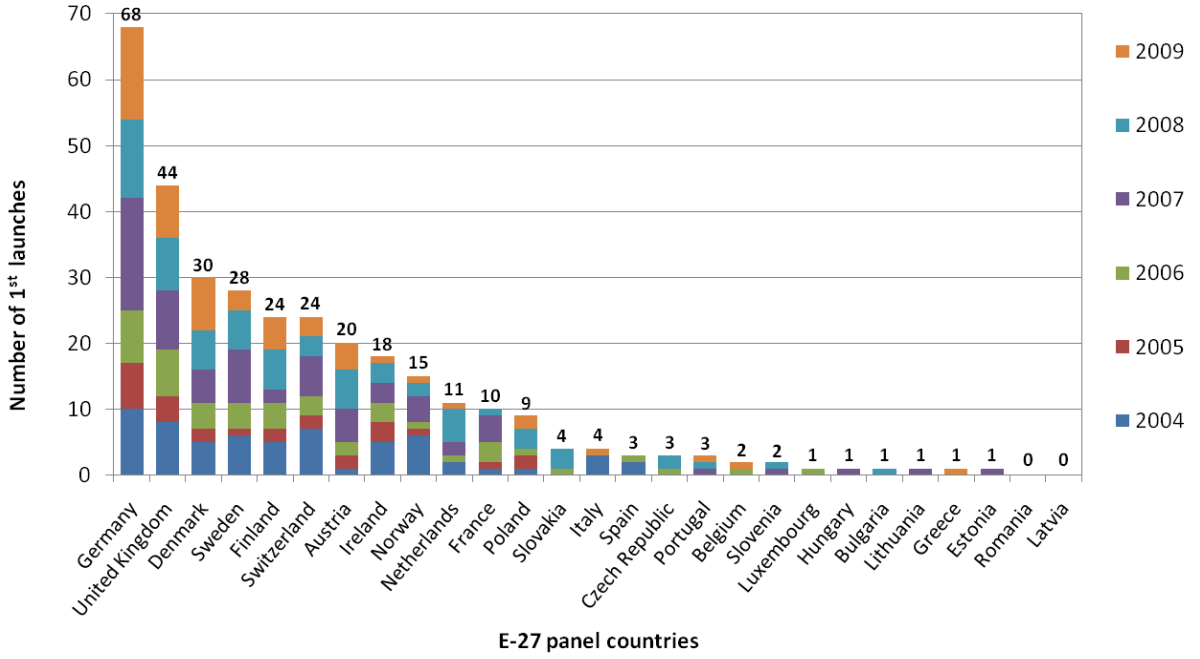
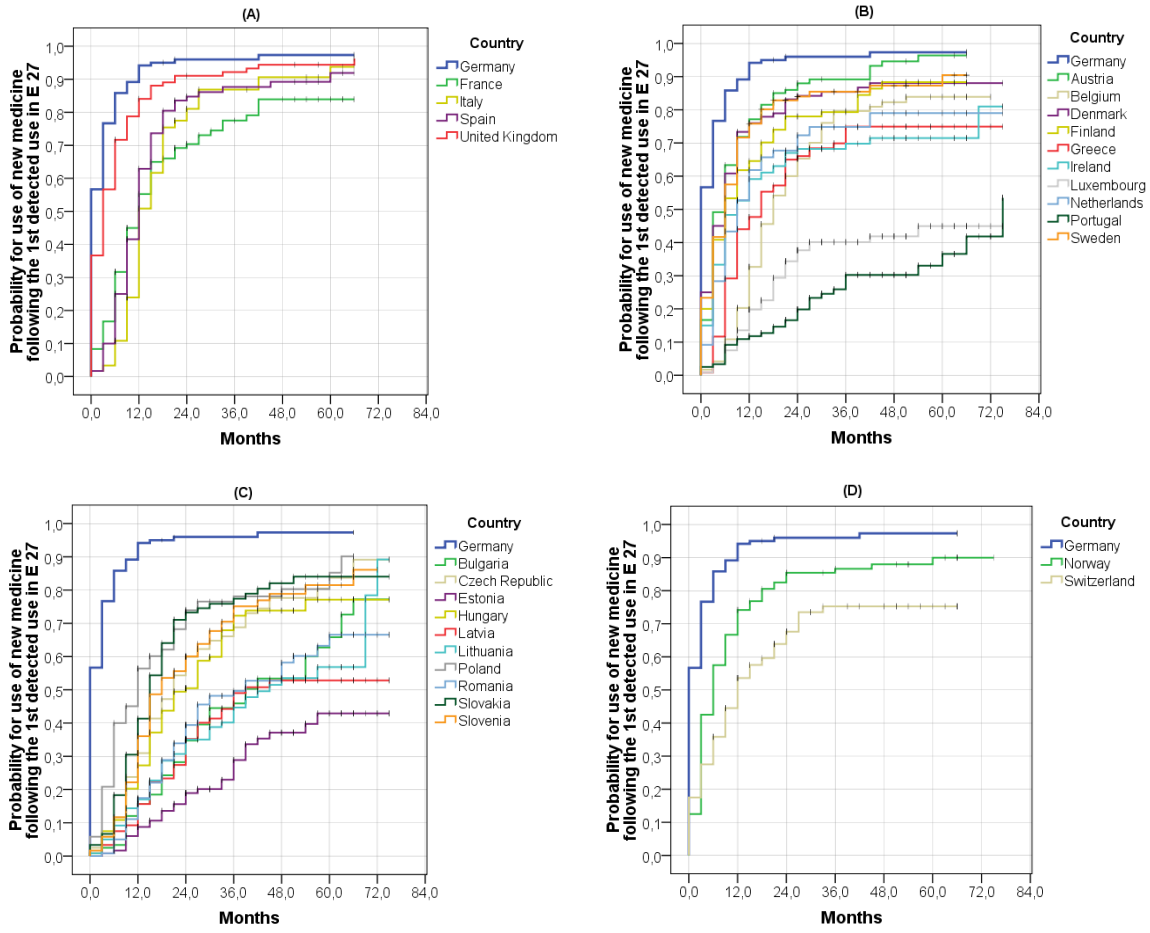


Figure 5. Number of times each country was amongst first (or first) to introduce novel pharmaceutical to market between 2004 and 2009. Split by year of first E-27-wide launch. Source: *IMS Health. Copyright 2010 All rights reserved.*

4.4.3 Time from the first European launch to the first use following in each country

In Figure 6-A, we can observe that overall, Germany has been the fastest in introducing novel pharmaceuticals with the mean time of 4.7 months after first use detected among E-27, standard error of mean (SEM) at 1.1 months and 95 % confidence interval (CI) between 2.6 and 6.9 (Table VI in Appendix 4). Moreover, Germany appears to be the country with more than 55 % probability of being the first country among E-27 to introduce a novel pharmaceutical to its patients. For this reasons we used Germany as a reference country used in comparison with the rest of the 26 European markets on Figure 6-A,B,C,D in this analysis.



E-27 = 27 European panel countries; EU-5 = Germany, France, Italy, Spain, United Kingdom

Figure 6. Kaplan-Meier (one minus survival) curves of time passed between 1st detected use of new innovative medicine in E-27 and first use of new medicine in individual EU-5 countries (A), EU accession countries before 2004 (B), EU accession countries during and after 2004 (C) and non-EU member countries (D). Germany is used as comparator (index) country on all 4 charts. Source: *IMS Health. Copyright 2010 All rights reserved.*

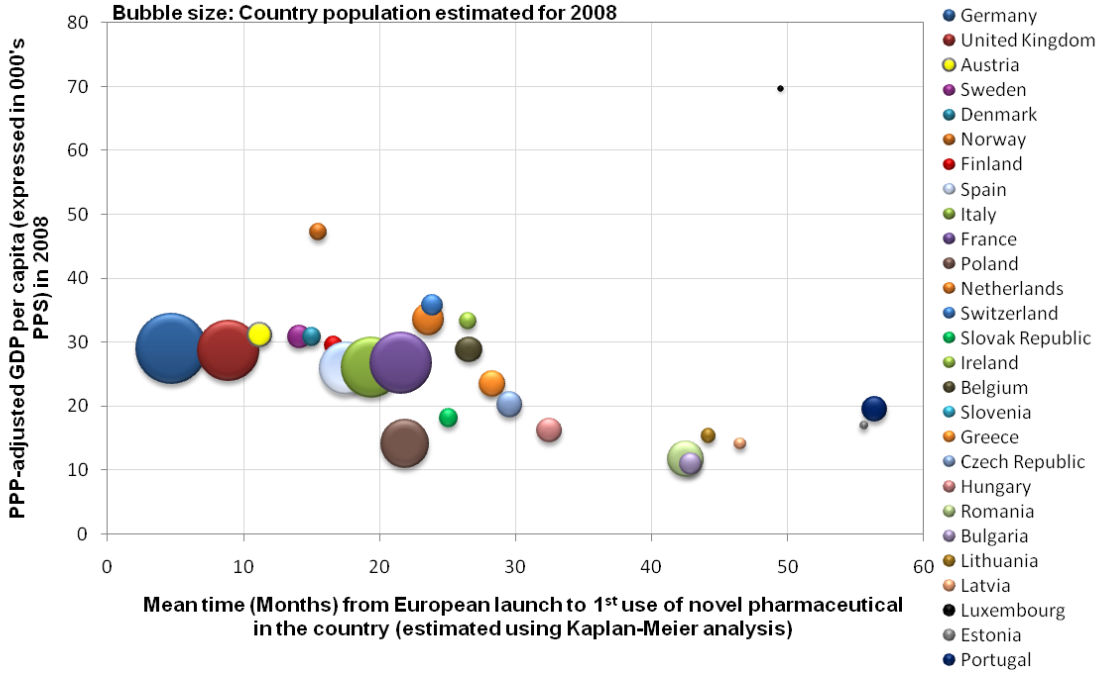
Following Germany is the UK with a 50% probability of having launched a novel pharmaceutical for the first time, between 2004 and 2009, within 3 months after first introduction among E-27. UK, with an estimated mean time of 8.9 months (95 % CI: 6.0 – 11.9) needed to secure patient access after first use detected in E-27, is still significantly slower than Germany. Detailed list of mean times, SEM and CIs for all E-27 can be found in Table VI in Appendix 4.

Spain, Italy and France are slower and less probable at being the first European countries to introduce novel pharmaceuticals, with mean times of 17.5 (SEM = 1.8), 19.4 (SEM = 1.7) and 21.6 (SEM = 2.2) months respectively, thereby being up to more than 4.5 times slower compared to Germany; on average these countries are still among the fastest ones, however

lagging behind Austria (the second quickest after Germany) and all three Nordic countries - Sweden, Denmark, Finland (Figure 6-B). Norway, as non-EU Member State, with the estimated mean time to first use after first European launch at 15.5 months (SEM = 2.1; 95 % CI: 11.3 – 19.6), is on the 6th place and thus significantly faster in making new medicines available to patients than Switzerland. In Switzerland, the mean time to first use after first European launch was calculated to amount to 23.9 months (Figure 6-D, Table VI). Overall, the Netherlands appears to have a higher probability of launching first among E-27 than Switzerland. Slovenia, with a mean time estimated at 28.2 months (SEM =2.4; 95 % CI = 23.5 – 32.9), has a higher probability of being the country of first launch in Europe compared to majority of all new EU Member States; with exception of Poland (21.9 months; SEM = 2.2; 95 % CI = 17.5 – 26.2) and Slovakia (25.1 months; SEM = 2.4; 95 % CI = 20.4 – 29.9) which have the highest number of first launches recorded among countries that joined the EU after 2004. Estonia is at the bottom of our list, just above Portugal, which with the mean time of 56.4 months (SEM = 2.7) appears to be the country with the lowest probability of first launch among E-27.

4.4.3.1 Relation of calculated mean times to country specific demographic and economic indicators

The chart in Figure 7 shows that larger bubbles representing countries such as EU-5 and



GDP = Gross Domestic Product (as a measure of income); PPP = Purchasing Power Parity; PPS = Purchasing Power Standards

Figure 7. Mean time to first use in each country in relation to country's income per capita and its total population. Source: *IMS Health. Copyright 2010 All rights reserved.*

Poland - countries with the largest total population recorded in 2008 - are generally concentrated to the left of the chart. Looking from another perspective we can generally observe countries with higher GDP per capita expressed in PPS being much faster in brining novel pharmaceuticals to their patients for the first time. A solitary exception appears to be Luxembourg that has the highest recorded income per capita among E-27, but still the smallest number of residents. Nevertheless we can also see that countries with relatively smaller income per capita such as majority of the CEE countries that joined the EU after 2004, as well as Portugal and Greece, from the group of the old EU member states, seem to be slower in introducing novel pharmaceuticals to patients. Slovakia and Poland seem to be the fastest countries in introducing novel pharmaceuticals to their patients among new EU Member States that joined the EU after 2004.

4.5 Market and patient uptake of novel pharmaceuticals

Sales of novel pharmaceuticals launched in Europe, between 2004 and 2009, are presented below and analysed in Figure 8, Figure 9, Figure 10 and Figure 11.

Figure 12 (A, B, C and D) shows cumulative uptake representing monetary utilisation for up to 125 novel pharmaceuticals launched in selected European countries between 2004 and 2009. We also observed cumulative uptake in relation to affordability of every country (Figure 13 (A, B, C and D)) and additionally in relation to affordability of their healthcare systems (Figure 14 (A, B, C and D)) to investigate if the differences become more evident.

4.5.1 Sales of novel pharmaceutical

According to IMS data, total sales of novel pharmaceuticals launched in all 27 selected European countries, between 2004 and 2009, increased significantly. Starting with just over 120 million EUR in 2004, total sales reached up to more than 10.6 billion EUR for novel pharmaceuticals sold by the end of 2009 (Figure 8).

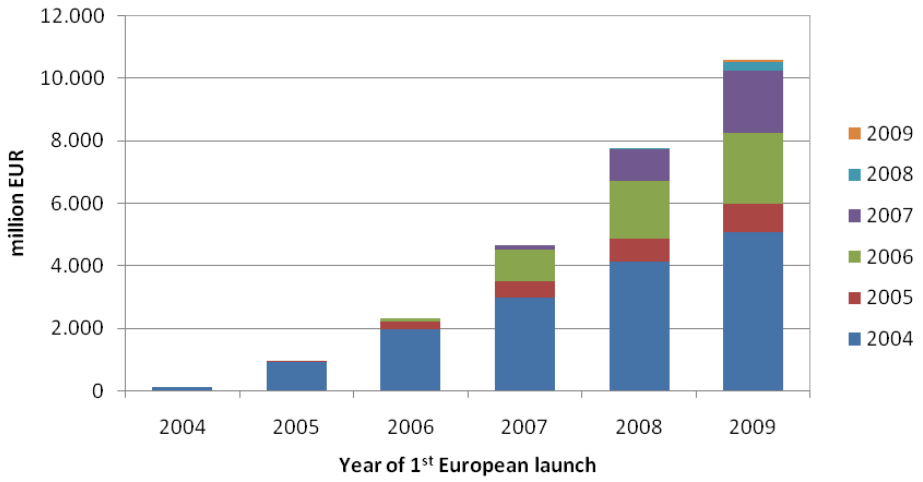


Figure 8. Total sales (in million EUR) of novel pharmaceuticals in all selected countries (E-27). 2004 - 2009 by year of first European launch. Source: *IMS Health. Copyright 2010 All rights reserved.*

In absolute terms, the quickest rise in expenditure was attributed to drugs launched in 2004 and it is evident that the rising expenditure of novel drugs was not impeded by further introduction of new innovative drugs launched in later years.

As shown on Figure 9, in relative terms, by 2009 the portion of sales of novel pharmaceuticals introduced in E-27 between 2005 and 2009 has superseded the portion of total sales of drugs launched in 2004, pushing them below 48% of total sales accounted for in 2009. The new innovative drugs launched in 2005 (8.6%), 2006 (21.3%), 2007 (19.0%), 2008 (2.6%) and 2009 (0.7%) therefore accounted for 52.2% of total sales reported in 2009.

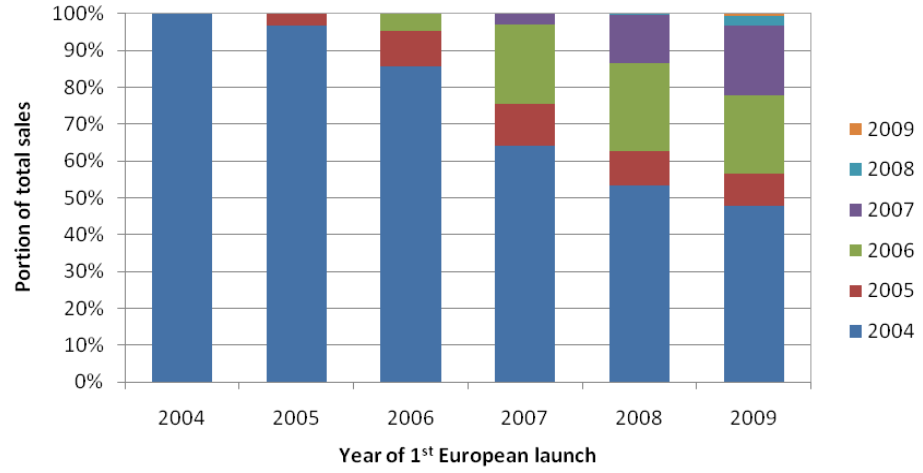
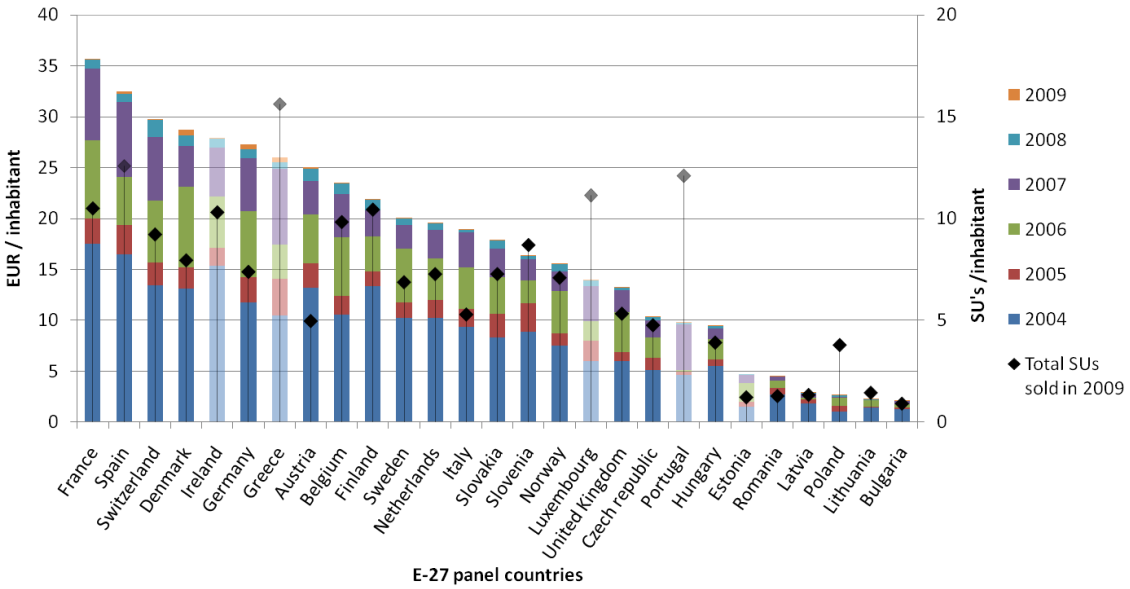


Figure 9. Portion of total sales of novel pharmaceuticals in all selected countries (E-27) by year of first European launch for each year between 2004 and 2009. Source: *IMS Health. Copyright 2010 All rights reserved.*

As illustrated in Figure 10, we can spot that there are significant differences between countries regarding the absolute per capita expenditure on novel pharmaceuticals launched

between 2004 and 2009. This is reflected and emphasised also in the analysis of cumulative uptake in the paragraphs below, where we can witness roughly similar arrangement of countries according to their speed of uptake of novel pharmaceuticals. Nevertheless, the intention of this figure is to compare the absolute monetary sales in the countries with the number of standard units (SU) sold. Even though the sales data for countries such as Greece, Luxembourg and Portugal is incomplete, we can still point out that while being placed onto the 7th, 17th and 20th place according to their sales per capita on novel pharmaceuticals, these countries along with Spain, clearly stand out in the number of SUs of new drugs purchased.



