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Executive Agency for Health and Consumers-EAHC-European Commission

EU Pharmaceutical expenditure forecast

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List of Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AHTAPoL	Polish Health Technology Assessment Agency
AMNOG	New health bill in Germany approved at the end of 2010
ASMR	Improvement of Medical Benefit of a drug (France)
ATC	Anatomic Therapeutic Chemical
AWMSG	All Wales Medicines Strategy Group
BH	Biosimilars Hospital
BMG	Ministry of Health in Germany
BR	Biosimilars Retail
CAGR	Compound Annual Growth Rate
CEPS	French Economic Committee on Healthcare Products
COPD	Chronic Obstructive Pulmonary Disease
CT	Transparency Committee (scientific committee of the French National Authority for Health)
DDD	Defined Daily Dose
DG	Directorate General
DG ECFIN	Directorate General for Economic and Financial Affairs (EU)
DGAE	Directorate-General of Economic Activities (Portugal)
DH	Department of Health (UK)
DKG	German Hospital Association
DRG	Diagnosis-Related Group
EAHC	Executive Agency for Health and Consumers (EU)
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic Medicines Association
EMA	European Medicines Agency

EOF	National Medicines Agency in Greece
EOPYY	National Organization for Health Care Provision (Greece)
EPC	Economic Policy Commitee (EU)
EPY	Health Procurement Committee (Greece)
EU	European Union
FDA	Food and Drug Administration (US)
GABI	Generics and Biosimilars Initiative
G-BA	Federal Joint Committee (Germany)
GDP	Gross Domestic Product
GKV-Spitzenverband	Federal Association of Statutory Health Insurance Funds (Germany)
GYEMSZI-OGYI	National Institute of Pharmacy (Hungary)
HAS	French Health Authority
HCV	Hepatitis C Virus
HFA-DB	European Health for All Database
HIV	Human Immunodeficiency Virus
HOM	Hospital-Only Medicine
HTA	Health Technology Assessment
ICER	incremental cost- effectiveness ratio
IKA-ETAM	Social Insurance Fund (Greece)
INFARMED	National Authority of Medicines and Health Products of Portugal
INN	International Nonproprietary Name
IP	Intellectual Property
IQWIG	Institute for quality and efficiency in Health Care (Germany)
ISPOR	International Society For Pharmacoeconomics and Outcomes
KBV	National Association of Statutory Health Insurance Physicians (Germany)
KZBV	Federal Association of Fund Dentists (Germany)
LMWH	Low molecular weight heparin
MA	Marketing Application

MGYK	Hungarian Chamber of Pharmacists
NCE	New Chemical Entity
NEFMI	Ministry of Health in Hungary
NHS	National Health Service
NHF	National Health Fund (Poland)
NICE	National Institute for Clinical and Health Excellence (UK)
OAEE	Fund for Merchants, Manufacturers and Related Occupations (Greece)
OECD	Organisation for Economic Co-operation and Development
OEP	National Health Insurance Fund Administration (Hungary)
OGA	Social Insurance Fund for Farmers (Greece)
OPAD	Fund for Civil Servants (Greece)
OTC	Over The Counter
PCT	Primary Care Trust
PHIS	Pharmaceutical Health Information System
PM	Ministry of Finance in Hungary
POM	Prescription-Only Medicine
PPP	Pharmacy Purchasing Price
PPRI	Pharmaceutical Pricing and Reimbursement Information
PRP	Pharmacy Retail Price
PPRS	Pharmaceutical Price Regulation Scheme
QALY	Quality Adjusted Life Years
RMP	Risk Management Plan
RPS	Reference Price System
Rx	Prescription medications
SDR	Standard Death Ratio
SHI	Social Health Insurance (Germany)
SIP	Social Insurance Price (Greece)
SMC	Scottish Medicines Consortium

SMH	Small Molecules Hospital
SMR	Medical Benefit of a drug (France)

(Pharmaceutical policies for France)

SMR (Model)	Small Molecules Retail
TÉB	Technology Appraisal Committee (Hungary)
TFR	Responsible payment tariff (France)
UK	United Kingdom
US	United States of America
WHO	World Health Organisation

Executive summary

Background

The evolution of pharmaceutical expenditures is mainly driven by the entrance of new branded products and products going off-patent. The large number of key small molecules brands that will be reaching generic status, will mainly impact the European pharmaceutical expenditures in the years to come. In addition to this, ageing populations, the growing prevalence of chronic disease, the greater use of expensive treatments and also the increasingly tough regulatory environment and cost-containment strategies introduced by healthcare payers in response to the global economic downturn, will impact pharmaceutical expenditures.

With constant incentives for healthcare payers to contain their pharmaceutical budgets it is crucial for the Member States of the European Union and for the European regulatory bodies to anticipate the expected baseline evolution of Member States' pharmaceutical budgets. Moreover, such impact will be important to understand for policy decision makers.

Objective and scope

The objective of the project was to build a model to assess the overall net effect of the entrance of new patented medicinal products versus medicinal products going off-patent, with a forecast horizon until 2016, on seven selected European Union Member States' pharmaceutical budgets: France, the United Kingdom, Germany, Poland, Portugal, Greece and Hungary. This model should take into account the ageing population, as well as current and future country-specific pricing, reimbursement and market access policies.