SU = Standard Unit - smallest common dose of a product form as defined by IMS HEALTH, for example a standard unit could be 1 tablet or capsule, 5 millilitres of syrup, 1 ampoule etc.

Figure 10. Per capita sales of novel pharmaceuticals (in EUR/inhabitant) in 22 panel countries in 2009 split by year of first European launch compared to total volume sold per capita (SUs/inhabitant) in each country in 2009. (Estonia, Greece, Ireland, Luxembourg and Portugal are shaded as they are excluded from analysis due to incomplete sales data). Source: *IMS Health. Copyright 2010 All rights reserved.*

Figure 11 illustrates the proportion of sales of new innovative drugs split by year of first European launch for all panel countries in 2009. There are obvious discrepancies between countries regarding the introduction and use of the latest new innovative pharmaceuticals by the end of 2009. Novel drugs launched in 2008 and 2009 appear to have gained the largest portion of sales rate in Switzerland, Austria, Denmark, Finland, Slovakia and Germany, however drugs launched just in 2009 gained the largest portion of total sales per capita in Denmark followed by Germany, Austria, Spain and Lithuania.

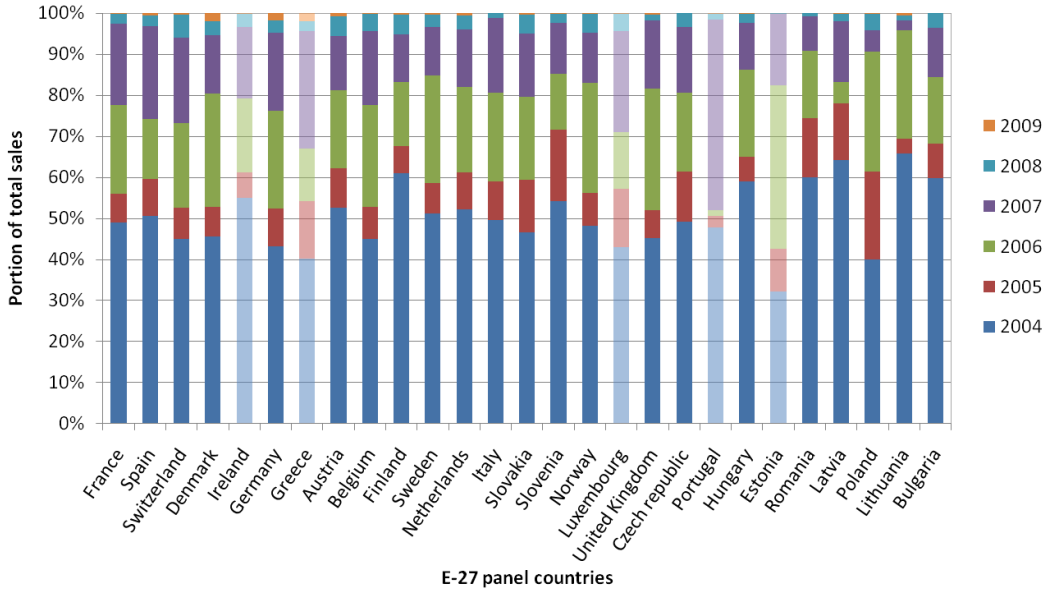


Figure 11. Portion of total sales of novel pharmaceuticals in 22 panel countries in 2009 split by year of first European launch. (Estonia, Greece, Ireland, Luxembourg and Portugal are shaded as they are excluded from analysis due to incomplete sales data). Source: *IMS Health. Copyright 2010 All rights reserved.*

4.5.2 Absolute cumulative uptake of novel pharmaceuticals

Figure 12-A shows that France with absolute cumulative uptake reaching 10.91 EUR per inhabitant for total of 88 new drugs made available to their patients, is clearly dominating the EU-5 and also all 21 European countries (E-21) formally included in this analysis. France therefore has the steepest absolute rise in uptake, overtaking the second fastest Spain (10.39 EUR/inhab.; 98 new drugs) by approximately 5 % and the average utilisation of E-21 and EU-5 by something less than 92 % and 36 % respectively. Germany (8.49 EUR/inhab.; 116 new drugs) appears to be slightly above the line of the EU-5 uptake (8.03 EUR/inhab.) by merely 5.7 %, while Italy's uptake (6.03 EUR/inhab.; 94 new drugs), significantly more gradual compared to that of Germany, reaches just above the E-21 uptake (5.69 EUR/inhab.) with a slightly higher utilisation by the end of the 2nd quarter (in June) of 2010. United Kingdom (4.34 EUR/inhab.; 111 new drugs) however appears to be lagging with its utilisation around 23.8 % and almost 46 % (two times) lower than the average utilisation of E-21 and EU-5 respectively.

Looking at the uptake of new drugs in EU member states that joined the EU before 2004 (old EU states) expressed in EUR spent per inhabitant (Figure 12-B), Denmark rises to 9.7% and 54.7 % above average uptake of new drugs recorded for EU-5 and EU-21, reaching its maximum at 8.81 EUR spent per inhabitant on as much as 102 novel pharmaceuticals accessible to patients in this country. This is followed by Belgium (8.36 EUR/inhab.; 88 new

drugs available), Austria (7.74 EUR/inhab.; 110 new drugs), Finland (7.13 EUR/inhab.; 97), Netherlands (5.98 EUR/inhab.; 87) and Sweden (6.19 EUR/inhab.; 103) all with utilisation above E-21 but below the EU-5 average. Additionally, on Figure 12-B we can see the cumulative uptake of all new drugs launched between 2004 and 2009 in non-EU member countries, Switzerland and Norway. Switzerland (9.21 EUR/inhab.; 84 new drugs accessed) has the 3rd fastest uptake amongst all selected European countries and is well above EU-5 average by almost 15 % and above E-21 average uptake by almost 62 %. However, Norway (5.24 EUR/inhab.; 104 new drugs available) appears to be about 8.0 % behind the E-21 average uptake.

Figure 12-C shows the utilisation in the EU member states that joined the EU after 2004 (new EU states). Leading country in market uptake represented by absolute cumulative sales of new drugs launched between 2004 and 2009 are Slovakia (5.57 EUR/inhab.; 88 new drugs) and Slovenia (5.39 EUR/inhab.; 81 new drugs), just under the average uptake of E-21. With almost 43 % and 44 % slower uptake than the E-21 average are Czech Republic (3.27 EUR/inhab.; 81 new drugs) and Hungary (3.20 EUR/inhab.; 76 new drugs). The slowest absolute uptake among E-21, expressed in EUR/inhabitant, can be attributed to Latvia (0.95 EUR/inhab.; 49 new drugs), Bulgaria (0.90 Eur/inhab.; 55 new drugs), Poland (0.81 EUR/inhab.; 92 new drugs) and Lithuania (0.67 EUR/inhab.; 55 new drugs) with more than 80 % slower uptake than the E-21 average.

As illustrated in Figure 12-D, the average uptake of new drugs in western European countries that accessed the EU before 2004 appears to be more than threefold higher than that of the average uptake of new EU member states with accession to EU after 2004.

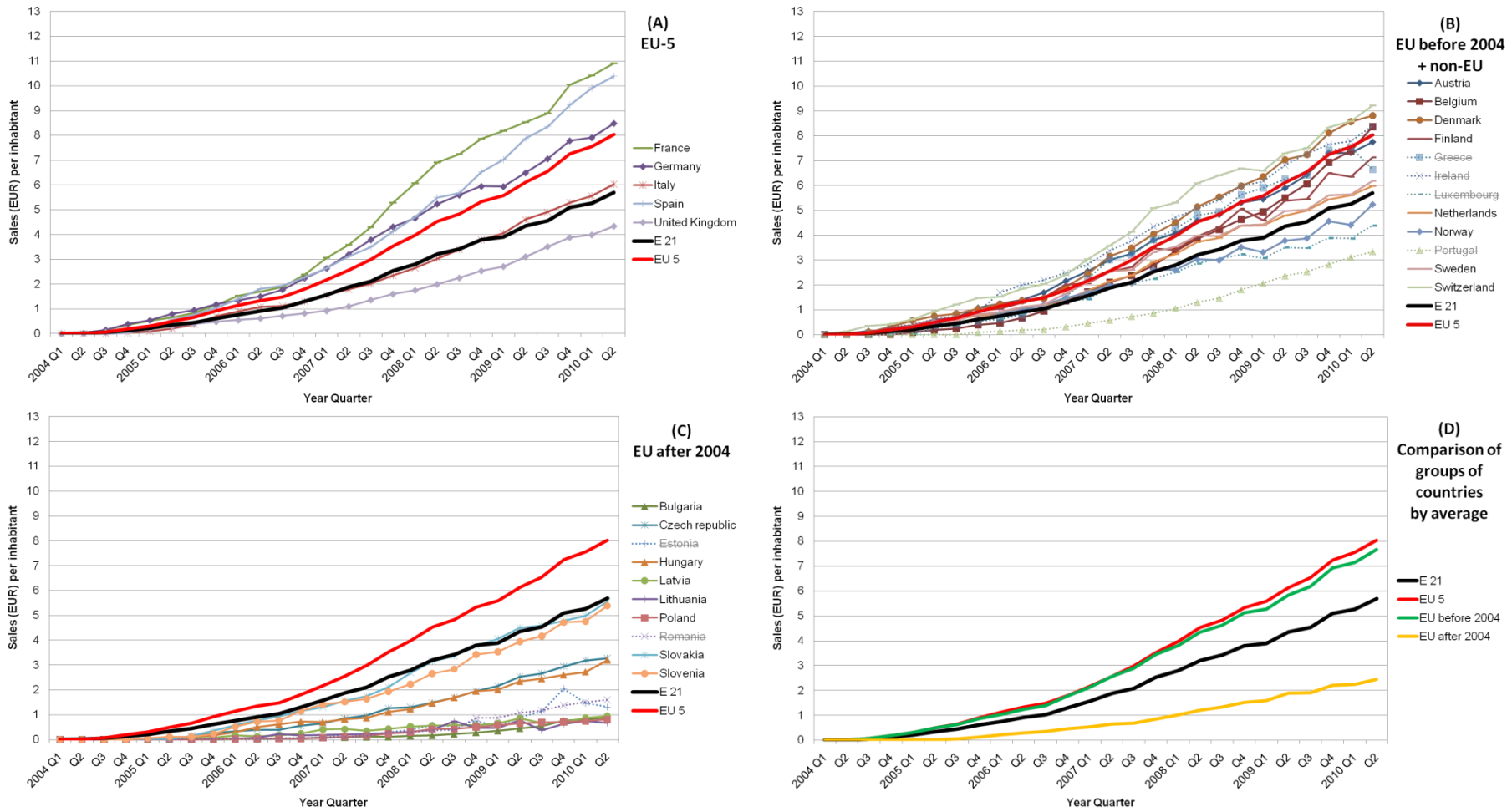
4.5.3 Absolute cumulative uptake valued against affordability of each country

When countries' affordability – expressed as income per capita in PPP-adjusted GDP per capita at market prices (indexed on Germany) from Table I - to uptake a new drug was considered, the uptake curve of all EU-5 (Figure 13-A) remained fairly stable, however the gap in the uptake between the fastest France and Spain slightly narrowed, as Spain moved slightly upward. The uptake recorded for UK however decreased slightly, while that of Italy increased, increasing the gap between these two countries. There was a coherent drop of uptake observed for Denmark, Austria and Sweden, whilst Belgium and Finland remained almost unchanged. The Netherlands and Norway were among countries that dropped the most, increasing the gap in the uptake with other older EU member states and impacting also the average uptake of E-21 (Figure 13-B). This was due to the fact that most of these

countries (except Finland) pertain to a group of economically more developed markets with higher income per capita as in Germany (index country). The opposite occurred with new EU member states (Figure 13-C) such as Slovakia that became the 3rd fastest country in the uptake of novel pharmaceuticals in Europe, even surpassing the average uptake of E-21. Spain continued with the 2nd fastest uptake of new drugs among E-21. The uptake of Switzerland dropped significantly below the average uptake of EU-5 and bellow the uptake of Belgium and Denmark due to its high GDP per capita (Figure 12-B vs. Figure 13-B) and almost levelled with Austria. The uptake of the Netherlands was below the uptake of Slovenia and even Hungary. Following were Czech Republic and only then, United Kingdom. A significant drop was noticed for Norway (Figure 13-D) that was almost 30 % slower in uptake than United Kingdom, but still above the countries with the slowest uptake of new drugs, such as Bulgaria, Latvia. Countries with the slowest uptake remain Poland and Lithuania.

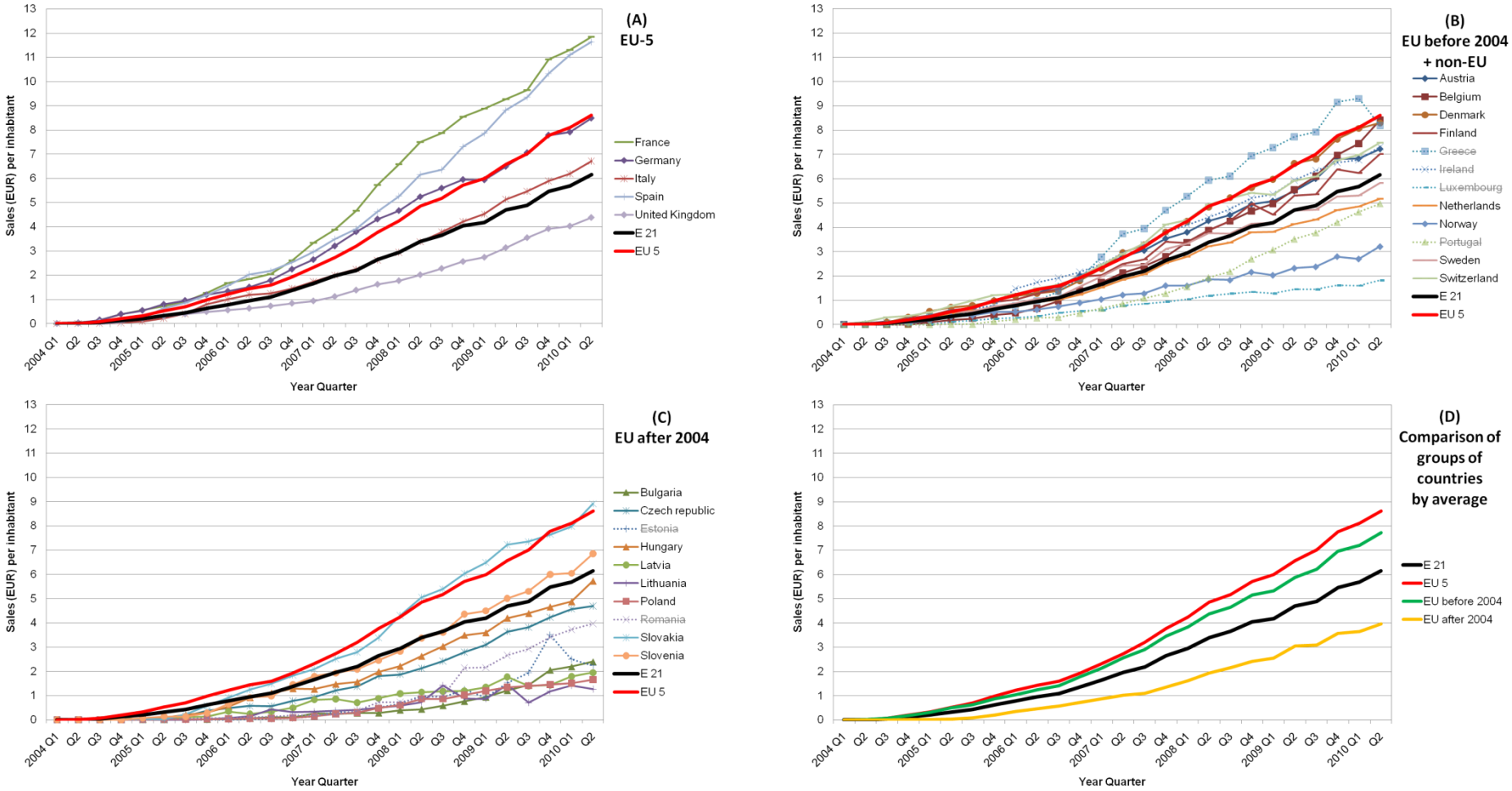
4.5.4 Absolute cumulative uptake valued against countries' total expenditure in health care

Moreover, when affordability of countries' healthcare systems to uptake new drugs was taken into account (applying % of total expenditure on health to the uptake measured against affordability), the uptake of new medicines in Spain surpassed the uptake of France, thus moving upwards due to Spain's relatively lower expenditure on heath and shifting France slightly lower due to their relatively high total healthcare expenditure (Figure 14-A). The country with the 3rd fastest uptake in Europe when adjusted by affordability of the healthcare system, appeared to be Slovakia (Figure 14-C). While no drastic changes; except for a small drop in the uptake of Austria and Switzerland and the rise in the uptake of Finland; have been observed for both non-EU countries and countries that joined the EU before 2004 (Figure 14-B), there were evident upward movements of uptake among CEE countries (Figure 14-C). Slovenia rose up to being the 4th fastest in the uptake of new drugs in Europe, leaving behind all countries displayed on Figure 14-B. Slovenia was followed by Hungary, with average uptake above that of E-21, and Czech Republic, which almost levelled with the E-21 average uptake. Countries with slower uptake than the E-21 average appeared to be Sweden, Netherlands, Norway (Figure 14-B) and the UK (Figure 14-A). Bulgaria, Latvia, Poland and Lithuania rose slightly, but still continued at the bottom of the chart with the slowest uptake among E-21 (Figure 14-C). In Figure 14-D average uptake of Western European countries, EU-5 and CEE countries moved closer together, however there were still distinct differences noticeable in the average uptake between these three groups of countries.



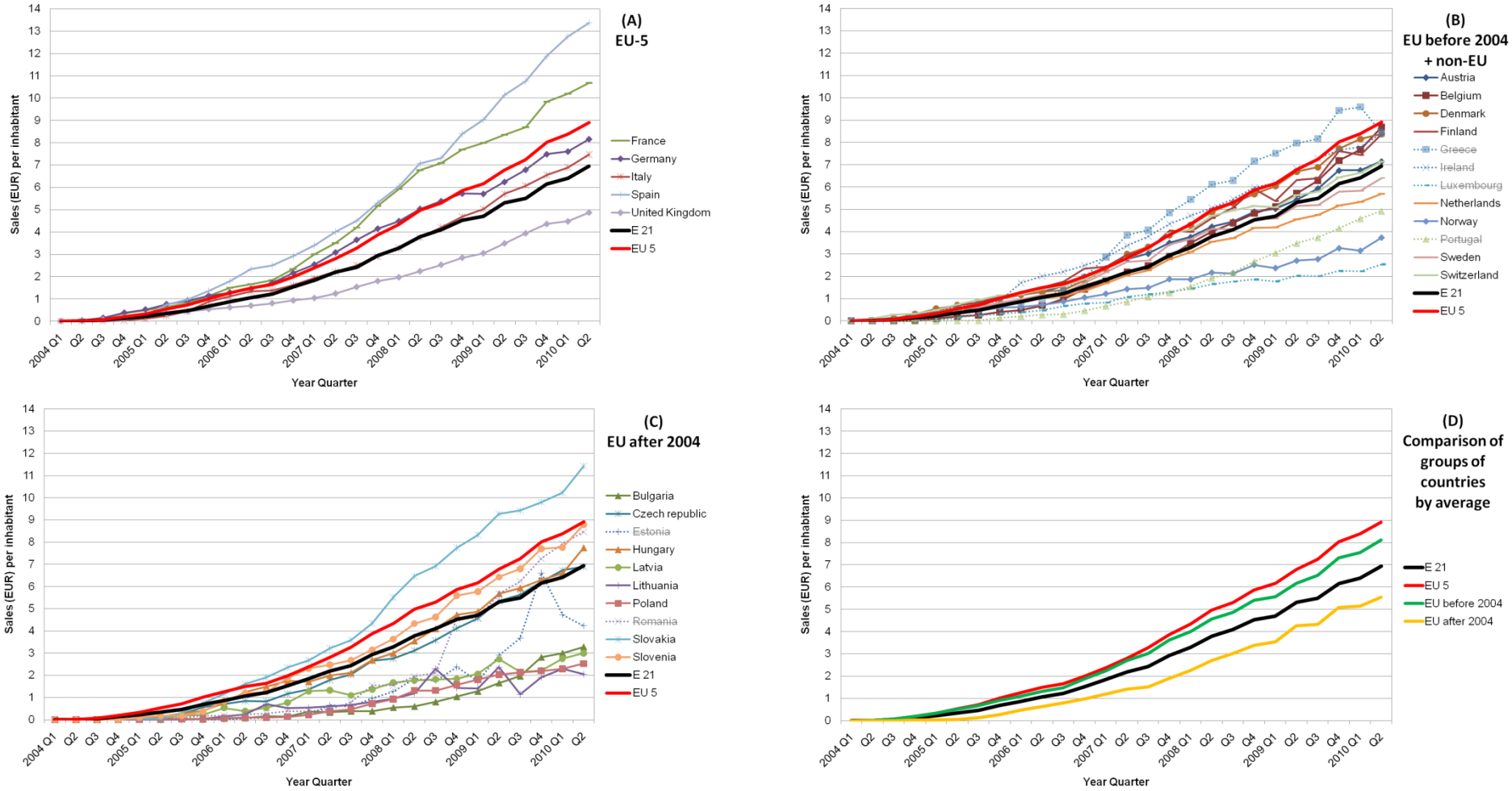
E-21 = average uptake of E-27, except Estonia, Greece, Ireland, Luxembourg, Portugal, Romania (for details please refer to page 35); E-5 = average uptake of Germany, France, Italy, Spain, United Kingdom

Figure 12. Cumulative monetary uptake of innovative pharmaceuticals launched in selected European countries (expressed in EUR/inhabitant) split by: EU-5 biggest European countries (A); old EU member states with accession to the 'EU before 2004' and 2 non-EU countries (B); new EU member states with accession to the 'EU after 2004' (C); average uptake of EU-5, old EU member states (non-EU countries not included) and new EU member states (D). Source: *IMS Health.*



E-21 = average uptake of E-27, except Estonia, Greece, Ireland, Luxembourg, Portugal, Romania (for details please refer to page 35); E-5 = average uptake of Germany, France, Italy, Spain, United Kingdom

Figure 13. Cumulative monetary uptake (expressed in EUR/inhabitant) of innovative pharmaceuticals launched in selected European countries weighed against PPP-adjusted GDP per capita (indexed on Germany) split by: EU-5 biggest European countries (A); old EU member states with accession to the 'EU before 2004' and 2 non-EU countries (B); new EU member states with accession to the 'EU after 2004' (C); average uptake of EU-5, old EU member states (non-EU countries excluded) and new EU member states (D). Source: *IMS Health. Copyright 2010 All rights reserved.*



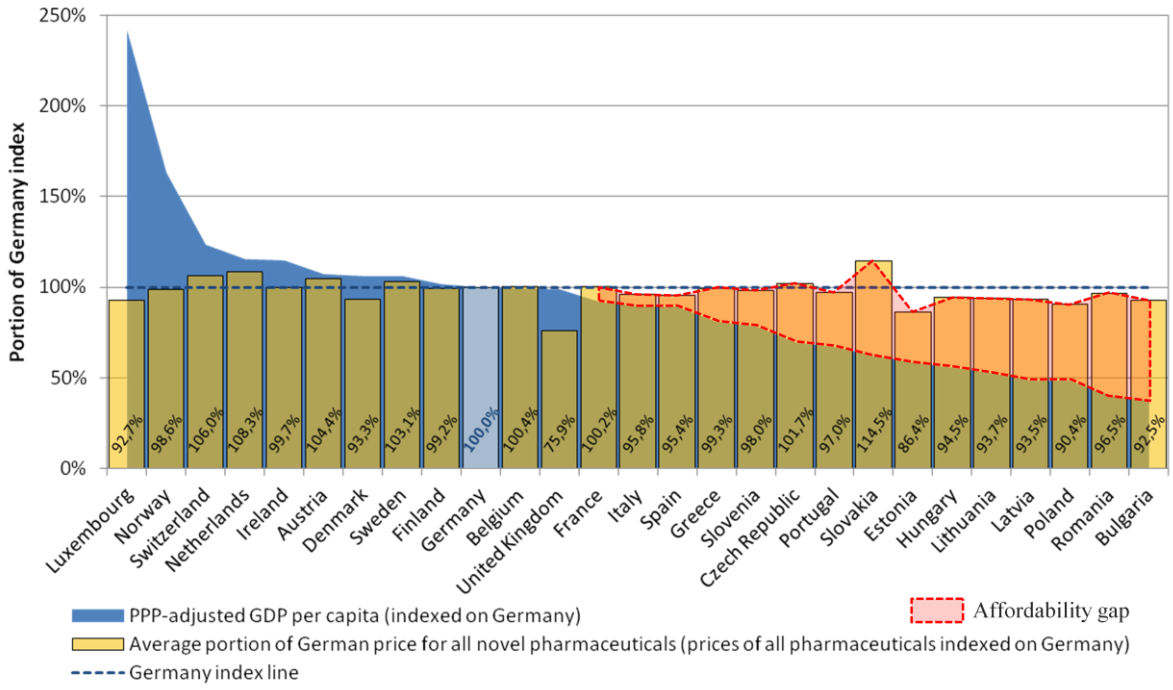
E-21 = average uptake of E-27, except Estonia, Greece, Ireland, Luxembourg, Portugal, Romania (for details please refer to page 35); E-5 = average uptake of Germany, France, Italy, Spain, United Kingdom

Figure 14. Cumulative monetary uptake (expressed in EUR/inhabitant) of innovative pharmaceuticals launched in selected European countries weighed against PPP-adjusted GDP per capita invested in health care split by: EU-5 biggest European countries (A); old EU member states with accession to the 'EU before 2004' and 2 non-EU countries (B); new EU member states with accession to the 'EU after 2004' (C); average uptake of EU-5, old EU member states (non-EU countries excluded) and new EU member states (D). Source: *IMS Health. Copyright 2010 All rights reserved.*

4.6 Affordability gap

As shown in Figure 15, average prices of pharmaceuticals in each of the E-27 remain comparable, with relatively small deviations from German index price across the whole of Europe. There are however much more evident disparities in the level of affordability observed when deviations in prices of new drugs are compared to deviations in the country's affordability. PPP-adjusted GDP per capita differs largely among E-27, dropping constantly from Luxembourg with the highest income per capita towards the "new EU states" of the CEE and reaching its lowest point in Bulgaria.

Observing the affordability of different countries through their PPP-adjusted GDP per capita (expressed in PPS) indexed on Germany on Figure 15, we can see a great affordability gab emerging between the relative average price of novel pharmaceuticals and the relative income per capita in all CEE countries.



CEE = Central and Eastern Europe; GDP = Gross Domestic Product; PPP = Purchasing Power Parity

Figure 15. Relative variation in average prices of pharmaceuticals in each country compared to three distinct indicators of country's affordability. Affordability gap between income per capita and the average price of pharmaceuticals in CEE countries. Source: *IMS Health. Copyright 2010 All rights reserved.*

5 DISCUSSION

In this paper we analysed and compared patient access of novel pharmaceuticals launched for the first time between 2004 and 2009 in 27 selected European countries. Trends and cross-country comparisons of patient access have been investigated through four selected measures. In the first part we observed delay to patient access impacted during regulatory approval and 'EMA time lag'. Secondly we identified most frequent launch sequence for new medicines in European countries and then examined the countries' ability to uptake new innovative drugs and bring them to their patients. In the last part we analysed the affordability gap and thus compared prices of novel pharmaceuticals to income per capita.

5.1 Novel pharmaceuticals included into scope of our research

There is a distinct prevail in the number of novel drugs emerging within the main anatomical group (1st level of ATC) of antineoplastic and immunomodulating agents (L), dominated by number of new antineoplastic agents and immunosuppressants launched during the study period. Such prioritisation of distinct pharmaco-therapeutic areas may be due to portfolio decision-making of main global players within the pharmaceutical industry. Kaitin et al. [50] found that particularly in oncology, a vast progress in scientific knowledge about cancer mechanisms and the relatively favourable reimbursement environment tend to offset some of the negative development challenges such as lengthy development times and high attrition rates of novel pharmaceuticals. On the other hand R&D strategies to invest into cardiovascular (C), anti-infective (J) and central nervous system drug area (N) seemed to be in decline by crowded markets in which there is significant reimbursement pressure and generic competition, which could in part explain a drop in new drug approvals in these therapeutic areas [50]. However, So and colleagues [51] argued that the industry's lack of investment into antibacterial drug discovery may also be due to relatively less favourable returns; after all, treating an infection may require a short course rather than a long-term treatment of chronic conditions, while additionally resistance may limit antibacterial life span.

Many incentives and other facilitations have been adopted in different parts of the world, including the EU, in order to facilitate the development and commercialisation of diagnostic tools and health technologies devoted to rare diseases [52] and a partial response to this could be seen in a relatively high number of orphan drugs – 25 accounting for one fifth of all drugs - introduced to E-27 between 2004 and 2009.

5.2 Selected European study countries

In terms of economical welfare and affordability measured through GDP per capita as well as the portion of GDP invested into health care, the old EU Member States represented by Western European countries are generally better off than the new Member States from the CEE. Interestingly enough, most CEE countries are much less economical in terms of the portion they spend on pharmaceuticals, however, we can observe the same for Greece and Portugal. This may be due to lack of restrictive measures or more conservative P&R policies in place, compared to the majority of the older EU members states. The EU-5, as the biggest by population size, have the highest sales volume potential, therefore we believe addressing them separately in some parts of our research can be justified.

To have the most complete and coherent set of economic and demographic indicators for all E-27, data reported for 2008 was collated and used in all further analyses. GDP per capita at market prices (expressed in purchasing power standards (PPS)) for E-27 was incomplete for year 2009 (missing for Bulgaria) and not yet reported for 2010. Total expenditure on health, reported as percentage of GDP, had been reported only up to 2008. Pharmaceutical expenditure as percentage of total expenditure on health obtained from OECD had been reported for up to 2008. Data was missing for some of our study countries that were not OECD members (Bulgaria, Latvia, Lithuania) or for those without data reported in this category for 2008 (Denmark, Greece, Portugal, Netherlands and Switzerland). Instead available data from most recent years had been used. In case of Belgium the data provided by OECD for 2008 was based on an estimate, without real-time data reported.

There are clear reasons why we chose the GDP per capita expressed in PPS as a measure of countries' affordability. According to the "EUROSTAT-OECD Methodological manual on purchasing power parities (PPPs)" GDP is the aggregate used most frequently to represent the economic size of countries and, on a per capita basis, the economic welfare of their residents: Wealthier usually means healthier, better educated and a less inequitable income distribution [53]. To assure that for cross-country comparison the currency unit in which GDP is expressed and the price level at which GDP is valued are the same, it is necessary to have conversion rates that both convert to a common currency and equalise the purchasing power of different currencies in the process of conversion. Such conversion rates are "purchasing power parities" or "PPPs" [53]. The purchasing power standard (PPS) is an artificial currency unit. PPS is the technical term used by Eurostat for the common currency in which national

accounts aggregates are expressed when adjusted for price level differences using PPPs. Thus, PPPs can be interpreted as the exchange rate of the PPS against the EUR [54].

5.3 Regulatory approval and 'EMA time lag'

5.3.1 Marketing authorisation of panel drugs

The choice of optimal MA procedure for novel pharmaceutical in Europe still remains at the discretion of the applicant - anyone with necessary supporting data that may apply for a licence to market a new drug. The type of procedure to be selected depends also on the specifics and nature of the active ingredient in the pharmaceutical for which the MA is being sought. Amongst manufacturers of innovative drugs the far most used appears to be the CP.

5.3.1.1 Centralised Procedure

To justify the predominating portion of novel pharmaceuticals registered through CP we should emphasise that the CP is compulsory for certain types of medicines and medicines pertaining to specific therapeutic groups (described in paragraph 1.1.1). Almost 41% of our panel drugs were designated as either orphan drugs or NBE and as such they must have mandatorily applied for CP to be issued a MA. As presented in Table III, medicines that had to be approved through CP were those intended for the treatment of cancer, auto-immune diseases and other immune dysfunctions, viral diseases, neurodegenerative disorders or diabetes. For all other drugs manufacturers alone opted to apply for MA through CP.

CP is very much worth-while for MA seekers as it is regulated to ensure that the opinion of the CHMP is given within 210 days (less 'clock-stops' for the applicant to provide answers to questions from the CHMP) which makes it relatively fast [55]. It requires a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community (all EU countries, as well as in Iceland, Liechtenstein and Norway). Thus having a high portion of drugs launched between 2004 and 2009, for which MA was sought through CP, does not come by surprise. This procedure, both logistically much simpler and also much faster, enables the applicant to gain regulatory approval for new drugs in more countries at the same time without further regulatory hurdles. However, the advantages of the CP are also accompanied by the fees that are significantly higher than those of other procedures.

CP definitely plays an important role also from the point of equal access to medicines and to a certain extent offers an answer to moral and ethical obligation of the EU regulators in

providing all EU patients and even patients in EEA countries with the benefit of equal access to new innovative medicines.

5.3.1.2 Decentralised Procedure and Mutual Recognition Procedure

Coming into effect only relatively recently (October 2005), it is not surprising that only in two cases for novel pharmaceuticals launched between 2004 and 2009 the licence holder opted to seek for MA through DcP. Unless there are particular reasons for restricting the launch to only some countries, any manufacturer or licence holder would obviously do their utmost to apply for the CP to try to make the new drug available to as many target patients as possible simultaneously, consequently maximising the chances for faster and higher return on investment. We could say that opting for the DcP instead of CP may be considered unjust or even unethical, as the DcP basically functions as a prerequisite for access to new medicines only in countries opted and prioritised by the manufacturer and thereby depriving the general EU and EEA population from equality in access to a new medicine.

5.3.1.3 National Authorisation Procedure

Among our panel drugs the national authorisation procedure was used by manufacturers only to obtain MA in Switzerland, where aforementioned Community procedures did not apply. It is evident that NP lost its popularity amongst manufacturers of new innovative medicines since the introduction of MRP in 1998 and later of DcP in 2005. Thus better, faster and administratively less complicated alternatives exist for seeking MA in more than one country, which is usually the aim when registering new innovative medicines in Europe.

5.3.1.4 Drugs without marketing authorisation during the time of recorded sales

Even though OK-432 (picibanil) had never been authorised in any European country first sales reported by IMS actually occurred in May 2005. Sales were only minor and were later recorded twice more during the 1st quarter of 2006 and 2009. Based on small and fragmented sales of OK-432 (picibanil) occurring abruptly between 2005 and 2009 as reported by IMS, we assumed that this particular drug had been purchased either through wholesaler with special authorisation for investigational purposes or for exceptional individual use. Additionally, we discovered that the manufacturer has worked with the non-profit Shuhei Ogita Fund to provide this medicine free of charge to patients in 60 nations around the world, including Poland, where sales were detected [48; 56]. As reported by IMS, minor sales of medicines containing dofetilide had only been recorded in Poland in the end of 2009, after its

marketing authorisation was no longer valid. Reasons for this may again be similar to those described above for picibanil.

5.3.2 Time lag during EMA centralised marketing authorisation procedure

Various gaps exist in data collated for our 105 drugs included into analyses of 'EMA time lag'. EMA annual reports were not always consistent in reporting time for each individual phase of 'EMA time lag': Some drugs were excluded from analyses of post-opinion phase and phase of EC decision process as in their cases times for these two phases of EMA approval procedure were either not available or not published in EMA annual reports. We compared and reconfirmed the accuracy of times passed during every phase published in EMA annual reports with times calculated from dates published in EPAR. Thus for every individual drug we made sure that the 'active time' and 'clock-stop' taken from EMA annual reports together accounted for the difference between the date of 1st Positive opinion given by CHMP and the date when assessment of dossier submitted for MA actually commenced. These two dates were both published in EPAR of individual drugs.