Methodology

The first step of the project was to gather the country-specific variables for each country from different databases, in order to identify the main inputs that would feed the model. Then, several databases were cross checked to identify, according to defined criteria, the range of products that would go off-patent and those that would enter the market between 2012 and 2016. Products that went off-patent and those that entered the market in 2010 and 2011 were also considered, regarding their potential impact on the budget of the forecasted period.The budget impact of generic entries and the impact of new approved innovative pharmaceutical products were separately analyzed and presented according to three perspectives (healthcare public payer, society and manufacturer), several types of distribution chain (retail, hospital, combined retail and hospital) and several outcomes (savings due to products going off-patent, additional costs due to new entrants products and net budget impact). The healthcare public payer perspective was selected as the base case.

This project was conducted under the supervision and validation at each stage, by a board of 6 independent experts. A model was developed for generics and biosimilars for each country. This model estimated a separate and combined effect of the direct and indirect impact on savings from the genericization of the market for each year in the forecasted period. A model was also developed for new entrants, which estimated the value of sales and the progression of market share in a competitive environment and taking into account the risk of failure regarding the development of the drug. For this project, new entrants were looked at individually to assess their clinical potential and translate into commercial potential. Probabilistic and deterministic sensitivity analyses were carried out regarding intrinsic uncertainty surrounding the estimations.

Moreover, several scenarios were built to analyze what the impact of various changes in the national pharmaceutical policies on the pharmaceutical budget would be.

The overall model was also supplied as a stand alone deliverable to allow to compute and assess various scenarios as per needed to support policy decision makers.

Results

In light of the pharmaceutical policies analysis for each country, far-reaching changes were seen in the drug market access environment in most of the Members States under the study. Pricing and reimbursement regulations have shown substantial strengthening trends. Moreover, it was found that there is a wide variability between countries concerning generics entry policy such as time to market entry (from 0 day for the United Kingdom and Germany, to 270 days for Greece), penetration rate (from 25% for Greece and Portugal, to 100% for Hungary) and price reduction versus the branded product (from 45% for Poland, to 75% for the United Kingdom). Even if Europe appears as a leader for the biosimilar market, accounting for 80% of global spending on these molecules, little information was available about biosimilar pricing and reimbursement policies.

During the period 2012-2016, we identified 202 generics, 10 major biosimilars and 254 new entrants. During the period 2010 and 2011, we identified 71 products that went off-patent and 66 new entrants.

There was a large disparity observed in the total pharmaceutical sales in 2011 between countries as shown in Table 1.

Table 1. Total pharmaceutical sales per capita in 2011 per country from the society perspective

Country	Total pharmaceutical sales per capita (euros)
United Kingdom	**339**
Germany	**485**
France	**608**
Poland	**138**
Greece	**446**
Portugal	**377**
Hungary	**203**

Budget impact analysis has shown that, during the period of interest, all countries will experience drug budget reduction with the exception of Poland, which will experience increases as reported in theTable 2. Savings appear to be among the highest for the United Kingdom, followed by France and far behind, at the same level, by Greece and Germany.

Table 2. Net pharmaceutical budget impact during 2012-2016 per country from the healthcare public payer perspective (million euros)

Country	Net pharmaceutical budget impact during 2012-2016 (million euros)
United Kingdom	-9,367
Germany	-831
France	-5,589
Poland	41
Greece	-808
Portugal	-243
Hungary	- 84

Savings will mainly impact the cardiovascular and central nervous system areas, followed by the respiratory area and biosimilar entry. The leading source for additional costs will be the oncology area, followed far behind by the immunology and inflammation area.

Deterministic sensitivity analysis, as well as analysis of the scenarios related to pharmaceutical policies' changes, exemplify the importance of the time to market of new branded products as a critical factor for budget impact, as well as the high sensitivity of the savings to the generic price, and to the generic penetration rate. Moreover, it appears that the impact of biosimilar savings is critically affected by the proportion of hospital distribution.

Discussion

Except in Poland where the market is in development, the drug market is likely to decrease. This decrease is driven by several factors such as, on the one hand, the genericization, which, if it tends to slow down around the end of 2016, will be progressively replaced by the arrival of the biosimilars and, on the other hand, the increase in pressure on pharmaceuticals to evidence additional clinical or economical benefit to achieve market access.

The Polish and Hungarian markets are still far from mature and will certainly, in the future, increase their investment to secure patient access to innovative products. In the five other countries, the market is quite mature, and with a thinner margin of progression. Moreover, Portugal and Greece are today widely impacted by the economic crisis, and that will be a brake to a potential progression of the market.

During the study period, unsurprisingly, the therapeutic areas that will be the drivers of the health expenditures are oncology, and immunology and inflammation. These disease areas are the ones where new biologic entities are expected to enter the market with substantial clinical benefits and high unmet needs. Other important areas substantially impacting the budget are cardiovascular, central nervous system and respiratory areas, with a negative overall net budget impact, as more savings will occur in relation to generic entry than additional cost related to new brands.