We found Box and Whisker plot chart to be the most appropriate way to graphically depict sets of numerical data (collated times) gathered for each phase of the 'EMA time lag' using the shortest time observed (minimum), lower quartile, median of all collated times, upper quartile, and the longest time detected (maximum). With this plot we were also able to compare the distribution of times collated for separate phases, its outliers as well as observe the changing trends in time spent for each phase of 'EMA time lag' between 2004 and 2009. Collated times of all drugs have been sorted according to year when drug was issued its first opinion by CHMP - positive or negative. Such methodology was used to enable comparison of our results with results presented by EMA in a form of stacked columns in EMA annual reports [57; 58]. In fact EMA used similar methodology to observe changing trends in time spent during their MA procedure.

1. Pre-assessment phase

Lack of observed fluctuations or major increasing or decreasing trend in number of days spent for validation of application during pre-assessment phase between 2004 and 2009, may be from the fact that the duration of this phase is fairly rigidly controlled by EMA. Submission deadlines and full procedural detailed timetables are planned in advance and published as a generic calendar on the EMA website [14], thus making it mandatory for applicants as well as CHMP members to obey strict timelines. Such timeline rigidity may be positive from perspective of EMA's internal management of workload, however on the other

hand, strictly defined duration may not allow for flexibility when process could be speeded up for the sake of faster approval of new innovative medicines.

A rather steadily increasing trend in median and also mean times of pre-assessment phase of EMA CP calculated for drugs that received CHMP's opinion between 2004 and 2009 may show that there is a potential for improvement and thus reduction rather than increase of pre-assessment time spent while EMA and their delegates (Rapporteur, Co-Rapporteur, CHMP members) wait to receive and validate the complete MA application [13]. The fact that in the calculation of pre-assessment time our analysis employed the actual dates when MA applications had been received by EMA, rather than the dossier submission deadlines, should not be neglected when trying to explain the observed trend. According to collated dates, in most cases, MA applications reach EMA before the actual submission deadline, thus giving the applicant some additional days on top of the time between the actual submission deadline and start of the CP. This secures some extra time for the applicant to provide additional data, information or clarification if required by EMA in order to complete their validation of the dossier during the pre-assessment phase. Thus the increasing trend in median and mean pre-assessment times observed could mean that in years subsequent to 2004 more applicants actually submitted their MA applications ahead of the submission deadlines.

Except in a some specific cases (tigecycline, rufinamid, micafungin, indacaterol), where time of pre-assessment phase reached or surpassed double the time duration scheduled by EMA (twice the time of 19 days), it does not seem probable that failure of applicants to simultaneously deliver complete documentation to all parties engaged in evaluation of dossier on behalf of EMA, could be the cause of the generally increasing time trend.

2. Assessment phase (ACTIVE TIME)

Judging from Figure 2, the 'active times' generally remain within a narrow range of around 210 days, which is the defined time-limit for the assessment conducted by CHMP [15]. This also proves that the 'active time' used for evaluation of the MA during the CP is well controlled by EMA, thus not allowing for higher deviations. Nevertheless, the median and mean duration of 'active time' has steadily been rising from 2004 to 2009, with exception in 2005, when it evidently surpassed the time-limit of 210 days. For MA applications of new innovative drugs assessed from 2007 onwards, the time has never again been surpassed above the defined time-limit. This undoubtedly demonstrates an encouraging improvement and EMA's tendency to assess the applications within the legally prescribed timeline. According to our analysis, for the majority of drugs assessed by EMA between 2004 and 2009 - excluding the drugs assessed in 2005 - the active assessment times have been shorter than 210

days and for 50% of drugs assessed during each of these years the ‘active times’ detected were significantly lower than the median ‘active time’. This shows, that in the future, the prescribed time-limit could be reduced to below 210 days for new innovative drugs.

At the same time we should not discard the fact that some of our drugs have applied also for accelerated procedure. However only two, Soliris® (eculizumab) and Isentress® (raltegravir), were considered eligible and were successfully approved below the regulatory timeline of 150 days. This can point out two distinct facts: (i) either accelerated procedure is not often enough applied for by innovative industry or (ii) the rules about what is considered to be a therapeutic innovation of considerable public health interest limit the applicability of this procedure.

3. Company phase (CLOCK-STOP)

Distribution and the range of times passed during this phase is significantly more dispersed and widespread compared to times accumulated during other phases of the EMA centralised procedure. Alone it can account to even more than a third of the total time spent during CP, significantly prolonging the duration of regulatory approval and delaying access. This is most likely the result of poor control and lack of rigorous regulatory timelines put in place by EMA that would encourage the pharmaceutical industry to submit the required documentation and information following strict deadlines. It is however understandable that due to very specific details of each product, circumstances and nature of every application, applicants may require very different periods of time to prepare and deliver information requested by EMA. The median ‘clock-stop’ times were in quite significant decline from 2004 to 2006. However, later during 2007 and 2009, the median times remained constant at 132 days. This can be considered as a significant improvement from the part of the pharmaceutical industry, lately supplying the requested information to EMA more efficiently and much faster.

4. EMA post-opinion phase

According to EMA timetable [12] the EMA post-opinion phase commences after the day 210 of the assessment procedure, once the CHMP issues their opinion. This phase should not exceed the 27-day timeframe (expiring on day 237), when the final opinions with all annexes in all EU languages are to be transmitted to EC, applicant, Members of the Standing Committee as well as Norway and Iceland. According to the EMA timetable, it seems applicants (i.e. pharmaceutical industry) are expected to follow strict deadlines when submitting the required documentation during the EMA post-opinion phase, whilst not quite the same level of rigorousness is expected from national agencies of the Member States when

they need to submit their linguistic comments on product information. Judging from our results and the published EMA timetable it seems that, for the EMA and national regulatory agencies of member states, the deadlines during the post-opinion phase serve rather as guiding milestones, still allowing them to adjust timelines of their activities to their workload. As our results show, no steady trend in median times and quite a significant dispersion of times can be observed during the post-opinion phases when compared to the ones collated for pre-assessment and assessment phase between 2004 and 2009. This trend indicates that there may be a lack of strong tendencies imposed by EMA and the EC to stick to scheduled milestones and deadlines planned in the EMA timetable for CP. A more firm regulation and equally strict rules for all parties involved in the assessment process should be put in place to make sure the required timelines are met and consequently improvement in the speed of evaluation could be achieved. As far as our results indicate, the only median and mean time durations of pre-assessment phase that did not exceed the prescribed timeline of 27 days were in 2004 and 2008. For drugs assessed by CHMP in years 2006, 2007 and in 2009, the median and also mean times just slightly surpassed the prescribed timeline, with exception of 2005, when the median and mean times relevantly exceeded the recommended timeline.

5. EC decision process

An immediate and steep drop of median time from 2004 to 2005 shall not come as a surprise if we compare it to the equally significant rise in EMA post-opinion phase time during period 2004 - 2005. In terms of median duration of the last two phases in 2004, it is clear that the length of one compensates for the short median duration of the other. This may either be due to actual improvement in the time spent or simply due to the differences in a way the times have been recorded during these two phases in 2004 and the following years. Only for MA application of drugs assessed in the years 2006 and 2007 have EC managed to retain the median time to issue MA valid across the EU under the 40-day limit, which may again indicate a lack of rigour and control in achieving the required deadlines. This is also confirmed by a relatively big dispersion of time spent during this phase for drugs that were assessed by CHMP during 2008 and 2009, indicating that EC should be much more consistent and rigorous in reaching the designated deadlines.

5.3.2.1 Median and average days spent during every stage of the centralised procedure

We compared the mean duration of five separate phases during approval of new innovative therapies analysed by us to mean times of all pharmaceuticals that underwent the CP reported in EMA annual reports [57; 58].

Proportionally, the mean times of each phase during the EMA assessment, for all medicines approved by EMA between 2004 and 2009, roughly correspond to the mean times spent during the assessment of only novel pharmaceuticals included in our research. Annual trends of mean times during EMA post-opinion phase and EC decision process reported by EMA seem to be comparable to the mean times calculated in our analysis. However, for all innovative drugs approved between 2004 and 2009 compared to overall mean time of all drugs approved through CP in the same years, we can observe that the mean number of days spent by CHMP during EMA assessment phase was noticeably higher than that of all pharmaceuticals approved by EMA. Comparison clearly indicates that on average CHMP needed at least 4% in 2004, but also up to almost 25% more time in 2009, to assess novel pharmaceuticals and issue an opinion from the start of evaluation during CP. Even though mean assessment times reported by EMA in their annual reports may have been calculated based on inclusion of all medicines, including some generic pharmaceuticals with shorter assessment times or even those that underwent the accelerated procedure, we do believe that time used during the assessment of exclusively novel pharmaceuticals could still be further reduced: EMA should separately consider the importance of novel pharmaceuticals to be evaluated as rapidly as possible, most importantly giving an additional priority to those that represent a true therapeutic innovation. So far, only two innovative medicines in the scope of our research have undergone the so called ‘accelerated assessment procedure’ targeting to reach the CHMP’s opinion in only 150 days. Thus it seems that during the previous years the full potential of ‘accelerated assessment procedure’ had not been exhausted. Additionally, more effort should be made in inciting the pharmaceutical industry to apply for such procedures, making sure that less time is spent until new medicine reaches the patient.

Observing distribution of collated times spent during each phase of the EMA assessment procedure, we can undoubtedly distinct that the biggest potential for improvement is in the ‘clock-stop’ phase as it represents the biggest dispersion of times and is the least regulated phase of the entire CP. It seems that in many phases there has been an enormous improvement in the times spent after the year 2004, which could be due to stricter regulation and control of

deadlines. It should be emphasised that in April 2004, at the time of the accession of the majority of the new EU Member States, a renewed EU legislation [15] was put in place stipulating the reduction of administrative time (duration of EMA post-opinion phase and EC decision process together) as described by Netzer T. [11]. With the new regulation, the deadlines and duration of EMA post-opinion phase and EC decision process had been redefined. Consequently, a noticeable reduction in additional administrative time spent once the CHMP had adopted their opinion as seen in Figure 3 and Figure 4 appeared from 2004 and 2005 to following years. This is well reflected also in reduction of mean and median total time spent during the CP (less the 'clock-stop' time) noticeable from 2006 onwards.

5.4 Launch delays

5.4.1 Novel pharmaceuticals introduced in E-27

The results of this analysis reflect the number of molecules launched per country by the end of our sales tracking period in June 2010 (2nd quarter in 2010). Thus we can expect the drugs launched during more recent years of 2007, 2008 and 2009 still to be made available in some of the E-27 in the years to follow; even more so for countries with the least new launches at the bottom of our list (of Table V). However, none of the study countries will ever reach the total of 125 novel pharmaceuticals made available in Europe. This is primarily because some of the drugs included in this analysis have been approved by NP only, and are only available in Switzerland, while others by MRP or either DcP, thus automatically allowing them to be made available in only some of the panel countries. Given results at hand, with the number of first European launches recorded in each country (Figure 5 in part 4.4.2 above) and time needed from the first European launch to the first use following in each country (Figure 6 in part 4.4.3 above), certainly give a more thorough picture of the level of equity and also time passed to first introduction and access to new innovative medicines across different European countries.

We see Germany, the UK and Nordic countries clearly dominating in numbers of NMEs made available to their patients. The reasons for that may be very much related to some of the specific features of these countries as discussed in the following Chapter 5.4.2 below. Spain, Italy and France are somewhat lagging behind mainly due to the low number of most recent NMEs from 2009 made available to date. It could be that due to time consuming P&R mechanisms in these countries, new drugs are made available with a slight delay, which we confirmed also in the Chapter 5.5 below. Poland, most probably due to its market size, has the

most of NMEs available compared to any of the new EU member states that joined the EU after 2004. New EU member states of CEE get more condensed closer to the bottom of the list, clearly indicating that CEE countries are not on the priority list for introducing NMEs by the innovative pharmaceutical industry. These countries are obviously lacking some of the drugs that have been made available in Europe already in 2004, but even more of those made available in 2005 and 2006. If we were to exclude Czech Republic, Hungary, Poland, Slovakia and Slovenia from this particular group of countries, the low figures of currently launched drugs become even more worrying. Surprisingly however, is to see Luxembourg and Portugal closer to the bottom of the list. Luxembourg, compared to any other E-27, mainly due to its size, is a rather insignificant market in terms of volume sales. Portugal, on the other hand, is quite a significant market but most likely suffering from huge launch delays due to companies' strategies to avoid early launches in Portugal with the objective to avoid price erosion and loss of profit in other E-27 as a consequence of parallel import coming from Portugal. In order to be able to fully substantiate such an argument, we would expect a similar situation to be observed for Greece. However, Greek patients appear to have access to more than twice as much NMEs as the Portuguese, which could also be due to incomplete IMS data showing only a portion of all new innovative drugs actually available to Portuguese patients.

5.4.2 Number of first European launches recorded in each country

For every novel pharmaceutical introduced, the country of the first European launch was detected by the occurrence of the first quarterly sales reported by IMS MIDAS Quantum for that pharmaceutical. Due to the accuracy of the reported quarterly sales data – one quarter equals three months – sales may have actually occurred during any of the three consecutive months. This said, it is likely that more countries report their first sales during the same quarter, making them all qualify as the country of first European launch for a particular drug. Consequently some countries exhibiting only one first introduction of new drug in Europe (i.e. Bulgaria, Estonia, Greece, Hungary, Latvia, Lithuania, Luxembourg, Romania), actually never were the first ones to launch, but are still reflected in the graph due to the accuracy with which introductions of novel pharmaceuticals have been recorded in these countries. In some cases we should consider that sales may have occurred even before the reimbursement of a drug was granted or sometimes even before the drug had been EMA approved (i.e. 'compassionate use programmes' enabling access to medicines for patients with severe illness using a new, unapproved drug when no other treatments are available [59]).

Seeing Germany and the UK to be most frequently the countries of first European launches of new innovative drugs should not come as a surprise, as similar was shown previously by Jönnson et al. when studying a pool of oncology drugs being introduced in some of the selected world markets until 2004 [31]. The results of our analysis suggest that new innovative drugs are most often first made available in bigger countries (Germany, UK) and those where free pricing (Germany, UK and Denmark) legislation is in place. The system of free pricing could have contributed to faster launch of new innovative drug in these countries, as distribution and prescribing (mostly for private market only) - generating first sales reported to IMS - may actually begin while reimbursement decision is still pending (as in the UK). This of course contributes to early detected launch, but not necessarily to optimal and equal patient access. Germany, with probably the largest absolute patient pool in majority of therapeutic indications – due to its demographic size – represents a large volume sales potential. Practically automatic reimbursement in Germany, enabling manufacturers to secure high list prices with favourable price-referencing impact in other countries, seem to represent the most advantageous conditions for the pharmaceutical industry, thus placing German patients amongst the first in Europe to gain access to innovative drugs. Almost alike is the UK, where free pricing allows manufacturers to secure high list prices of new medicines at least right at launch thus again securing a positive impact on prices in other European countries where price-referencing system taking into account UK is put in place [24]. In Nordic countries (Denmark, Sweden, Finland and Norway), where due to relatively high prices the income generated on novel pharmaceuticals could be imperilled by a significant share of parallel import [24] - coming from countries such as Belgium, Italy, Portugal and Spain - it is in the interest of the companies to launch products first or at least far ahead before new drugs will be launched in countries that are parallel exporters. This is valid also for discussion in the following chapter 5.4.3. and even more so for first-in-class drugs that often have a first mover advantage and retain relatively large sales, compared with follower products, for several years after launch. Thus first-in-class products may be more at risk for parallel trade than follower products [60].

Countries such as Belgium, Italy, Portugal and Spain are definitely not amongst the priority countries for introduction of new innovative drugs in Europe as these markets are known to have strict regulation and have traditionally been major parallel exporters with usually somewhat lower prices than in other countries [61]. However in Spain and Italy, a partial cause for delay may be in the fact that before a drug is actually being prescribed, its price needs to be approved and a drug needs to be placed onto regional formularies or even

accepted by hospital formularies (for hospital-only drugs). Interestingly, also France, belonging to the EU-5 countries, does not appear to be particularly often the first country to introduce a new drug to the European markets. Apparently France and Italy both share common requirements by which prices of pharmaceuticals need to be negotiated with payers before drugs can actually be placed on the list and prescribed to patients [24; 62]. It is this requirement that delays the occurrence of first reported sales and thus the first launch detected in this analysis. There is no need to emphasise that Luxembourg, as a small economy with low potential in volume sales, does not represent a very important market in terms of early access for the innovative pharmaceutical industry. High rate of first introduction of novel pharmaceuticals observed in Switzerland, on the other hand, could be related to the fact that this country is home to a significant number of successful and highly productive innovative pharmaceutical companies that encourage early launch and access of new products to patients in their own country of origin. The hypothesis around local registration advantage for drugs originated by local companies, such as in the case of Switzerland, was confirmed also by Danzon and Epstein [28].

Interestingly, with the exception of Poland, countries that have joined the EU since 2004, have hardly ever appeared to be among the first ones to launch in the E-27. After all, it seems that generally first European launches remain the attribute of economically more developed western European countries, where the larger part of the innovative pharmaceutical industry also originates from. However the carefully planned locations of first launch are very much related to P&R regulations governed in each of the E-27. Nevertheless, all the above conclusions can only be tentative as full interpretation of these results is also best performed together with the previous and the following chapter.

5.4.3 Time from the first European launch to the first use following in each country

The main advantage of applying Kaplan-Meier survival curve method is that when the mean time for all drugs followed from the first European launch to the first use in a particular country is being calculated, for cases where countries may be due to introduce a new innovative drug following the end of our observation period (thereby beyond our control), it allows us to consider at least the fully observed portion of time passed since the first European launch to the end of the observation period at the 2nd quarter of 2010. On the contrary, calculating the mean time each country needed to introduce new drugs to their patients, by applying only the drugs effectively introduced within the time scope of our research within each European country, would give an incomplete estimation of the mean

time needed to make novel pharmaceuticals available in our study countries after first European launch.

As shown on the Figure 6-A, Germany and the UK appear to be leading in bringing pharmaceutical innovation to patients. Being among the 5 biggest European markets in terms of their population size these two countries evidently represent a significantly large proportion of the European market size and therefore offer an opportunity for generating big profits and faster return on investment for new medicines, particularly in their initial launch stages. Moreover, as concluded by Garattini et al., in Germany and in the UK pricing and reimbursement systems appear to be amongst the only ones (also in Denmark) where free pricing formally applies and where broader regulations are represented by therapeutic reference pricing systems and ceilings for companies' profitability, respectively [63]. Besides, in these two countries, no reimbursement process needs to be completed before new medicines can be prescribed to patients [64; 65; 66]. As exposed in the previous chapter 5.4.2, all this provides additional stimulation for early launches and thereby early patient access in Germany and in the UK. Mean times elapsing from first launch in Europe to patient access in other three biggest EU markets represented by Spain, Italy and France appear to be similar, ranging from estimated mean times (Kaplan-Meier analysis) of 17.5, 19.4. to 21.6 months respectively. Pertaining to the group of the big EU 5 markets, these three countries still lag significantly in time to access compared to Germany and the UK. This may be due to numerous factors, however partial cause may be in the fact that Italy and Spain have undertaken a strong decentralisation in the health care sector, which resulted in regional legislation regarding the organisation and funding of health care [24]. Russo at al. showed that in the case of Italy, such decentralisation has a significant influence on the time to access. They have concluded that in the case of selected oncology products authorised by *Agenzia Italiana del Farmaco* (AIFA), it was proved that not all products were subsequently released in every Italian region, and the mean delay from patient access was 5.3 months [1]. A further barrier to patient access in Italy appears to be represented by the dominant role gained by regional formularies over the national formulary [1]. Substantial delay with estimated mean time to patient access of novel pharmaceutical in France could certainly be partially attributed to the fact that drug P&R in France results in a sophisticated and complex mix of regulations and negotiations. Community drugs are first assessed by the Transparency Committee (*Commission de la Transparence*, CT) and then by the Pricing Committee (*Comité Economique des Produits de la Santé*, CEPS) [63], which could potentially amount for the additional estimated mean time lag to first launch of novel pharmaceuticals in France.

However, we have to point out that already before 2004, French authorities introduced efficient measures to speed up the average time for granting a P&R status for new products approved through the CP by allowing the innovative industry to submit pre-applications directly to the CEPS and the CT, which are then able to start the assessment of the dossier and reach P&R decision earlier [63]. A more relevant reason to observe Italy, Spain and France in obtaining new medicines with significant delay after Germany and the UK, could lie in the fact that these 3 countries proved to be important parallel exporters into destination countries such as Sweden, Denmark, the Netherlands, Finland, Germany, and the UK [61].

In Denmark and Switzerland the role of economic evaluation and cost-effectiveness is not a formalised part of the decision-making process when securing reimbursement. Whilst in Finland, Sweden, Norway and the Netherlands there is a formalised decision-making process where economic evaluation and the issue of cost-effectiveness play an important role [4], we believe that these decision making regulations may not have had a great impact on time to patient access. The most significant impact on time to first detected use in the country after first detected launch in E-27 can certainly be attributed to factors such as external price benchmarking, (i.e. influence on pricing in other countries due to the settled price in a specific country), parallel trade, and local market size [1].

It is not surprising to see that new medicines reach Greece and Portugal relatively late after the 1st launch in E-27. These two countries are known to be active in parallel export of new medicines [61], therefore companies' endeavours to launch new medicines in these two markets may be postponed intentionally. Portugal, with its relatively low prices, has been a legal source of parallel exports to other EU countries since 1995 [67]. As far as countries of the CEE are concerned, it is evident that launch delays are mainly a cause of low prices and small market sizes. Nevertheless, also Danzon et al. confirmed that launch decisions are influenced by expected price and sales volume rather than simply by general characteristics of each country’s regulatory and market environment [60].

5.4.3.1 Relation of calculated mean times to country specific demographic and economic indicators

As our results suggest, countries with generally higher purchasing power and larger population size tend to be among those that are often the first to launch novel pharmaceuticals in Europe or at least among those that most rapidly follow the first launch of novel pharmaceutical in Europe. Obviously, a rapid or either slow introduction of new medicines in a specific European country generally reflects the market access decisions made by the

pharmaceutical companies. Such decisions are certainly driven by opportunity for return on investment and potential profits generated from sales of such medicines in European countries. When launching a new medicine, pharmaceutical companies employ different market access strategies taking into account factors such as the size of the target population corresponding the indication of new medicine, price level and availability of cost-benefit data, price flexibility, influence on international price comparisons (reference pricing), competitors and also internal European marketing strategies [68]. Looking at the first four conditions for defining a company's market access strategy, we can understand that strategies employed by companies mostly respond to the so called 'fourth and fifth hurdle' imposed by pricing and reimbursement procedures which can differ substantially from country to country.

GDP, as the indicator of an economic development of the country, may not have direct correlation with the time to launch, but we certainly can look for other implicit relation between the GDP per capita (expressed in PPS) and the country's probability of launch among E-27. Generally, more developed western European economies, such as those with GDP above the average GDP of EU-27 member states (Table I), seem to have more timely and efficient pricing and reimbursement mechanisms in place that may work in favour of launches of new medicines, at least in some of these markets.

A very important aspect is also the market size, usually predefined by absolute number of patient population. Countries with more inhabitants thus represent an opportunity for high volume sales. With the exception of Luxembourg, whose lag in patient access to new medicines is obviously related to the small market size and thereby most likely a low interest in initial launches by the pharmaceutical industries, majority of the countries on the right site of the bubble chart on Figure 7 belong to the group of eastern and central European countries that joined the EU in 2004. These are, as the figures (Figure 7) show, smaller economies (with exception of Romania) with lower purchasing power that were included into the scope of the EMA Centralised procedure only in 2004 with accession to the EU. Countries such as Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Slovakia, Slovenia and also Romania are among the countries that lag the most in introducing new medicines to patients. On the contrary, countries such as Slovakia and Poland remain in the middle of the scale, being the fastest of all new EU member states in introducing new medicines to patients.

5.5 Market and patient uptake of novel pharmaceuticals

To perform the analyses of cumulative sales and cumulative uptake for all novel pharmaceuticals together, monetary sales data (expressed in EUR) seemed the far best and

only reasonable option to be used in such a calculation. However, the results of these analyses are rather an approximate indicator of countries' monetary ability and affordability to uptake new drugs and unfortunately could not be directly related to the number of patients actually receiving the new innovative treatments. Still, considering the data available, results of our analysis offer a good enough and accurate reflection of the increasing expenditure incurred by novel pharmaceuticals in each of the European countries from 2004 to 2009. Nevertheless, for previously mentioned countries that are known to be a popular origin of parallel export, the market uptake as well as country specific sales data should be interpreted with a critical eye.

As illustrated in "Appendix 6: IMS Retail and Hospital Audit detailed description", local pharmaceutical audits performed by IMS in each country can report sales at either ex-manufacturer price (manufacturer selling price or wholesale purchase price), trade price (pharmacy purchase price or wholesale selling price) or public price (pharmacy selling price). Additionally, sales depend on the kind of price charged at each point in the distribution chain and prices depend on various specifics of commercial relationships: marketing discounts, buying quantities, delivery size, payment terms and other factors may affect the true cost incurred by the purchaser. In multiple-country analyses, such as ours, IMS MIDAS Quantum converts the sales and pricing information to a standardised ex-manufacturer level using an average factor determined for each country [69]. Such factors are updated continuously and are derived from information provided by health authorities, the manufacturers and wholesalers. This allows us to compare sales figures directly across countries and avoids greater biases likely to be incurred by price level differences.

However a disadvantage of using monetary sales is that price variations between countries – especially for drugs with high volume sales reported – may have quite a significant effect on the actual uptake or sales in cross-country comparison. The extent of such an effect can be estimated from average cross-country price comparison presented in part 4.6 above. Additionally, more expensive drugs (i.e. antineoplastic agents, immunosuppressants, orphan drugs), especially if sold in bigger volumes, have more significant effect on the uptake curve and cumulative sales than other less expensive medicines.

When measuring uptake expressed as monetary sales per capita, ideally sales of every drug should be weighed up against the number of patients that obtained it. The closest realistic alternative would be to use either prevalence or mortality data (in case of cancer therapy) related to specific diseases or therapy area of each of the 125 novel pharmaceuticals. However, collating such data would be very difficult, if not impossible, since sources specific to the therapeutic indication of each novel pharmaceutical are incomplete or inexistent even.

Thereby the best approximation of relative prevalence of all diseases covered by our novel pharmaceuticals has been addressed in a simplified manner using number of residents in each country. This approach had been suggested as an alternative also by Kos et al. [32].

5.5.1 Sales of novel pharmaceutical

Novel pharmaceuticals introduced between 2004 and 2009 added about 10.6 billion EUR to the drug sales in selected European countries by 2009, amounting to approximately 7% of the total drug sales reported by European Federation of Pharmaceutical Industries and Associations (EFPIA) [70]. Thus novel pharmaceuticals may represent a significant budgetary burden for healthcare systems, at least until the first generic alternatives become available once the patent protection for rewarded innovation has expired.

In terms of portion of total sales, the predominating expenditure incurred by drugs introduced in 2004 prevailed all until 2009. A significant share of total sales attributed to new innovative drugs in 2009 was also attributed to groups of drugs launched in 2006 and in 2007, whilst for drugs launched in 2005, the portion of total sales slightly decreased between 2007 and 2009. The total sales of drugs certainly do tell about the ability of E-27 as a whole to spend and provide newly launched innovative drugs during the study period. However, the portions of drugs sold according to their year of launch, as presented in Figure 9, may be strongly related to the type of indication for which drugs were launched, hence their ex-manufacturer price.

IMS sales data for Greece, Luxembourg and Portugal, consisting mainly of retail sales, may be incomplete, however these three countries certainly stand out in total number of Standard Units (SUs) sold. As previously mentioned, Greece and Portugal, with the addition of Spain – where cumulative volume sales (expressed in SUs) also stands out – are countries known to be the biggest parallel exporters of new innovative medicines to other European countries, therefore the higher than usual volume sales should not come as a surprise. Nevertheless, correlation between higher volume sales and lower monetary sales in these countries also indicated that most probably, those less expensive drugs are a more popular object of parallel trade. This may further increase a problem of availability of novel pharmaceuticals within the parallel export countries as companies employ tactics to limit parallel trade: including ‘supply quota systems’ and ‘dual pricing systems’ [71].

Examining the portion of total sales of novel pharmaceuticals in individual countries it is clear that in older EU member states, the newly launched medicines present a larger portion

of sales than in the new EU member states, which is once again an indicator of better availability of more recent medicines in more developed countries.

Figure 11 illustrates noticeable differences with regard to the use of older and more recent innovative drugs among E-27. Such discrepancies are strongly related to the differences in the level of uptake of new innovative drugs following their introduction in E-27. Interestingly, once made available, drugs first launched in 2005 and 2006 had a much more significant uptake in Poland compared to the rest of the countries, however, generally countries with a faster uptake and introduction of new drugs are those of the old EU member states, whilst the new EU member states lag behind in access of new innovative therapies.

5.5.2 Absolute cumulative uptake of novel pharmaceuticals

As Jönsson and Wilking summarised in their report, even though considering only oncology drugs [31], the uptake of new innovative drugs appears to be related to the country's affordability and thereby their income per capita. Our analysis confirms that countries with a lower income such as those of the CEE (Table I), that joined the EU after 2004, absolutely appear to have a much slower monetary uptake on average, from countries pertaining to the Western European region that accessed the EU already before 2004. The latter are economically more advanced, with a higher income per capita and can enable faster uptake of new expensive treatments to their patients. This is clearly visible when we apply the ‘weight’ of affordability of an individual country expressed in GDP per capita (in PPS) (Figure 13-D) to its sales and even further apply the percentage of health care expenditure (Figure 14-D). In these two cases, the average uptake curves of EU accession countries that joined before 2004 and of those that joined the EU after 2004 indeed move closer together, but do not level out. This indicates that reasons for inequalities in the uptake of new medicines between these two groups of countries may as well lie elsewhere and are obviously more profound.

So it seems there are no simple explanations for the differences in uptake of innovative pharmaceuticals among different countries in Europe, since a series of factors play a role and their combination may vary across countries [72]. It has been previously noted that two of the most important factors are however the macro-economic conditions and treatment guidelines, however we can reasonably assume that limited usage is a consequence of a low GDP, restrictive treatment guidelines, budget restrictions, administrative hurdles and possibly also access to specialists [72]. Certainly a cause of steady or slow uptake presented in our results for some countries (i.e. Bulgaria, Hungary, Latvia, Lithuania and most likely also Estonia, Portugal, Romania, Luxembourg) may also be in significant launch delays.

Even though there may be a number of reasons and a complex interdependency of these to be able to explain a slow uptake of innovative pharmaceuticals, an effect in the differences of the sales and uptake of innovative drugs could to some extent be related also to diverse marketing and sales strategies employed by the pharmaceuticals companies and their local branch offices in different countries across Europe. These may be adapted to cultural differences as well as to national and even local legislation.

There appears to be quite significant differences in the uptake of new innovative medicines among old EU member states and more so among the EU- 5.

Taking under the scope only the EU-5, in France for example, a steep uptake of new expensive novel pharmaceuticals could partially be related to considerable prescribing freedom present among physicians [73] and also due to freedom of choice of physicians amongst patients that are allowed to change their *médecin traitant* as often as they wish [74]. This may further be substantiated by the fact that out of 100 consultations only 9.8% of visits end without a prescription in France, compared to 27.7% in Germany, 16.9% in Spain, and 56.8% in the Netherlands [75]. Moreover, drug consumption by volume in France is the highest in the world; 1.2 million people over 70 years of age take more than seven drugs a day [74].

In comparison to France, Germany's lower uptake could as well be partially explained by well established demand-side market interventions introduced in the German pharmaceutical market since 1983: Especially physician spending caps and patient co-payments imposed by Health Care Structure Act in 1993 to control overall spending of pharmaceuticals as well as somewhat milder measures like prescription guidelines and negative lists containing all approved pharmaceuticals not covered by sickness funds for insured over 18 years old [76]. In Spain, high absolute uptake of new therapies made available between 2004 and 2009 may be influenced by Spain's significant role in parallel-export of innovative drugs to other EU member states with higher prices of new drugs (i.e. UK, Germany, Denmark, etc.). Therefore the uptake of new medicines in Spain may be an over-estimate of the real absolute pharmaceutical uptake and expenditure designated to its patients. Similarly, this could be seen in the case of Greece and Portugal, even though the IMS sales data for these countries are incomplete. However, a relatively high sales and steep uptake may also be due to the fact that Spain has no positive list for reimbursement and therefore all drugs in principle are reimbursable at rates between 60% and 100% [63].

No simple answer exists as to why Italy has a relatively slow uptake compared to the majority of the older EU accession states. Partial explanation could be that due to strong

process of power decentralisation during the past two decades, today 21 Italian Regional Governments are individually accountable for any deficit in their healthcare budget and are individually responsible for pharmaceutical policies [77]. Consequently Italian Regions are employing different strategies to control drug utilisation and expenditure, thus not only influencing the uptake of innovative drugs, but also access to innovative therapies available to patients in Italy. This is due to the dominant role gained by regional formularies over the national formulary [1; 77].

At the bottom of the average uptake recorded for old EU member states and also below the uptake of new drugs in Norway and Switzerland, UK's relatively slow uptake of oncology-specific drugs was similarly observed already by Drs Jönsson and Wilking, Kos et al. and Obradović et al. [32; 31; 33]. Some of these authors and also others [78] have underlined the so called 'fourth hurdle' as a partial cause of slow uptake and restricted access to new therapies in the United Kingdom. As previously noted by Drs. Jönsson and Wilking, we can now also clearly observe that countries leading the HTA development (i.e. The Netherlands, Spain, Sweden, Switzerland the United Kingdom) are not the leading countries (Austria, Belgium, Denmark, Finland, France), with exception of Spain, in regard to the uptake of new drugs and thus patient access to new innovative medicines [4].

Among the rest of the older EU member states – excluding Greece, Ireland and Portugal – there are less noticeable differences in the uptake than among the EU-5. Approximately levelled with Germany, but faster than Italy, are the uptakes of new innovative drugs in Denmark, Belgium, Austria. Drugs in Finland may be reaching the patients slightly slower in absolute terms, but the picture changes when we take into account the country's affordability and its expenditure in the healthcare system.

The countries of the CEE, pertaining to the group of latest EU accession states have evidently much slower uptake than the more developed Western European countries, also spending significantly less resources per inhabitant on novel pharmaceuticals than do most of the Western European countries, with the most evident exception of the UK and Norway. The fact that CEE countries, but also Greece and Portugal, generally spend a larger proportion of their healthcares budgets (Table I) for pharmaceuticals, indicates that the smaller economies with less income per capita struggle to afford expensive, new innovative drugs. Uptake and sales, as such, do resonate the outcome of various hurdles and issues that may have an impact on securing optimal access of new medicines to patients in these countries.

5.5.3 Absolute cumulative uptake valued against affordability of each country

As differences in price levels, currency conversion rates (particularly for countries outside the Economic and Monetary Union (EMU)) and quantity differences exist between E-27, we decided to adjust the uptake expressed in monetary sales per capita by dividing it with GDP per capita (expressed in PPS). For countries with higher income per capita, represented mostly by old EU member states, the cumulative uptake decreased and for new EU member states represented by CEE countries, the cumulative uptake increased slightly. Bringing countries' affordability into the equation, the curves moved closer together generally also reducing the differences between average uptake of new and old EU member states. However, we observed a slight increase in the relative gap between the average uptake of EU-5 and average uptake of old EU member states that joined the EU before 2004. Even though to a great extent we managed to level the countries in their affordability to secure optimal uptake to novel pharmaceuticals, our results indicate that significant differences in the speed of uptake, witnessed for these countries, still persist. This does confirm to significant differences in uptake among countries.

5.5.4 Absolute cumulative uptake valued against countries' total expenditure in health care

When cumulative monetary uptake (expressed in EUR/inhabitant) of innovative pharmaceuticals launched in selected European countries is weighed up against PPP-adjusted GDP per capita invested in healthcare, we can get a different perspective of uptake indicating a more realistic ability of an individual country to uptake new innovative drugs considering its investment in healthcare. The countries move even closer together reducing the gap between countries, but differences are still significant and no equalisation is observed.

5.6 Affordability gap

SU prices (at ex-manufacturer level), reported during first 2 quarters after the launch of a drug in each individual country, were assumed the most appropriate for the calculation of the average SU price used in calculation of relative deviation (from German index price) as prices negotiated or defined at launch are usually closely related to payer's reimbursement and pricing decision and regulation, thus reflecting the real impact of pricing decisions (and policy) in each country. Calculating a mean price deviation of novel pharmaceuticals across E-27, we decided to index every country-specific drug price to price reported for Germany. Germany has a free pricing system; it is a leading country of first launches in E-27 and is also

the quickest country in introducing new innovative medicines to its patients after first European launch. Thus we believed the German price could likely have the attributes of the European target price that innovative industry is striving to achieve at launch of new innovative drugs across Europe. Additionally Germany is a country with the highest portion of panel drugs made available among E-27 (Table V), thus enabling the largest range of panel drugs from each country to be included in calculation. Germany was also the index country of choice used in analyses described in previous chapters.