Conclusion

The model developed in this study has been used to generate impact of changes in pharmaceutical policies. The most important leverages that were identified are driven by generic and biosmilar prices and distribution. Reducing, even slightly, the prices of generics will have a major impact. The reduction of generic prices, the distribution of biosimilars through hospital chain and increased share of generics are among the best options to boost savings across Member States of the European Union.

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Background information

One of the main drivers of pharmaceutical expenditure is the entrance of new branded products and technologies onto the market, the cost of which can be extremely high for healthcare payers. On the other hand, when products go off-patent, substantial savings can be achieved by healthcare payers.

Since 2011 and over a five year period to come (2012 to 2016), a large number of key small molecules brands will be reaching generic status in Europe.

A number of other factors have and will continue to impact pharmaceutical expenditure such as ageing populations and the growing prevalence of chronic disease, but also the greater use of expensive treatments.

In addition to this, the increasingly tough regulatory environment together with a number of cost-containment strategies introduced by healthcare payers in response to the global economic downturn, will impact pharmaceutical expenditure.

According to IMS Health forecasts[1], the annual global spending on medicines will reach nearly €933.7 billion by 2016 driven by pharmaemerging markets, biologics and generics with global brand spending expected to increase from €463.7 billion in 2011 to €478.5-501.8 billion by 2016 and a global generic spending expected to increase from €188.3 billion in 2011 to €311.2-334.6 billion by 2016[2]. In Europe, spending on medicines is expected to grow between -1% to 2% through 2016 (estimated for the five major European Union markets -France, Germany, United Kingdom, Spain and Italy)[1].
According to Datamonitor forecasts[3], a slowdown is expected by 2016, with forecast sales growth at a CAGR (compound annual growth rate) of 1.9% in the five major European Union markets.

1.1 Drugs going off-patent

In the next decade, the sales potential for generic products is very high worldwide. Blockbuster drugs which have historically been the key growth drivers for the pharmaceutical industry are facing patent expiry, resulting in generic competition within Europe between 2011 and 2016. The patent cliff reaches its peak in 2011-2012[4] and will decrease from 2013[5].

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[1] IMS Health-The global Use of Medicines: Outlook through 2016-July 2012.

[2] Converter US dollars in euros=http://www.oanda.com/currency/average

1US dollar in euros	Average
2012	0.778045

[3] Datamonitor-Branded prescription pharmaceutical sales outlook to 2016-HC00229-001/Published 02-2012

[4] EGA- 2011 Market Review (Part 2)-The European Generic-Medicines Markets - European Panorama-May 2011.

[5] IMS Health-Press information-Le marché pharmaceutique en France et dans le monde : quel bilan dresser de 2011 et quelles perspectives envisager ? (The pharmaceutical market in France and worldwide: what is the outcome of 2011 and what prospects for the future?)-Results of the study Intelligence.360-29 march 2012.

The European Generic Medicines Association (EGA) estimated that generic medicines have reached €30 billion in savings per year[6]. IMS Health projected that, with the expansion of the European Union to 27 member states, that this value could be doubled[7].

Moreover, in the medium-long term, market for biosimilars also has a very high potential for growth, producing actual savings of €1.4 billion[8]. The European market, regarding its regulatory approval pathway for biosimilar drugs, is seen to take the lead in terms of market penetration of biosimilars.

The approval of a new generic product entering the market and its impact on the drug budget of a Member State will be influenced by several factors which are specific to each Member State such as current pharmaceutical policies in force, level of industry competition, physician practices and the patient's acceptability of generics. Each of these factors will influence the relationship between generic and branded medicines within the same therapeutic classes.

The introduction of a generic product can have a direct effect on an entire therapeutic class when stipulated by regulation and/or an indirect effect when driven by competition and tendering. The competitive environment is a crucial factor behind the expected pressure on prices, with rapid price erosions in very competitive markets. In this competitive environment, industry life cycle management strategies such as the development of new formulations or new modes of administration represent serious barriers to competition[9].

Moreover, an update of previous health technology assessments is often triggered by the introduction of a generic product in a branded therapeutic class, with health authorities often recommending the newly genericized product as first-line therapy, thus displacing the whole market that has to adapt its pricing policies to these new recommendations.

1.2 New drug entries

From an industry development viewpoint, it is crucial that medicinal products go off-patent because it provides incentives for pharmaceutical companies to invest resources towards innovation rather than solely relying on the monopoly power provided by branded products.

A major trend in the Research and Development focus is the shift from small molecule drugs towards developing high value biologics, for niche indications with high unmeet needs (Figure 1).[10]

[6] EGA- 2011 Market Review (Part 2)-The European Generic-Medicines Markets - European Panorama-May 2011.

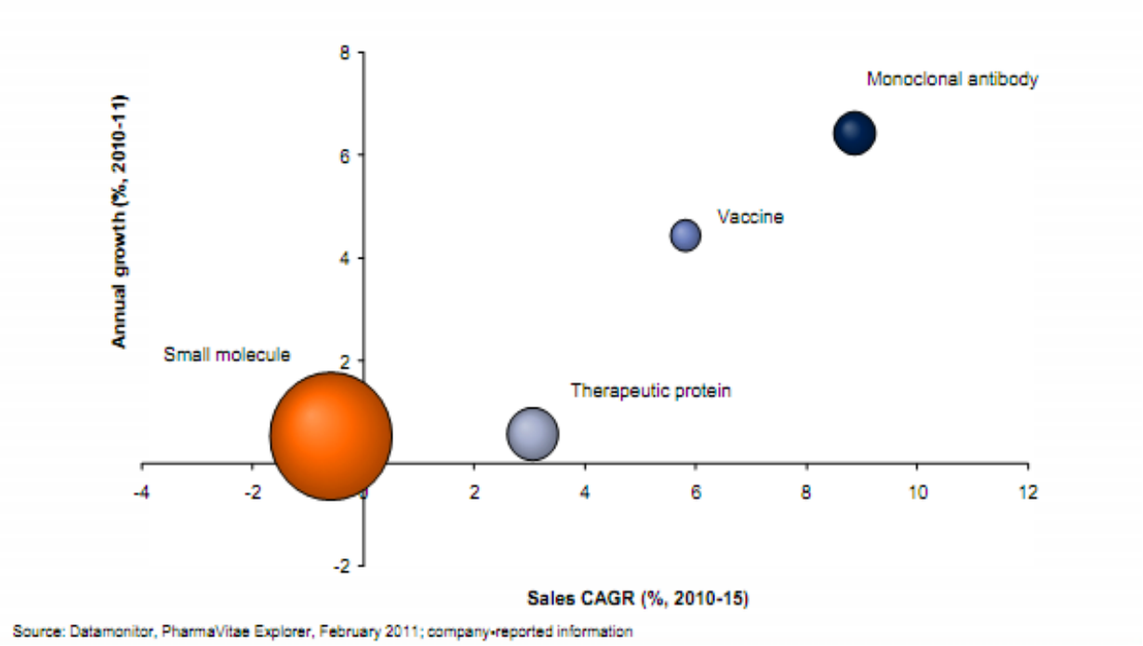
[7] IMS Health-Alan Sheppard. Generic Medicines: essential contributors to the long-term health of society - sector sustainability challenges in Europe (2010).

[8] EGA- 2011 Market Review (Part 2)-The European Generic-Medicines Markets - European Panorama-May 2011.

[9] Finding new formulas for pharma success. Nat Rev Drug Discov, n°6 (June 2007): 423.

[10] Datamonitor-Pharmaceutical key trends 2011-Pharmaceutical industry Infrastructure Overview-HC00062-008/Published 03/2011.

Figure 1. Forecast prescription pharmaceutical sales growth according to molecule type (%) 2010-15: focus on high value biologic therapies[11]



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CAGR=Compound Annual Growth Rate

According to Datamonitor forecasts, it is expected that newly launched and core drugs (not facing patent expiry between 2011 and 2016) will offset the net sales loss from genericized products during the 2011-2016 period, taking into account the country specific environment [12]. Indeed, the impact from the arrival of branded products on the Member State's pharmaceutical expenditure is also dependent upon many country-specific parameters such as:

- National epidemiology
- An availability of alternatives on the national market and expected additional benefits provided by the new entrant
- Health Technology Assessment requirements and methodologies regarding the added value of a new drug
- Pricing policies (supply side practices and demand side practices)

Although experts at Datamonitor consider this macro-environment when they produce their forecasts, some of the assumptions are explicitly stated while some others are implicit.

[11] Datamonitor-Pharmaceutical Key Trends 2011 – Pharmaceutical Industry Infrastructure Overview-HC00062-008/Published 03-2011

[12] Datamonitor-Branded prescription pharmaceutical sales outlook to 2016-HC00229-001/Published 02-2012

Therapeutic classes expected to be the principal growth drivers by 2016 are oncology, endocrine, infectious diseases, and immunology/inflammation. Those expected to decrease are mainly cardiovascular and central nervous system areas due to the patent cliff and the saturation of these markets with me-too drugs, even if these areas are expected to remain among the dominant therapy areas.

According to IMS health forecasts[13], therapeutic classes expected to have the highest levels of spending on medicines in 2016 include oncology, diabetes and asthma/chronic obstructive pulmonary disease (COPD).