Analysing the results, it is clear that a distinct "affordability gap" exists mainly for the countries of CEE that joined the EU after 2004. These countries appear to have their income per capita well below the one of Germany, however, the reported mean prices of drugs launched in these countries are almost levelled with the prices in Germany. Such a gap clearly needs to be addressed at a European level and more generous price reductions or discounts should be given to economically weaker Member States, so they will continue to afford new innovative drugs at prices that are in line with their economical capabilities.

Remarks need to be brought to bear regarding the accuracy and possible skewness of the calculated prices. Price deviation reported for the UK may be an underestimate as price levelled with other countries would be expected. As mentioned earlier, the IMS MIDAS database reporting sales at the ex-manufacturer price is not taking into account administration costs, pharmacy margins and VAT. Administration costs could be significant, especially for drugs used in outpatient treatment. Originally prices may be audited at levels (as described in part 5.5 above) different from the ex-manufacturer price depending on the country. IMS conversation rates are then used to convert prices from different price levels to ex-manufacturer price used in reported sales. The portions of average price indexed on Germany may thus be an over or underestimate for some countries. To be most accurate, price to patient would need to be used; however prices at ex-manufacturer level still offer a good base for cross-country comparison of international price deviations among E-27.

6 CONCLUSION

- Antineoplastic agents (15.2 %) and immunosuppressants (8.8%) clearly dominate amongst new innovative medicines introduced between 2004 and 2009.
- CP is the most employed and greatly contributes to optimised, transparent and also timely regulatory approval of new innovative medicines. It drastically reduces the time to gain EU-wide marketing authorisation and is a prerequisite to overcome the first three hurdles for equal and more rapid patient access to new drugs in EU and EEA.
- Even though the average and median 'EMA time lag' has reduced between 2004 – 2009, there is still room for further reduction of time spent:
  - Pre-assessment phase deadlines could be less rigid, enabling earlier start of assessment process conducted by EMA/CHMP;
  - Prescribed deadline of 210 days for active assessment time has been surpassed on several occasions and should be considered more strictly by EMA. Accelerated assessment of 150 days could be more accessible for new innovative medicines;
  - Company phase ('clock-stop') has the most significant effect on the prolongation of EMA lag time: stricter and clear deadlines should be put in place or agreed with applicants during the procedure to reduce the time companies spend for preparation of additional documentation;
  - There are still inconsistencies in the duration of EMA post-opinion phase and EC decision process. EMA and EC should work more strictly within the regulatory deadlines.
- MRP and DcP have been employed for regulatory approval of only a handful of new innovative medicines launched between 2004 and 2009.
- Significant demographic differences as well as differences in affordability and expenditure in health exist among E-27. Some old EU Member States (particularly EU-5) are considerably larger in population size (hence patient population); together with Norway and Switzerland, old EU Member States have generally higher income per capita and also invest considerably more in healthcare care than new EU Member States that joined the EU after 2004. Generally new EU Member States spend considerably higher portion of their health care resources on pharmaceuticals than old EU Member States (exceptions are Greece and Portugal).

- Western countries (with the exception of Greece, Portugal and Luxembourg) generally dominate in providing patients with faster access to new innovative treatments:
  - In CEE countries (with the exception of Slovakia and Poland) only 65% or even less of all novel pharmaceuticals introduced between 2004 and 2009 were made available.
  - New treatments were first introduced to E-27 mostly in old EU member states. Belgium, Greece, Italy, Portugal, Spain are not among them due to established parallel export.
  - Western European countries (excluding Luxembourg) are much faster (from the average of 4.7 months needed by Germany to the maximum of 26.6 months needed by Belgium) in introducing new drugs to their patients after a drugs was first made available in E-27, while CEE countries take at least 21.9 months (the fastest Poland) and up to 55.6 months (Estonia).
- France, Spain, Denmark and Germany have the fastest uptake, above the fastest average uptake of EU-5, while Italy and UK are much slower in the uptake of new medicines, most likely due to their national/local P&R policies. Overall, CEE countries (except Slovakia and Slovenia) have the slowest uptake of new medicines, below the average uptake reported for E-21.
- Countries with well developed HTA such as the Netherlands, Spain, Sweden, and the UK are not leading in regard to optimal uptake of new innovative drugs, with the exception of Spain.
- A combination of free-pricing system and high absolute size of patient population (Germany, UK) has proven to be a major contributing factor for earlier launches and fast access.
- Prices of new innovative drugs across E-27 are comparable and thus discriminatory towards CEE countries with significantly lower income per capita.

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APPENDICES

Appendix 1

Table III. List of new innovative drugs launched for the first time in E-27 between 2004 and 2009, their total numbers and proportion split by 2nd level of ATC classification

ATC CODE	ATC THERAPEUTIC SUBGROUP	INNOVATIVE ACTIVE INGREDIENT	No. (% of total)
A04	ANTIEMETICS & ANTINAUSEANTS	Palonosetron, Fosaprepitant	2 (1.6%)
A06	LAXATIVES	Methylnaltrexone Bromide	1 (0.8%)
A08	ANTI-OBESITY PREPARATIONS, EXCL. DIET PRODUCTS	Rimonabant	1 (0.8%)
A10	DRUGS USED IN DIABETES	Insulin Detemir(B), Insulin Glulisine(B), Exenatide, Sitagliptin, Vildagliptin, Liraglutide(B), Saxagliptin	7 (5.6%)
A16	OTHER ALIMENTARY TRACT & METABOLISM PRODUCTS	Alglucosidase Alfa(B)*, Galsulfase(B)*, Idursulfase*	3 (2.4%)
B01	ANTITHROMBOTIC AGENTS	Bivalirudin, Argatroban, Treprostinil*, Antithrombin Alfa(B), Dabigatran Etexilate, Rivaroxaban(B), Prasugrel	7 (5.6%)
B02	ANTIHEMORRHAGICS	Romiplostim(B)*	1 (0.8%)
B03	ANTIANEMIC PREPARATIONS	Epoetin Delta(B), Methoxy Peg-Epoetin Beta(B)	2 (1.6%)
C01	CARDIAC THERAPY	Nesiritide(B), Ivabradine, Icatibant*, Dofetilide, Dronedarone, Ranolazine	6 (4.8%)
C02	ANTIHYPERTENSIVES	Sitaxentan*, Ambrisentan*	2 (1.6%)
C03	DIURETICS	Eplerenone, Tolvaptan	2 (1.6%)
C09	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	Aliskiren	1 (0.8%)
C10	LIPID MODIFYING AGENTS	Laropiprant	1 (0.8%)
D06	ANTIBIOTICS & CHEMOTHER. FOR DERMATOLOGICAL USE	Retapamulin, Docosanol	2 (1.6%)
G03	SEX HORMONES & MODULATORS OF THE GENITAL SYSTEM	Ulipristal Acetate	1 (0.8%)
G04	UROLOGICALS	Solifenacin, Darifenacin, Fesoterodine, Dapoxetine	4 (3.2%)
H01	PITUITARY & HYPOTHALAMIC HORMONES & ANALOGUES	Mecasermin(B)*	1 (0.8%)
H05	CALCIUM HOMEOSTASIS	Cinacalcet, Parathyroid hormone(B)	2 (1.6%)
J01	ANTIBACTERIALS FOR SYSTEMIC USE	Cefditoren Pivoxil, Prulifloxacin, Daptomycin(B), Tigecycline, Doripenem, Ceftobiprole Medocaril	6 (4.8%)
J02	ANTIMYCOTICS FOR SYSTEMIC USE	Posaconazole, Anidulafungin, Micafungin	3 (2.4%)
J05	ANTIVIRALS FOR SYSTEMIC USE	Fosamprenavir, Tipranavir, Entecavir, Telbivudine, Darunavir, Maraviroc, Raltegravir, Etravirine	8 (6.4%)
L01	ANTINEOPLASTIC AGENTS	Bevacizumab(B), Bortezomib, Cetuximab(B), Pemetrexed, Azacitidine*, Erlotinib, Clofarabine*, Dasatinib*, Sorafenib*, Sunitinib*, Lapatinib, Nelarabine, Nilotinib*, Temsirolimus*, Trabectedin*, Panitumumab(B), Catumaxomab(B), Ixabepilone, Vinflunine	19 (15.2%)
L02	ENDOCRINE THERAPY	Fulvestrant, Degarelix	2 (1.6%)
L03	IMMUNOSTIMULANTS	Picibanil, Plerixafor*	2 (1.6%)
L04	IMMUNOSUPPRESSANTS	Efalizumab(B), Everolimus*, Natalizumab(B), Abatacept(B), Eculizumab(B)*, Lenalidomide*, Certolizumab Pegol(B), Tocilizumab(B), Canakinumab*,	11 (8.8%)

ATC CODE	ATC THERAPEUTIC SUBGROUP	INNOVATIVE ACTIVE INGREDIENT	No. (% of total)
		Golimumab(B), Ustekinumab(B)	
M01	**ANTIINFLAMMATORY & ANTIRHEUMATIC PRODUCTS**	Lumiracoxib	**1 (0.8%)**
M05	**DRUGS FOR TREATMENT OF BONE DISEASES**	Strontium Ranelate	**1 (0.8%)**
N02	**ANALGESICS**	Ziconotide*	**1 (0.8%)**
N03	**ANTIEPILEPTICS**	Pregabalin, Rufinamide*, Lacosamide(B), Eslicarbazepine Acetate	**4 (3.2%)**
N04	**ANTI-PARKINSON DRUGS**	Rasagiline, Rotigotine	**2 (1.6%)**
N05	**PSYCHOLEPTICS**	Aripiprazole, Paliperidone	**2 (1.6%)**
N06	**PSYCHOANALEPTICS**	Duloxetine, Agomelatine	**2 (1.6%)**
N07	**OTHER NERVOUS SYSTEM DRUGS**	Varenicline	**1 (0.8%)**
R01	**NASAL PREPARATIONS**	Fluticasone furoate	**1 (0.8%)**
R03	**DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES**	Omalizumab(B), Ciclesonide, Indacaterol	**3 (2.4%)**
S01	**OPHTHALMOLOGICALS**	Loteprednol, Pegaptanib, Ranibizumab(B), Nepafenac, Tafluprost	**5 (4.0%)**
V03	**ALL OTHER THERAPEUTIC PRODUCTS**	Deferasirox*, Lanthanum, Palifermin(B), Sugammadex	**4 (3.2%)**
V10	**THERAPEUTIC RADIOPHARMACEUTICALS**	Ibritumomab Tiuxetan(B)	**1 (0.8%)**
		Novel pharmaceuticals in total	**125 (100%)**

ATC = Anatomical Therapeutic Chemical classification system; E-27 = 27 European panel countries; No. = number
*Drug with orphan designation granted by the European Commission; (B) = New biological entity or biological drug

Appendix 2

Table IV. List of all novel pharmaceuticals, dates of their marketing authorisation (MA) grated with MA procedures undertaken and countries launched prior to MA granted

Drugs	MA date (MA procedure)	Country launched before MA (or RMS)	Drugs	MA date (MA procedure)	Country launched before MA (or RMS)	Drugs	MA date (MA procedure)	Country launched before MA (or RMS)
Launched in 2004			**Launched in 2005**			**Launched in 2006**		
Bortezomib	Apr 2004 (C)	NO	Ciclesonide	Apr 2004 (M)	(UK)	Clofarabine	May 2006 (C)	UK
Cetuximab	Jun 2004 (C)	CH	Darifenacin	Oct 2004 (C)		Daptomycin	Jan 2006 (C)	
Everolimus	Jul 2003 (M)	(SE)	Erlotinib	Sep 2005 (C)	FR,CH,NO	Entecavir	Jun 2006 (C)	PL
Fulvestrant	Mar 2004 (C)		Loteprednol	Mar 2003 (M)	(UK)	Galsulfase	Jan 2006 (C)	
Ibritumomab Tiuxetan	Jan 2004 (C)		Tipranavir	Oct 2005 (C)	FR	Pegaptanib	Jan 2006 (C)	
Insulin Detemir	Jun 2004 (C)	CH	Palifermin	Oct 2005 (C)	NO	Rotigotine	Feb 2006 (C)	
Aripiprazole	Jun 2004 (C)		Palonosetron	Mar 2005 (C)		Sorafenib	Jul 2006 (C)	FR,CH
Efalizumab	Sep 2004 (C)	CH	Picibanil	N.A.		Sunitinib	Jul 2006 (C)	FR,ES,NO
Fosamprenavir	Jul 2004 (C)	UK	Argatroban	Oct 2004 (M)	(SE)	Treprostinil	Feb 2005 (M)	(FR)
Nesiritide	Oct 2003 (N)	CH	Azacitidine	Dec 2008 (C)	CH,PL	Alglucosidase Alfa	Mar 2006 (C)	
Pemetrexed	Sep 2004 (C)	CH	Rasagiline	Feb 2005 (C)		Parathyroid Hormone	Apr 2006 (C)	
Cinacalcet	Oct 2004 (C)	FR,NO	Deferasirox	Aug 2006 (C)	CH,PL	Rimonabant	Jun 2006 (C)	
Duloxetine	Aug 2004 (C)		Ivabradine	Oct 2005 (C)		Tigecycline	Apr 2006 (C)	
Omalizumab	Oct 2005 (C)	NO	Lanthanum	Mar 2004 (M)	(SE)	Natalizumab	Jun 2006 (C)	
Pregabalin	Jul 2004 (C)		Lumiracoxib	Sep 2003 (M)	(UK) d	Ranibizumab	Jan 2007 (C)	CH,AT, NO,PL
Solifenacin	Dec 2003 (M)	(NL)	Posaconazole	Oct 2005 (C)		Ziconotide	Feb 2005 (C)	
Bevacizumab	Jan 2005 (C)	CH,PL				Dasatinib	Nov 2006 (C)	
Bivalirudin	Sep 2004 (C)					Sitaxentan	Aug 2006 (C)	
Cefditoren Pivoxil	Dec 2003 (M)	(ES)				Telbivudine	Apr 2007 (C)	CH
Eplerenone	Mar 2004 (M)	(NL)				Varenicline	Sep 2006 (C)	
Insulin Glulisine	Sep 2004 (C)							
Prulifloxacin	Jun 2004 (M)	(IT)						

Strontium Ranelate	Sep 2004 (C)							
Launched in 2007			**Launched in 2008**			**Launched in 2009**		
Darunavir	Feb 2007 (C)		Certolizumab Pegol	Oct 2009 (C)	CH	Ceftobiprole Medocaril	Nov 2008 (N)	c
Epoetin Delta	Mar 2002 (C)	a	Fluticasone Furoate	Jan 2008 (C)		Laropiprant	Jul 2008 (C)	
Idursulfase	Jan 2007 (C)		Panitumumab	Dec 2007 (C)		Prasugrel	Feb 2009 (C)	
Lapatinib	Jun 2008 (C)	DE,FR,PL, CH,NO,LT	Ambrisentan	Apr 2008 (C)		Ranolazine	Jul 2008 (C)	
Lenalidomide	Jun 2007 (C)	FR	Dabigatran Etexilate	Mar 2008 (C)		Ustekinumab	Jan 2009 (C)	
Abatacept	May 2007 (C)		Docosanol	Nov 2003 (M)	(SE)	Agomelatine	Feb 2009 (C)	
Exenatide	Nov 2006 (C)		Fesoterodine	Apr 2007 (C)		Catumaxomab	Apr 2009 (C)	
Paliperidone	Jun 2007 (C)		Fosaprepitant	Jan 2008 (C)		Dapoxetine	Dec 2008 (D)	(SE)
Rufinamide	Jan 2007 (C)		Tafluprost	Mar 2008 (D)	(DE)	Degarelix	Feb 2009 (C)	
Sitagliptin	Mar 2007 (C)		Doripenem	Jul 2008 (C)		Ixabepilone	Feb 2009 (N)	c
Aliskiren	Aug 2007 (C)		Icatibant	Jul 2008 (C)		Romiplostim	Feb 2009 (C)	
Eculizumab	Jun 2007 (C)		Lacosamide	Aug 2008 (C)		Canakinumab	Oct 2009 (C)	CH
Methoxy Peg-Epoetin Beta	Jul 2007 (C)		Methylnaltrexone Bromide	Jul 2008 (C)		Eslicarbazepine Acetate	Apr 2009 (C)	
Nelarabine	Aug 2007 (C)		Micafungin	Apr 2008 (C)		Liraglutide	Jun 2009 (C)	
Nilotinib	Nov 2007 (C)	CH	Nepafenac	Dec 2007 (C)		Tolvaptan	Aug 2009 (C)	
Anidulafungin	Sep 2007 (C)		Plerixafor	Aug 2009 (C)	SI,LT	Ulipristal Acetate	May 2009 (C)	
Maraviroc	Sep 2007 (C)		Sugammadex	Jul 2008 (C)		Dofetilide	Nov 1999 (C)	b
Mecasermin	Aug 2007 (C)		Antithrombin Alfa	Jul 2006 (C)		Dronedarone	Nov 2009 (C)	
Raltegravir	Dec 2007 (C)		Rivaroxaban	Sep 2008 (C)		Golimumab	Oct 2009 (C)	
Retapamulin	May 2007 (C)		Tocilizumab	Jan 2009 (C)	CH	Indacaterol	Nov 2009 (C)	
Temsirolimus	Nov 2007 (C)					Saxagliptin	Oct 2009 (C)	
Trabectedin	Sep 2007 (C)					Vinflunine	Sep 2009 (C)	
Vildagliptin	Sep 2007 (C)							

a = Voluntarily withdrawn by marketing authorisation holder in Mar 2009; b = voluntarily withdrawn by marketing authorisation holder in Jan 2004; c = Refused by CHMP; d = CHMP on 13.12.2007 recommended withdrawal of the marketing authorisations

C = Centralised Procedure; D = Decentralised Procedure; M = Mutual Recognition Procedure; E-27 = 27 European panel countries; MA = Marketing Authorisation; N = National Procedure (only applicable for Switzerland); N.A. = never approved in Europe; RMS = Reference member state in Mutual Recognition procedure or Decentralised Procedure; CHMP = Committee for Medicinal Products for Human Use at the European Medicines Agency (EMA)

Appendix 3

Table V. Total number and percentages of all novel pharmaceuticals launched per year in E-27