1.3 Ageing population

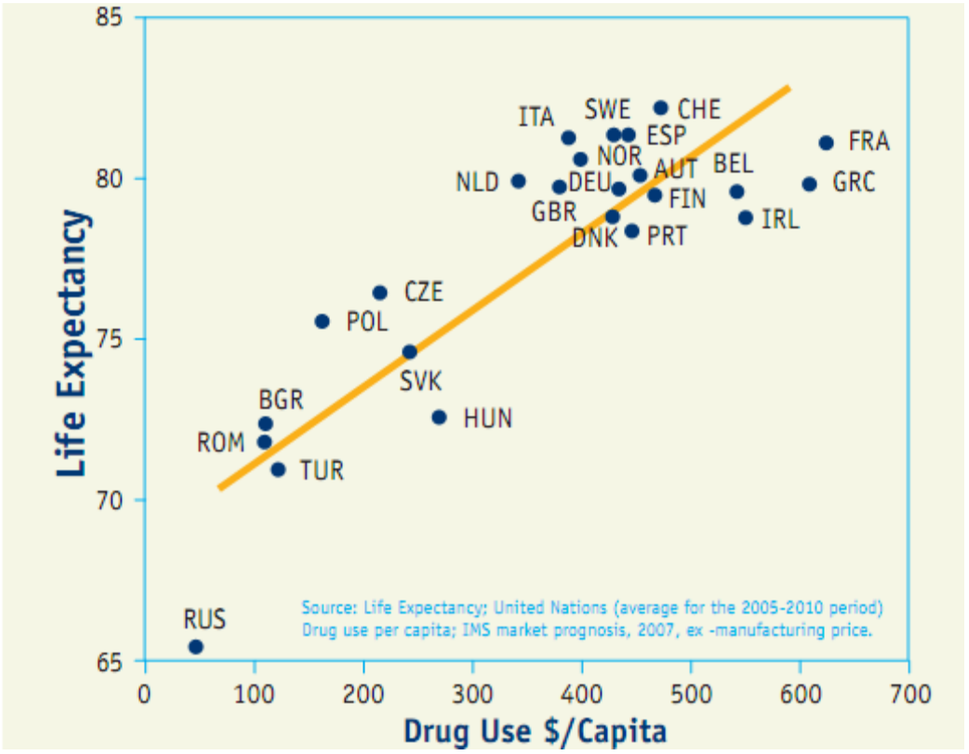
Improvements to the standards of living and healthcare are resulting in increased life expectancies, inevitably increasing the ageing population. According to Eurostat's population projections[14] covering the period from 2011 to 2060, ageing is likely to affect all the Member States of the European Union. Ageing of the population for the period 2011 to 2012 is thought to be well anticipated for the Member States through demographic forecasts[14]. The increasingly ageing population and the changes in lifestyle habits are leading towards a growing prevalence of chronic diseases. As such, there is an increasing demand for healthcare services that make greater use of new medical technologies and biologic drugs, driving the growth of pharmaceutical expenditure in European markets[15] (Figure 2).

[13] IMS Health-The global Use of Medicines: Outlook through 2016-July 2012.

[14] http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Population_structure_and_ageing

[15] Datamonitor-Pharmaceutical key trends 2011 Overview-HC00062-002/Published 05/2011.

Figure 2. Link between drug use and life expectancy in an ageing Europe (2005-2010) [16]



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1.4 Cost-containment and regulatory pressures

Rising healthcare costs as well as the global economic downturn has led healthcare payers to opt for austerity measures such as a reduction of healthcare budgets, price and reimbursement cuts, growing price negotiations, greater use of pharmacoeconomics, together with the enhancement of generic uptake.

Moreover, recent regulatory changes emphasize the willingness for governments to reinforce the assessment of the benefit/risk ratio of drugs throughout the product's life cycle. Firstly, over the last few years there is a greater focus on pharmacovigilance with more structured procedures based on specific studies dedicated to estimate the magnitude of a risk or a relative risk (e.g. Establishment of Risk Management Plans (RMPs) in Europe). Then, the European Directive 2010/84/EU of 15 December 2010 (*amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use*) and the European Regulation No 1235/2010 of 15 December 2010 (*amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products*) provide the legal basis to the European

[16] IMS Health-Alan Sheppard. Generic Medicines: essential contributors to the long-term health of society - sector sustainability challenges in Europe (2010).

Commission and the competent authorities to request post-authorization studies on effectiveness, at the time of granting the marketing authorization or later, and conditioning the marketing authorization. As such, post-marketing safety and effectiveness studies will become greater requirements, which could impact the marketing authorization and reimbursement of drugs.

2. Objectives of the project

With constant incentives for healthcare payers to contain their pharmaceutical budgets, particularly in the context of the current global economic downturn, it is crucial for the Member States and for European regulatory bodies to understand the key drivers of pharmaceutical expenditure. Moreover, a better understanding of the expected baseline evolution of Member State pharmaceutical budgets will improve any pre-assessment of likely patient health effects at play from possible fiscal reforms presented in terms of overall amounts.

The objective of the project is to assess the overall net effect of the two contradictory trends – the entrance of new patented medicinal products versus medicinal products going off-patent on selected Member States' pharmaceutical budgets, accounting for the ageing population, with a forecast horizon until 2016.

Moreover, in order to correctly assess this budget impact, an insight into country-specific variables will be provided in terms of generic drug policies, pricing and reimbursement policies and market rules to understand the specific regulatory and economic mechanisms in place in each Member State.

This project is part of a complex set of objectives currently ongoing as part of the European Commission's activities. At the European level, numerous initiatives related to the pharmaceutical sector have been undertaken, including recommendations and directives, among others on the transparency of pricing and reimbursement procedures[17], the safety and efficacy of medicines[18], or increasing the assessment of cost-effectiveness of pharmaceutical spending[19]. The "Joint Report on Health Systems"[20] prepared by the European Commission (Directorate General for Economic and Financial Affairs -DG ECFIN) and the Economic Policy Committee (EPC) (European Commission 2010) has stressed the need to keep public budgets under control through targeted policies promoting the rational use of drugs. This has also been pointed to extensively by the High Level Pharmaceutical Forum[21], the Pharmaceutical Sector Inquiry[22] by DG Competition (European Commission 2009), the report on pricing and reimbursement systems in Europe[23] funded by DG Entreprise and Industry of the European commission (Jaime Espín, 2007) and the Pharmaceutical Pricing and Reimbursement Information (PPRI) initiative[24] partly funded by DG for Health and Consumers.