COUNTRY	Number / Percentage of total launched in E-27													
	2004		2005		2006		2007		2008		2009		Total of panel drugs	
Germany	20	87,0%	15	93,8%	20	100,0%	23	100,0%	19	90,5%	19	86,4%	**116**	92,8%
UK	20	87,0%	14	87,5%	19	95,0%	23	100,0%	20	95,2%	15	68,2%	**111**	88,8%
Austria	21	91,3%	14	87,5%	19	95,0%	21	91,3%	18	85,7%	17	77,3%	**110**	88,0%
Norway	18	78,3%	12	75,0%	19	95,0%	20	87,0%	19	90,5%	16	72,7%	**104**	83,2%
Sweden	20	87,0%	14	87,5%	17	85,0%	20	87,0%	15	71,4%	17	77,3%	**103**	82,4%
Denmark	19	82,6%	12	75,0%	17	85,0%	21	91,3%	19	90,5%	14	63,6%	**102**	81,6%
Spain	21	91,3%	11	68,8%	19	95,0%	22	95,7%	16	76,2%	9	40,9%	**98**	78,4%
Finland	20	87,0%	12	75,0%	19	95,0%	17	73,9%	16	76,2%	13	59,1%	**97**	77,6%
Italy	21	91,3%	12	75,0%	20	100,0%	22	95,7%	13	61,9%	6	27,3%	**94**	75,2%
Poland	20	87,0%	14	87,5%	15	75,0%	18	78,3%	14	66,7%	11	50,0%	**92**	73,6%
Belgium	18	78,3%	12	75,0%	15	75,0%	21	91,3%	14	66,7%	8	36,4%	**88**	70,4%
France	20	87,0%	9	56,3%	18	90,0%	21	91,3%	13	61,9%	7	31,8%	**88**	70,4%
Slovak Rep.	18	78,3%	12	75,0%	16	80,0%	20	87,0%	14	66,7%	8	36,4%	**88**	70,4%
Netherlands	19	82,6%	12	75,0%	16	80,0%	14	60,9%	16	76,2%	10	45,5%	**87**	69,6%
Switzerland	20	87,0%	11	68,8%	15	75,0%	17	73,9%	12	57,1%	9	40,9%	**84**	67,2%
Ireland	17	73,9%	11	68,8%	14	70,0%	19	82,6%	11	52,4%	11	50,0%	**83**	66,4%

Czech Rep.	20	87,0%	11	68,8%	13	65,0%	19	82,6%	12	57,1%	6	27,3%	**81**	64,8%
Greece	19	82,6%	10	62,5%	15	75,0%	14	60,9%	13	61,9%	10	45,5%	**81**	64,8%
Slovenia	20	87,0%	12	75,0%	16	80,0%	16	69,6%	12	57,1%	5	22,7%	**81**	64,8%
Hungary	19	82,6%	11	68,8%	11	55,0%	15	65,2%	11	52,4%	9	40,9%	**76**	60,8%
Bulgaria	17	73,9%	7	43,8%	11	55,0%	13	56,5%	7	33,3%	4	18,2%	**59**	47,2%
Romania	15	65,2%	9	56,3%	9	45,0%	15	65,2%	6	28,6%	4	18,2%	**58**	46,4%
Lithuania	19	82,6%	6	37,5%	10	50,0%	9	39,1%	8	38,1%	3	13,6%	**55**	44,0%
Latvia	15	65,2%	8	50,0%	9	45,0%	8	34,8%	7	33,3%	2	9,1%	**49**	39,2%
Luxembourg	13	56,5%	6	37,5%	6	30,0%	10	43,5%	5	23,8%	5	22,7%	**45**	36,0%
Estonia	12	52,2%	3	18,8%	7	35,0%	7	30,4%	3	14,3%	2	9,1%	**34**	27,2%
Portugal	12	52,2%	4	25,0%	2	10,0%	7	30,4%	4	19,0%	5	22,7%	**34**	27,2%
E-27	**23**	**100%**	**16**	**100%**	**20**	**100%**	**23**	**100%**	**21**	**100%**	**22**	**100%**	**125**	**100%**

E-27 = 27 European panel countries; UK = United Kingdom

Appendix 4

Table VI. Total number of panel drugs included in analysis (up to 120), Means and Medians of time passed between 1st detected use of new innovative medicine in E-27 and the use following in every panel country (Kaplan-Meier analysis output)

Country	Drugs analysed	Censored		Mean[a]		Median	
		N	Percent	Estimate (95% CI)	SE	Estimate (95% CI)	SE
Germany	116	4	3.3%	4.7 (2.6 – 6.9)	1.096	0.0	.
United Kingdom	111	9	7.5%	8.9 (6.0 – 11.9)	1.522	3.0 (1.7 – 4.3)	0.679
Austria	110	10	8.3%	11.2 (8.2 – 14.1)	1.500	6.0 (4.9 – 7.1)	0.566
Sweden	103	17	14.2%	14.1 (10.2 – 17.9)	1.955	6.0 (4.3 – 7.7)	0.855
Denmark	102	18	15.0%	15.0 (10.6 – 19.4)	2.249	6.0 (4.3 – 7.7)	0.844
Norway	104	16	13.3%	15.5 (11.3 – 19.6)	2.132	6.0 (4.2 – 7.8)	0.903
Finland	97	23	19.2%	16.6 (12.6 – 20.7)	2.077	6.0 (3.4 – 8.6)	1.302
Spain	98	22	18.3%	17.5 (14.0 - 21.0)	1.777	12.0 (10.7 – 13.3)	0.643
Italy	94	26	21.7%	19.4 (16.1 – 22.8)	1.696	12.0 (10.5 – 13.5)	0.757
France	88	32	26.7%	21.6 (17.3 – 25.9)	2.206	12.0 (9.3 – 14.7)	1.366
Poland	90	30	25.0%	21.9 (17.5 – 26.2)	2.226	12.0 (8.7 – 15.3)	1.671
Netherlands	87	33	27.5%	23.6 (18.2 – 29.1)	2.767	9.0 (6.1 – 11.9)	1.483
Switzerland	81	39	32.5%	23.9 (19.0 – 28.9)	2.533	12.0 (7.8 – 16.2)	2.132
Slovakia	88	32	26.7%	25.1 (20.4 – 29.9)	2.419	15.0 (12.6 – 17.4)	1.243
Ireland	82	38	31.7%	26.5 (20.7 – 32.2)	2.939	9.0 (5.9 – 12.1)	1.594
Belgium	87	33	27.5%	26.6 (22.3 – 31.0)	2.212	18.0 (14.9 – 21.1)	1.562
Slovenia	80	40	33.3%	28.2 (23.5 – 32.9)	2.409	18.0 (13.7 – 22.3)	2.219
Greece	81	39	32.5%	28.3 (22.8 – 33.8)	2.804	15.0 (10.1 – 19.9)	2.489
Czech republic	81	39	32.5%	29.6 (24.9 – 34.4)	2.425	21.0 (16.4 – 25.6)	2.342
Hungary	76	44	36.7%	32.5 (27.3 – 37.7)	2.651	24.0 (18.4 – 29.6)	2.854
Romania	58	62	51.7%	42.5 (37.0 – 48.0)	2.805	39.0 (25.7 – 52.3)	6.792
Bulgaria	59	61	50.8%	42.9 (37.7 – 48.0)	2.642	39.0 (22.9 – 55.1)	8.223
Lithuania	54	66	55.0%	44.2 (38.8 – 49.6)	2.772	45.0 (26.1 – 63.9)	9.633
Latvia	49	71	59.2%	46.5 (40.8 – 52.3)	2.945	39.0 (N/A)	.
Luxembourg	45	75	62.5%	49.5 (43.7 – 55.2)	2.942	.	.
Estonia	34	86	71.7%	55.6 (50.4 – 60.8)	2.669	.	.

Portugal	34	86	71.7%	56.4 (51.0 – 61.7)	2.732	75.0 (N/A)	.
Overall	**2,189**	**1,051**	**32.4%**	**28.0 (26.9 – 29.0)**	**0.537**	**15.0 (14.1 – 15.9)**	**0.450**

a = Estimation is limited to the largest survival time if it is censored; Up to 120 panel drugs were included in this analysis

CI = Confidence Interval; SE = Standard Error; N/A = Not applicable; N = Number of censored drugs/time, Drugs analysed = Number of new innovative medicines actually launched in every country between Q1 2004 and Q2 2010.

Appendix 5: List of all novel pharmaceuticals included in the scope of our research

Table VII. List of all novel pharmaceuticals included in the scope of our research

No.	Molecules	Brand name	Launch QUARTER	NBE/ NCE	Regulatory Procedure	Date of opinion issued by CHMP	Manufacturer	ACT class	ATC (1st level, anatomical main group)	ATC (2nd level, therapeutic subgroup)
1	Bevacizumab	Avastin	Q4 2004	NBE	CP	21.10.2004	Roche	L01XC07	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
2	Pregabalin	Lyrica	Q3 2004	NCE	CP	24.3.2004	Pfizer	N03AX16	NERVOUS SYSTEM	ANTIEPILEPTICS
3	Ranibizumab	Lucentis	Q3 2006	NBE	CP	16.11.2006	Novartis	S01LA04	SENSORY ORGANS	OPHTHALMOLOGICALS
4	Aripiprazole	Abilify	Q4 2004	NCE	CP	26.2.2004	Otsuka / BMS	N05AX12	NERVOUS SYSTEM	PSYCHOLEPTICS
5	Lenalidomide	Revlimid	Q1 2007	NCE	CP	22.3.2007	Celgene Europe Ltd.	L04AX04	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
6	Duloxetine	Yentreve	Q3 2004	NCE	CP	24.3.2004	Eli Lilly & Co Ltd	N06AX21	NERVOUS SYSTEM	PSYCHOANALEPTICS
7	Sitagliptin	Januvia	Q4 2007	NCE	CP	24.1.2007	Merck & Co	A10BH01	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES
8	Sunitinib	Sutent	Q1 2006	NCE	CP	27.4.2006	Pfizer	L01XE04	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
9	Pemetrexed	Alimta	Q4 2004	NCE	CP	23.6.2004	Eli Lilly & Co Ltd	L01BA04	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
10	Cetuximab	Erbitux	Q1 2004	NBE	CP	24.3.2004	Merck KGaA	L01XC06	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
11	Natalizumab	Tysabri	Q3 2006	NBE	CP	27.4.2006	Elan Pharma International / Biogen Idec	L04AA23	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
12	Erlotinib	Tarceva	Q1 2005	NCE	CP	23.6.2005	Roche	L01XX34	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
13	Bortezomib	Velcade	Q1 2004	NCE	CP	21.1.2004	J & J	L01XX32	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
14	Sorafenib	Nexavar	Q1 2006	NCE	CP	27.4.2006	Bayer	L01XE05	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
15	Raltegravir	Isentress	Q4 2007	NCE	CP	15.11.2007	Merck & Co	J05AX08	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
16	Solifenacin	Vesicare	Q3 2004	NCE	MRP	/	Astellas	G04BD08	GENITO URINARY SYSTEM AND SEX HORMONES	UROLOGICALS
17	Strontium Ranelate	Protelos	Q4 2004	NCE	CP	23.6.2004	Servier	M05BX03	MUSCULO-SKELETAL SYSTEM	DRUGS FOR TREATMENT OF BONE DISEASES
18	Darunavir	Prezista	Q1 2007	NCE	CP	14.12.2006	J & J	J05AE10	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
19	Omalizumab	Xolair	Q3 2004	NBE	CP	27.7.2005	Novartis	R03DX05	RESPIRATORY SYSTEM	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
20	Dasatinib	Sprycel	Q4 2006	NCE	CP	21.9.2006	BMS	L01XE06	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS

21	Varenicline	Champix	Q4 2006	NCE	CP	27.7.2006	Pfizer	N07BA03	NERVOUS SYSTEM	OTHER NERVOUS SYSTEM DRUGS
22	Vildagliptin	Galvus	Q4 2007	NCE	CP	19.7.2007	Novartis	A10BH02	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES
23	Eculizumab	Soliris	Q3 2007	NBE	CP	26.4.2007	Alexion Europe SAS	L04AA25	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
24	Rasagiline	Azilect	Q3 2005	NCE	CP	18.11.2004	Teva	N04BD02	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS
25	Alglucosidase Alfa	Myozyme	Q4 2006	NBE	CP	26.1.2006	Genzyme Europe B.V.	A16AB07	ALIMENTARY TRACT AND METABOLISM	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
26	Entecavir	Baraclude	Q1 2006	NCE	CP	27.4.2006	BMS	J05AF10	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
27	Exenatide	Byetta	Q4 2007	NCE	CP	21.9.2006	Eli Lilly & Co Ltd	A10BX04	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES
28	Eplerenone	Inspra	Q4 2004	NCE	MRP	/	Pfizer	C03DA04	CARDIOVASCULAR SYSTEM	DIURETICS
29	Idursulfase	Elaprase	Q1 2007	NCE	CP	18.10.2006	Shire Human Genetics Therapies	A16AB09	ALIMENTARY TRACT AND METABOLISM	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
30	Everolimus	Certican	Q1 2004	NCE	MRP, later CP	29.5.2009	Novartis	L01XE10	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
31	Aliskiren	Tekturna	Q3 2007	NCE	CP	21.6.2007	Novartis	C09XA02	CARDIOVASCULAR SYSTEM	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
32	Fulvestrant	Faslodex	Q1 2004	NCE	CP	20.11.2003	Astra Zeneca	L02BA03	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ENDOCRINE THERAPY
33	Nilotinib	Tasigna	Q3 2007	NCE	CP	20.9.2007	Novartis	L01XE08	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
34	Posaconazole	Noxafil	Q4 2005	NCE	CP	27.7.2005	Schering-Plough	J02AC04	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIMYCOTICS FOR SYSTEMIC USE
35	Lapatinib	Tykerb	Q1 2007	NCE	CP	13.12.2007	GSK	L01XE07	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
36	Panitumumab	Vectibix	Q1 2008	NBE	CP	24.5.2007	Amgen	L01XC08	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
37	Paliperidone	Invega	Q4 2007	NCE	CP	26.4.2007	Janssen Cilag Ltd	N05AX13	NERVOUS SYSTEM	PSYCHOLEPTICS
38	Azacitidine	Vidaza	Q3 2005	NCE	CP	23.10.2008	Celgene Europe Ltd.	L01BC07	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
39	Ivabradine	Procoralan	Q4 2005	NCE	CP	27.7.2005	Servier	C01EB17	CARDIOVASCULAR SYSTEM	CARDIAC THERAPY
40	Rotigotine	Neupro	Q1 2006	NCE	CP	14.12.2005	Schwarz Pharma	N04BC09	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS
41	Fosamprenavir	Lexiva	Q4 2004	NCE	CP	24.3.2004	GSK	J05AE07	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
42	Abatacept	Orencia	Q4 2007	NBE	CP	22.3.2007	BMS	L04AA24	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
43	Lanthanum	Fosrenol	Q4 2005	NCE	MRP	/	Shire Pharm	V03AE03	VARIOUS	ALL OTHER THERAPEUTIC PRODUCTS
44	Tigecycline	Tygacil	Q4 2006	NCE	CP	23.2.2006	Wyeth	J01AA12	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE
45	Anidulafungin	Eraxis	Q4 2007	NCE	CP	19.7.2007	Pfizer	J02AX06	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIMYCOTICS FOR SYSTEMIC USE

46	Tocilizumab	Actemra	Q4 2008	NBE	CP	20.11.2008	Roche	L04AC07	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
47	Treprostinil	Remodulin	Q1 2006	NCE	MRP	/	United Therapeutics	B01AC21	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
48	Etravirine	Intelence	Q1 2008	NCE	CP	26.6.2008	J&J	J05AG04	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
49	Ciclesonide	Alvesco	Q1 2005	NCE	MRP	/	Nycomed Ltd.	R03BA08	RESPIRATORY SYSTEM	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
50	Fesoterodine	Toviaz	Q4 2008	NCE	CP	22.2.2007	Pfizer	G04BD11	GENITO URINARY SYSTEM AND SEX HORMONES	UROLOGICALS
51	Trabectedin	Yondelis	Q4 2007	NCE	CP	19.7.2007	PharmaMar S.A.	L01CX01	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
52	Temsirolimus	Torisel	Q4 2007	NCE	CP	20.9.2007	Wyeth	L01XE09	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
53	Galsulfase	Naglazyme	Q1 2006	NBE	CP	15.9.2005	BioMarin Europe Ltd.	A16AB08	ALIMENTARY TRACT AND METABOLISM	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
54	Maraviroc	Selzentry	Q4 2007	NCE	CP	19.7.2007	Pfizer	J05AX09	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
55	Sitaxentan	Thelin	Q4 2006	NCE	CP	1.6.2006	Encysive Limited	C02KX03	CARDIOVASCULAR SYSTEM	ANTIHYPERTENSIVES
56	Darifenacin	Emselex	Q1 2005	NCE	CP	29.7.2004	Novartis	G04BD10	GENITO URINARY SYSTEM AND SEX HORMONES	UROLOGICALS
57	Daptomycin	Cubicin	Q1 2006	NBE	CP	17.11.2005	Novartis	J01XX09	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE
58	Ambrisentan	Volibris	Q4 2008	NCE	CP	21.2.2008	GSK	C02KX02	CARDIOVASCULAR SYSTEM	ANTIHYPERTENSIVES
59	Cefditoren Pivoxil	Meiact	Q4 2004	NCE	MRP	/	GSK	J01DD16	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE
60	Clofarabine	Evoltra	Q1 2006	NCE	CP	23.2.2006	Genzyme Europe B.V.	L01BB06	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
61	Prulifloxacin	Unidrox	Q4 2004	NCE	MRP	/	/	J01MA17	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE
62	Lacosamide	Vimpat	Q3 2008	NBE	CP	26.6.2008	UCB Pharma S.A.	N03AX18	NERVOUS SYSTEM	ANTIEPILEPTICS
63	Rivaroxaban	Xarelto	Q4 2008	NBE	CP	24.7.2008	Bayer	B01AX06	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
64	Palonosetron	Aloxi	Q4 2005	NCE	CP	15.12.2004	Helsin Birex Pharmaceuticals Ltd.	A04AA05	ALIMENTARY TRACT AND METABOLISM	ANTIEMETICS AND ANTINAUSEANTS
65	Pegaptanib	Macugen	Q1 2006	NCE	CP	15.9.2005	Pfizer	S01LA03	SENSORY ORGANS	OPHTHALMOLOGICALS
66	Dabigatran Etexilate	Pradaxa	Q4 2008	NCE	CP	24.1.2008	BI	B01AE07	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
67	Bivalirudin	Angiomax	Q4 2004	NCE	CP	23.6.2004	The Medicines Company UK Ltd.	B01AE06	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
68	Tafluprost	Taflotan	Q4 2008	NCE	DcP	/	MSD	S01EE05	SENSORY ORGANS	OPHTHALMOLOGICALS
69	Tipranavir	Aptivus	Q1 2005	NCE	CP	27.7.2005	BI	J05AE09	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE

70	Ibritumomab Tiuxetan	Zevalin	Q1 2004	NBE	CP	25.9.2003	Bayer Schering Pharma AG	V10XX02	VARIOUS	THERAPEUTIC RADIOPHARMACEUTICALS
71	Argatroban	Argatra	Q3 2005	NCE	MRP	/	/	B01AE03	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
72	Sugammadex	Bridion	Q3 2008	NCE	CP	30.5.2008	Schering-Plough	V03AB35	VARIOUS	ALL OTHER THERAPEUTIC PRODUCTS
73	Telbivudine	Sebivo	Q4 2006	NCE	CP	22.2.2007	Novartis	J05AF11	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIVIRALS FOR SYSTEMIC USE
74	Rufinamide	Inovelon	Q4 2007	NCE	CP	16.11.2006	Eisai	N03AF03	NERVOUS SYSTEM	ANTIEPILEPTICS
75	Certolizumab Pegol	Cimzia	Q1 2008	NBE	CP	25.6.2009	UCB Pharma S.A.	L04AB05	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
76	Micafungin	Mycamine	Q3 2008	NCE	CP	21.2.2008	Astellas	J02AX05	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIMYCOTICS FOR SYSTEMIC USE
77	Ziconotide	Prialt	Q3 2006	NCE	CP	18.11.2004	Eisai	N02BG08	NERVOUS SYSTEM	ANALGESICS
78	Ranolazine	Ranexa	Q1 2009	NCE	CP	24.4.2008	A. Menarini Pharma	C01EB18	CARDIOVASCULAR SYSTEM	CARDIAC THERAPY
79	Methylnaltrexone Bromide	Relistor	Q3 2008	NCE	CP	24.4.2008	Wyeth	A06AH01	ALIMENTARY TRACT AND METABOLISM	LAXATIVES
80	Plerixafor	Plerixafor Gzym	Q3 2008	NCE	CP	29.5.2009	Genzyme Europe B.V.	L03AX16	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSTIMULANTS
81	Loteprednol	Lotemax	Q1 2005	NCE	MRP	/	Bausch & Lomb Inc	S01BA14	SENSORY ORGANS	OPHTHALMOLOGICALS
82	Mecasermin	Increlex	Q4 2007	NBE	CP	24.5.2007	Ipsen Pharma Ltd.	H01AC03	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES	PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES
83	Doripenem	Doribax	Q3 2008	NCE	CP	30.5.2008	Janssen-Cilag Ltd.	J01DH04	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE
84	Icatibant	Firazyr	Q3 2008	NCE	CP	24.4.2008	Jerini AG	C01EB19	CARDIOVASCULAR SYSTEM	CARDIAC THERAPY
85	Nepafenac	Nevanac	Q3 2008	NCE	CP	18.10.2007	Alcon Laboratories	S01BC10	SENSORY ORGANS	OPHTHALMOLOGICALS
86	Retapamulin	Altabax	Q4 2007	NCE	CP	22.3.2007	GSK	D06AX13	DERMATOLOGICALS	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGIC
87	Fosaprepitant	Ivemend	Q4 2008	NCE	CP	15.11.2007	Merck & Co	A04AD12	ALIMENTARY TRACT AND METABOLISM	ANTIEMETICS AND ANTINAUSEANTS
88	Nesiritide	Natrecor	Q4 2004	NBE	NP	/	J & J	C01DX19	CARDIOVASCULAR SYSTEM	CARDIAC THERAPY
89	Epoetin Delta	Dynepo	Q1 2007	NBE	CP (before)	in 2002	Shire Pharma.	B03XA01	BLOOD AND BLOOD FORMING ORGANS	ANTIANEMIC PREPARATIONS
90	Docosanol	Erazaban	Q4 2008	NCE	MRP	/	/	D06BB11	DERMATOLOGICALS	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGIC
91	Picibanil	Picibanil Roch	Q4 2005	NCE	N/A	/	Roche	L3A	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Not Available
92	Efalizumab	Raptiva	Q4 2004	NBE	CP	23.6.2004	Serono Europe Limited	L04AA21	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
93	Insulin glulisine	Apidra	Q4 2004	NBE	CP	3.6.2004	Sanofi-Aventis	A10AB06	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES

94	Insulin Detemir	Levemir	Q1 2004	NBE	CP	26.2.2004	NovoNordisk	A10AE05	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES
95	Palifermin	Kepivance	Q4 2005	NBE	CP	27.7.2005	Biovitrum AB	V03AF08	VARIOUS	ALL OTHER THERAPEUTIC PRODUCTS
96	Parathyroid hormone	Preotact	Q4 2006	NBE	CP	23.2.2006	Nycomed Ltd.	H05AA03	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES	CALCIUM HOMEOSTASIS
97	Antithrombin alfa	Atryn	Q4 2008	NBE	CP	20.2.2006	Leo Pharma A/S	B01AB02	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
98	Methoxy Peg-Epoetin Beta	Mircera	Q3 2007	NBE	CP	24.5.2007	Roche	B03XA03	BLOOD AND BLOOD FORMING ORGANS	ANTIANEMIC PREPARATIONS
99	Nelarabine	Arranon	Q3 2007	NCE	CP	21.6.2007	GSK	L01BB07	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
100	Deferasirox	Exjade	Q4 2005	NCE	CP	28.6.2006	Novartis	V03AC03	VARIOUS	ALL OTHER THERAPEUTIC PRODUCTS
101	Lumiracoxib	Prexige	Q4 2005	NCE	MRP	/	Novartis	M01AH06	MUSCULO-SKELETAL SYSTEM	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
102	Fluticasone furoate	Veramyst	Q1 2008	NCE	CP	18.10.2007	GSK	R01AD12	RESPIRATORY SYSTEM	NASAL PREPARATIONS
103	Cinacalcet	Cinacalcet	Q3 2004	NCE	CP	29.7.2004	Amgen Ltd	H05BX01	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES	CALCIUM HOMEOSTASIS
104	Rimonabant	Acomplia	Q4 2006	NCE	CP	27.4.2006	Sanofi-Aventis	A08AX01	ALIMENTARY TRACT AND METABOLISM	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
105	Ustekinumab	Stelara	Q1 2009	NBE	CP	20.11.2008	Janssen-Cilag International	L04AC05	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
106	Romiplostim	Nplate	Q4 2009	NBE	CP	20.11.2008	Amgen Europe B.V.	B02BX04	BLOOD AND BLOOD FORMING ORGANS	ANTIHEMORRHAGICS
107	Agomelatine	Valdoxan	Q4 2009	NCE	CP	20.11.2008	Les Laboratoires Servier	N06AX23	NERVOUS SYSTEM	PSYCHOANALEPTICS
108	Liraglutide	Victoza	Q3 2009	NBE	CP	23.4.2009	NovoNordisk	A10BX07	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES
109	Golimumab	Simponi	Q4 2009	NBE	CP	25.6.2009	Centocor B.V.	L04AB06	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
110	Prasugrel	Efient	Q1 2009	NCE	CP	18.12.2008	Eli Lilly & Co Ltd	B01AC22	BLOOD AND BLOOD FORMING ORGANS	ANTITHROMBOTIC AGENTS
111	Dapoxetine	Priligy	Q4 2009	NCE	DcP	/	J & J	G04BX14	GENITO URINARY SYSTEM AND SEX HORMONES	UROLOGICALS
112	Dronedarone	Multaq	Q4 2009	NCE	CP	24.9.2009	Sanofi-Aventis	C01	CARDIOVASCULAR SYSTEM	CARDIAC THERAPY
113	Indacaterol	Onbrez Breezhaler	Q4 2009	NCE	CP	24.9.2009	Novartis	R03AC18	RESPIRATORY SYSTEM	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
114	Laropiprant	Tredaptive	Q1 2009	NCE	CP	24.4.2008	MSD	C10AD52	CARDIOVASCULAR SYSTEM	LIPID MODIFYING AGENTS
115	Degarelix	Firmagon	Q4 2009	NCE	CP	18.12.2008	Ferring Pharmaceuticals	L02BX02	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ENDOCRINE THERAPY
116	Saxagliptin	Onglyza	Q4 2009	NCE	CP	25.6.2009	Bristol-Myers Squibb/Astra Zeneca EEIG	A10BH03	ALIMENTARY TRACT AND METABOLISM	DRUGS USED IN DIABETES

117	Canakinumab	Ilaris	Q3 2009	NCE	CP	23.7.2009	Novartis	L04AC04	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	IMMUNOSUPPRESSANTS
118	Eslicarbazepine Acetate	Zebinix	Q3 2009	NCE	CP	19.2.2009	Bial - Portela & Ca., S.A.	N03AF04	NERVOUS SYSTEM	ANTIEPILEPTICS
119	Catumaxomab	Removab	Q4 2009	NBE	CP	19.2.2009	Fresenius Biotech GmbH	L01XC09	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
120	Vinflunine	Javlor	Q4 2009	NCE	CP	25.6.2009	Pierre Fabre Médicament	L01CA05	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
121	Tolvaptan	Samsca	Q3 2009	NCE	CP	28.5.2009	Otsuka	C03XA01	CARDIOVASCULAR SYSTEM	DIURETICS
122	Ixabepilone	Ixempra	Q4 2009	NCE	NP (Switzerland only)	REFUSED on 20.11.2008	BMS	L01DC04	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ANTINEOPLASTIC AGENTS
123	Ceftobiprole Medocaril	Zeftera	Q1 2009	NCE	NP (Switzerland only)	REFUSED on 18.02.2010	Janssen-Cilag International	J01DI01	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE
124	Dofetilide	Tikosyn	Q4 2009	NCE	CP (before)	In 1999	Pfizer	C01BD04	CARDIOVASCULAR SYSTEM	CARDIAC THERAPY
125	Ulipristal Acetate	Ellaone	Q3 2009	NCE	CP	19.3.2009	Laboratoire HRA Pharma	G03	GENITO URINARY SYSTEM AND SEX HORMONES	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM

CP = Centralised Procedure, DcP = Decentralised Procedure, MRP = Mutual Recognition Procedure, NBE = New Biological Entity, NCE = New Chemical Entity, NP = National Procedure, N/A = Not applicable, / = Not available

Appendix 6: IMS Retail and Hospital Audit detailed description

Table VIII. IMS Retails Audit details. Source: *IMS Health - Retail Audit Synopsis 2008. Copyright 2010 All rights reserved.*

Retail Audit	Available	Audit first available	Audit Sales level	Tax included in Sales	Level of Printed Unit Price	Tax included in Price	Available on MIDAS	Audit LC	MIDAS LC
Austria	Monthly & Quarterly	1962	Ex-Manufacturer	No	Ex-Manufacturer	No	Yes	Euro	Euro
Belgium	Quarterly & Monthly	1965	ex-manufacturer	No	Public	No	Yes	Euro	Euro
Bulgaria	Quarterly	1993	Public	Yes	Public	Yes	Yes	Bulgarian Lev	Bulgarian Lev
Croatia	Quarterly	1997	Trade	No	Trade	No	Yes	Croatian Kuna (Kn)	Croatian Kuna (Kn)
Czech Republic	Monthly & Quarterly	1993	Ex-Manufacturer	No	Public	Yes – 9%	Yes	Czech Crown (CZK)	Czech Crown (CZK)
Denmark	Monthly & Quarterly	1977	Trade	No	Trade	No	Yes	Danish Krone	Danish Krone
Estonia	Monthly & Quarterly	1998	Trade	No	Trade	No	Yes	Estonian Kroon 100s	Estonian Kroon 1000s
Finland	Monthly & Quarterly	1966	Trade	No	Trade	No	Yes	Euro	Euro

Retail Audit	Available	Audit first available	Audit Sales level	Tax included in Sales	Level of Printed Unit Price	Tax included in Price	Available on MIDAS	Audit LC	MIDAS LC
France	Monthly & Quarterly	1959	Ex-Manufacturer	No	Public	Yes	Yes	Euro	Euro
Germany	Monthly & Quarterly	1959	Ex-Manufacturer	No	Ex-Manufacturer	No	Yes	Euro	Euro
Greece	Monthly & Quarterly	1993	Trade	No	Trade	No	Yes	Euro	Euro
Hungary	Monthly & Quarterly	1991	Ex-manufacturer	No	Public	No	Yes	Hungarian Forint	Hungarian Forint
Ireland	Monthly & Quarterly	1967	Trade	No	Trade	No	Yes	Euro	Euro
Italy	Monthly & Quarterly	1960	Ex-Manufacturer	No	Public	Yes	Yes	Euro	Euro
Latvia	Monthly & Quarterly	1996	Trade	No	Trade	No	Yes	Lati 1000s	Lati 1000s
Lithuania	Monthly & Quarterly	1996	Trade	No	Trade	No	Yes	Litai 100s	Litai 100s
Luxembourg	Monthly & Quarterly	1988	Ex-Manufacturer	No	Public	Yes	Yes	Euro	Euro
Netherlands	Monthly & Quarterly	1967	Ex-Manufacturer	-	Ex-Manufacturer	-	Yes	Euro	Euro
Norway	Monthly & Quarterly	200	Trade	No	Trade	No	Yes	Norwegian Krone 1000s	Norwegian Krone 1000s
Poland	Monthly & Quarterly	1991	Ex-Manufacturer	No	Public	Yes	Yes	Polish Zloty	Polish Zloty
Portugal	Monthly & Quarterly	1973	Ex-Manufacturer	Yes	Public	Yes – 5%	Yes	Euro 100s	Euro 1000s
Romania	Quarterly	1995	Trade	No	Trade	No	Yes	Romanian Lei	Romanian Lei
Slovakia	Monthly & Quarterly	1993	Ex-Manufacturer	No	Public	Yes – 19%	Yes	Slovak Crown (SKK)	Slovak Crown (SKK)
Slovenia	Quarterly	1992	Trade	No	Trade	No	Yes	Euros	Euros
Spain	Monthly & Quarterly	1962	Ex-manufacturer	No	Public	Yes : 4%	Yes	Euro	Euro
Sweden	Quarterly & Monthly	1965 (Quarterly) 1997 (Monthly)	Trade	No	Trade	No	Yes	Swedish Crowns (SEK)	Swedish Crowns (SEK)
Switzerland	Monthly & Quarterly	1961 (APO)	Ex-Manufacturer	No	Public	No	Yes	Swiss Francs	Swiss Francs
United Kingdom	Monthly & Quarterly	1960	Trade	No	Trade	No	Yes	Pound Sterling	Pound Sterling

Table IX. IMS Hospital Audit details. Source: ***IMS Health - Hospital Audit Synopsis 2008. Copyright 2010 All rights reserved.***

Hospital Audit	Type of audit	Available	Audit first available	Audit Sales Level	Tax included in Sales	Level of Printed Unit Price	Tax included in Price	Available on MIDAS	Audit LC	MIDAS LC
Austria	Hospital Consumption	Quarterly	1967	Ex-Manufacturer	No	Ex-Manufacturer	No	Yes	Euro	Euro
Belgium	Hospital Consumption	Monthly & Quarterly	1983	Ex-Manufacturer	No	Ex-Manufacturer	Yes - 6%	Yes	Euro	Euro
Bulgaria	Wholesaler Sales	Monthly and Quarterly	1995	Trade	Yes	Public	Yes	Yes	Bulgarian Lev	Bulgarian Lev
Croatia	Wholesaler Sales (HRHI)	Monthly & Quarterly	2008	Trade	No	Trade	No	Yes	Croatian Kuna (Kn)	Croatian Kuna (Kn)
Czech Republic	Wholesaler Sales (CRHI)	Monthly & Quarterly	1993	Ex-Manufacturer	Yes	Public	Yes – 9%	Yes	Czech Crown	Czech Crown
Denmark	Wholesaler & Local Pharmacy Sales	Monthly & Quarterly	1977	Trade	No	Trade	No	Yes	Danish Krone	Danish Krone
Estonia	Wholesaler Sales	Monthly & Quarterly	2003	Trade	-	Trade	-	Yes	Estonian Kroon	Estonian Kroon
Finland	Wholesaler Sales	Monthly & Quarterly	1985	Trade	No	Trade	No	Yes	Euro	Euro
France	Hospital Consumption	Monthly & Quarterly	1984	Ex-Manufacturer	No (but when public price level used, 5.5% for non reimbursed products, 2.1% for reimbursed)	Ex-Manufacturer	No (but when public price level used, 5.5% for non reimbursed products, 2.1% for reimbursed)	Yes	Euros	Euros
Germany	Hospital Consumption	Monthly & Quarterly	1969	Ex-Manufacturer	No	Ex-Manufacturer excluding VAT	No	Yes	Euro	Euro
Greece	Wholesaler Sales	Monthly & Quarterly	2009	Ex-Manufacturer	No	Trade	No	No	Euro	n/a
Hungary	Wholesaler Sales	Monthly & Quarterly	1998	Ex-Manufacturer	No	Public	No	Yes	Hungarian Forint	Hungarian Forint
Ireland	Wholesaler sales	Monthly	1998	Trade	No	No	Trade	Yes	Euro	Euro
Italy	Hospital Consumption	Monthly & Quarterly	1970	Ex-Manufacturer	No	Public	No	Yes	Euro	Euro
Latvia	Wholesaler Sales	Monthly & Quarterly	2003	Trade	No	Trade	No	Yes	Lat	Lat

Hospital Audit	Type of audit	Available	Audit first available	Audit Sales Level	Tax included in Sales	Level of Printed Unit Price	Tax included in Price	Available on MIDAS	Audit LC	MIDAS LC
Lithuania	Wholesaler Sales	Monthly & Quarterly	2003	Trade	No	Trade	No	Yes	LTL	LTL
Luxembourg										
Netherlands	Wholesaler Sales	Monthly & Quarterly	1977	Ex-manufacturer	No	Ex-manufacturer	No	Yes	Euro	Euro
Norway	Wholesaler Sales	Monthly & Quarterly	1994	Trade	23% only applied to public level analyses.	Trade	23% only applied to public level analyses.	Yes	Norwegian Kroner	Norwegian Kroner
Poland	Wholesaler Sales	Monthly & Quarterly	1991	Ex-manufacturer	No	Public	Yes	Yes	Polish Zloty	Polish Zloty
Portugal	Hospital Consumption	Quarterly	1999	Trade	No	Trade	Yes	No	Euro	N/A
Romania	Wholesaler Sales	Monthly	2005	Trade	No	Trade	No	Yes	Romanian Lei	Romanian Lei
Slovakia	Hospital Consumption	Monthly & Quarterly	1993	Ex-manufacturer	10% applied only to public level analyses	Public	Yes – 19%	No	Slovak Crown	Slovak Crown
	Wholesaler Sales	Monthly & Quarterly	2000	Ex-manufacturer	10% applied only to public level analyses	Public	Yes – 19%	Yes	Slovak Crown	Slovak Crown
Slovenia	Wholesaler sales and Consumption data	Monthly & Quarterly	1992	Trade	No	Trade	No	Yes	Euro	Euro
Spain	Hospital Consumption	Monthly & Quarterly	1999	Ex-Manufacturer	No; incl at Public level	Public, incl VAT; excl Vat at Trade & MNF level	4%	Yes	Euro	Euro
Sweden	Wholesaler Sales	Monthly & Quarterly	1965	Trade	No	Trade	No	Yes	Swedish Kroner	Swedish Kroner
Switzerland	Wholesaler Sales	Monthly & Quarterly	2005	Ex-Manufacturer	No	Public	No	Yes	Swiss Francs	Swiss Francs
United Kingdom	Hospital Consumption	Monthly & Quarterly	1991	Trade	No	Trade	No	Yes	GB Pounds	GB Pounds