Indeed, Member State policy makers have to devise pharmaceutical policies that overall achieve cost effective spending for healthcare payers, while at the same time setting industrial policies directed both at the innovation, and the generic and

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[17] Directive 89/105/EEC relating to the transparency of measures regulating the pricing and reimbursement of medicinal products for human use.

[18] E.g. the European Medicines Agency (EMA) being responsible for the evaluation and supervision of medicines for human and veterinary use: http://www.ema.europa.eu/ema/

[19] E.g. EUnetHTA, increasing the collaboration of national health-technology assessment agencies at European level: http://www.eunethta.eu

[20] http://ec.europa.eu/economy_finance/publications/occasional_paper/2010/pdf/ocp74_en.pdf

[21] http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf

[22] http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf

[23] http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/study_pricing_2007/andalusian_school_public_health_report_pricing_2007_en.pdf

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

biosimilar markets[25]. It is important that generics and biosimilars enter the market to push the research based pharmaceutical industry to deliver new products with intellectual propriety protection. It is also important that the research based industry gets the right reward to be stimulated to invest in risky developments. Besides, the cost-effectiveness of pharmaceutical markets will only be achieved if the pharmaceutical industry evolves into a truly competitive environment, barriers to which have been identified in the recent studies by the European Commission[26]. It is also the healthcare authority's role to ensure that overall expected public health gains of medicinal products are achieved through the implementation of the best manufacturing practice and pharmacovigilance[27]. The present analysis was conducted in support of the above policy goals, to be achieved at Member State level.

[25] http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/monitoring/index_en.htm

[26] http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/

[27] http://ec.europa.eu/health/human-use/index_en.htm

3. Scope of the project

3.1 Countries selection

The selection of the countries was based on several parameters impacting the pharmaceutical budgets such as:

- The market size: large (eg. Germany) to small (eg. Hungary).
- The date of entry in the European Union. Indeed, for new Member States such as Poland or Hungary, the patent cliff will not have the same impact as for the "old" ones due to the application of different rules on patents and data protection on already marketed product at the time of entry in the European Union.
- The Bismarck (eg. Germany) versus Beveridge system (eg. United Kingdom) (the latter we expect to be more engaged in central procurement/tendering, the former in national/international price referencing).
- Expected heterogeneity based on other indicators such as gross domestic product, healthcare expenditures, available health services and socio-demographic indicators.

In order to account for heterogeneity of the various Member States described above, seven Member States were selected for this project: France, the United Kingdom (UK), Germany, Poland, Portugal, Greece and Hungary, to have a relevant and well-balanced representation of small and large, Eastern and Western countries across the European Union. The economic and health statuses of these Member States are illustrated in Table 3, Table 4 and Table 5. They evidence the differences between those countries in term of welfare, health care investment, pharmaceutical distribution chain, available health services and the health status of the population. The Growth Domestic Product (GDP) in 2011 varies across the countries from €156 billion in Hungary (GDP per capita of €12424) to €2316 billion in Germany (GDP per capita of €24740). Public healthcare expenditures in 2010 account for 60% to 83 % of the total expenditure on health in Greece and the United Kingdom respectively. Pharmaceutical expenditure in terms of the percentage of total health expenditure is higher in Hungary, Poland, Greece and Portugal (between 21% and 33%) compared to the United Kingdom, Germany and France (between 12% and 16%). Life expectancy at birth in 2010 is quite similar for the United Kingdom, Germany, France, Portugal and Greece (between 76.5 years (male) and 82.4 years (female) to 78.3 years (male) and 84.6 years (female)) but a little bit lower for Poland (71.7 years (male) and 80.1 years (female) and Hungary (70.4 years (male) and 78.4 years (female)). The highest number of hospital beds is seen in Germany (8.3 per 1000 inhabitants in 2010) and the lowest number of hospital beds is seen in the United Kingdom (3.0 per 1000 inhabitants in 2010). France and Greece have the highest density of pharmacists (about 117 (in 2010) and 88 pharmacists (in 2006) per 100 0000 inhabitants respectively).

Regarding distribution margins, wholesale and pharmacy margins are regulated with the exception of the United Kingdom. The average wholesale margin applied to medicines ranges from 4% for Germany and Greece (total market) to 12.5% for United Kingdom (reimbursable market). The average pharmacy margins applied to medicines is about 20%, but was only available for

Germany, Hungary and Portugal[28]. In most countries the margin is not proportional and based on formulas that are not the same for different medicine price ranges.

There is much heterogeneity between these Member States in their levels of pharmaceutical expenditures, generic market penetration rates and public policy approaches towards the price regulation of branded and off-patent pharmaceutical products (Refer to Section 5.1 and Appendix 0). Heterogeneity provides an opportunity to assess how these baseline differences affect the budget impact predictions. It will permit us to extend the forecasting results to the Member States not included in this analysis, and those sharing similar baseline features.

[28] Kanavos P, Schurer W., Vogler S.The pharmaceutical distribution chain in the European Union: Structure and impact on pharmaceutical prices-March 2011

Table 3. Healthcare expenditures and pharmaceutical distribution margins in the selected Member States[29]

Country	GDP (billions of euros)-2011	GDP per capita (constant prices and purchasing power parities, reference year 2005) (euros)-2011	Healthcare Expenditure					Purchasing power parity for GDP-2011	Distribution margins	
			Public Healthcare expenditure (% of total expenditure on Health)-2010	Pharma expenditure (% of total health expenditure)	Pharma expenditure per capita, euros purchasing power parity	Total Healthcare expenditure (% of GDP)-2010	Total Healthcare expenditure per capita, euros purchasing power parity-2010		Average wholesale distribution margins (% PPP) *	Average pharmacy distribution margins (%PRP)*
United Kingdom	1644.1	23309.2	83.2	11.6% (2008)	260.6 (2008)	9.6	2591.1	0.659	12.5% (2007)	na
Germany	2315.5	24739.7	76.8	14.9% (2009)	451.6 (2009)	11.6	3274.1	0.798	4-6.1% (Total market, 2007)	24% (2004)
France	1655.5	21521.4	77.0	16.1% (2009)	460.3 (2009)	11.6	2999.4	0.867	6.2% (Total market, 2007)	na
Poland	584.7	13089 (2010)	71.7	22.4% (2009)	225.0 (2009)	7.01	1048.4	1.87	9.78% (2007)	na
Greece	218.5	16207.5	59.4	24.8% (2007)	494.5 (2007)	10.2	2199.4	0.708	4% (Total market, 2007)	na
Portugal	194.5	15304.6	65.8	20.6% (2008)	353.8 (2008)	10.7	2059.0	0.632	6.87%(2007)	18.25% (2008)
Hungary	155.8	12424.1	64.8	32.6% (2009)	354.6 (2009)	7.8	1208.4	129.9	6.04-6.36% (Total market, 2007)	19.46% (2005)

GDP=Gross domestic product/PPP=Pharmacy Purchasing Price/PRP=Pharmacy Retail Price/ *The margins refer to the reimbursement market, unless otherwise indicated

The table above shows the differences among Member States for health care expenditure. It is interesting to notice that France and Germany remain very close while, United Kingdom holds an outlying position. Among the small countries, the separation happens between new entrants Poland and Hungary and the former Member States Greece and Portugal.

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[29] Source: [GDP, Healthcare expenditure] Statistics from OECD (Organisation for Economic Co-operation and Development)/[Distribution margins] Kanavos P, Schurer W., Vogler S.The pharmaceutical distribution chain in the European Union: Structure and impact on pharmaceutical prices-March 2011.
Converter US dollars in euros=http://www.oanda.com/currency/average

1US dollar in euros	Average
2007	0.73071
2008	0.68331
2009	0.719055
2010	0.75476
2011	0.718865

Table 4. Socio-demographic indicators in the selected Member States[30]

Country	Total Fertility Rate (# of birth per women)-2010	Life expectancy at birth (years)				Life expectancy at 65 years old (years)				Infant death rate, per 1000 live births	Standard Death Ratio (SDR) all causes, all ages, per 100000	Overweight (% of people with a BMI>25 kg/m^2)		Death for cancer (Mortality per 100000)	
		Male		Female		Male		Female				Male	Female	Male	Female
		2010	2015	2010	2015	2010	2015	2010	2015						
United Kingdom	1.94	78.3	79.1	82.4	83.2	18.0	18.5	20.7	21.2	4.65 (2009)	562.64 (2009)	NA	NA	216.9 (2010)	234.5 (2010)
Germany	1.36	77.6	78.5	82.7	83.4	17.4	17.9	20.6	21.1	3.51 (2009)	575.92 (2009)	60.1 (2009)	42.9 (2009)	186.1 (2010)	227.5 (2010)
France	2.00	77.9	78.7	84.6	85.2	18.5	19.0	22.7	23.1	3.52 (2008)	522.45 (2008)	49.9 (2010)	36.7 (2010)	170.4 (2008)	265.2 (2008)
Poland	1.40	71.7	73.0	80.1	81.0	14.8	15.5	19.1	19.7	5.57 (2009)	809.66 (2009)	61.4 (2009)	44.6 (2009)	201.4 (2010)	305.1 (2010)
Greece	1.52	77.8	78.6	82.8	83.4	17.9	18.4	20.2	20.7	3.15 (2009)	577.2 (2009)	62.9 (2009)	49.0 (2009)	166.2 (2009)	236.7 (2009)
Portugal	1.32	76.5	77.4	82.5	83.2	17.1	17.6	20.4	20.9	3.65 (2009)	611.93 (2009)	56.0 (2005)	47.5 (2006)	158.9 (2010)	248.1 (2010)
Hungary	1.32	70.4	71.8	78.4	79.5	14.0	14.8	18.1	18.8	5.13 (2009)	914.91 (2009)	59.4 2009)	48.5 2009)	239.1 2009)	374.7 (2009)

This table again highlights important differences that are mainly separating new European Member States from older ones. Those disparities will definitely have an impact and be impacted on by new health intervention access and availability for different Member States.

[30] Sources: [Total Fertility rate] Commission services, Eurostat, EUROPOP2010/ [Life expectancy at birth, Life expectancy at 65 years old] OECD health data 2011/ [Infant death rate, SDR all causes, Death for cancer] European health for all database (HFA-DB).

Table 5. Health resources in the selected Member States[31]

Country	Total hospital beds, per 1 000 population-2010	Curative (acute) care beds, per 1 000 population-2010	Physicians, Density per 1 000 population (head counts)-2010	Pharmacists, Density per 100 000 population
United Kingdom	3.0	2.4	2.8 (2011)	64.15 (2009)
Germany	8.3	5.7	3.7	60.94 (2009)
France	6.4	3.5	3.3 (2011)	116.74 (2010)
Poland	6.6	4.4	2.2	63.53 (2009)
Greece	4.9 (2009)	4.1 (2009)	6.1	88.24 (2006)
Portugal	3.4	2.8	3.8	70.23 (2009)
Hungary	7.2	4.1	2.9	57.18 (2009)

[31] Source: [Hospital beds, acute care hospital beds, active physicians] OECD (Organisation for Economic Co-operation and Development) Health Data 2012/ [Pharmacists] European health for all database (HFA-DB).

3.2 Timeframe

The timeframe of the analysis is between 2012 and 2016. The projection over a 5-year period is a good compromise between the uncertainty related to any forecasting exercise and the need to inform decisions for better planning. Indeed, we can have quite a good outlook of the pharmaceutical market over a 5 year period and the accuracy and credibility of the forecasts can be reasonably guaranteed within this timeframe.

This 5-year period is commonly used to do economic forecasting regarding the sales outlook of drugs by company such as IMS Institute[32] or Datamonitor [33]. Moreover, business plans are often developed on a 5 year-period[34]. We can also cite the 5-year plan for the national economy of several countries such as France or China.

3.3 Type of products

The following types of products were considered in the project:

- Branded medicinal products
- Biosimilar and generic medicinal products

In its glossary of terms published in December 2010, the European Medicines Agency (EMA) defined generic medicinal product and biosimilar medicinal products as follows:

Generic medicinal product: "*A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. (Reg. 726/2004, Art 10, 2b). Generic "copies" can only be marketed after the originator's patent protection and/or marketing exclusivity has expired.*"

Biosimilar medicinal product: "*A biosimilar medicinal product is a medicinal product which is similar to a biological medicinal product that has already been authorised (the 'biological reference medicinal product'). The active substance of a biosimilar medicinal product is similar to the one of the biological reference medicinal product. The name, appearance and packaging of a biosimilar medicinal product may differ to those of the biological reference medicinal product. It may also contain different inactive ingredients*."

For vaccines, research was conducted to see if new and important vaccines that could potentially have a significant impact on a country's budget were expected to come into market in the next 5 years. Indeed, the delay in coverage for new vaccines is considerably longer than that for pharmaceutical products. With the exception of some breakthrough vaccines (e.g. potential vaccine against HIV), on average it takes 4 years for a new vaccine to be launched, with some countries approving new vaccines within 1 year whereas other countries can take up to 10 years to incorporate new vaccines into their vaccination

[32] Eg. IMS Health-The global Use of Medicines: Outlook through 2016-July 2012.

[33] Eg. Datamonitor-Branded prescription pharmaceutical sales outlook to 2016-HC00229-001/Published 02-2012.

[34] Eg. Thames water in the United Kingdom- https://www.thameswater.co.uk/cps/rde/xchg/corp/hs.xsl/6759.htm

programs[35]. This means that, unless the vaccine has a breakthrough effect, it is unlikely that vaccines approved between 2012 and 2016 will generate any significant sales due to the delays in recommendation and implementation.

[35] R.R. Reinert CSS, S. Gaisch, J. Patris: Quantifying the 'population access time' for new vaccine: a European comparative study, ISV Annual Global Congress 2010

4. Methodology

4.1 Collection of information regarding specific pharmaceutical policies in place for each country

As described above, one of the underlying drivers behind the impact of generic entry and the approval of innovative medicine of Member State's pharmaceutical budgets is the healthcare policy in place for the pricing and reimbursement of generic and branded products.

As such, pharmaceutical pricing and reimbursement information was gathered for each country:

From publicly available sources:

- National government websites (publication of applicable laws)
- National drug agencies
- National health technology assessment organization websites
- European Federation of Pharmaceutical Industries and Associations (EFPIA) website
- European Generic Association (EGA) website (EGA Report-2009-How to increase patient access to generic medicines in European healthcare systems// 2011 Market Review (Part 1)-The European Generic Medicines Markets- Price and Reimbursement Systems)
- Country-specific Pharmaceutical Industries Associations websites
- Country-specific Generic Associations websites (as well as direct contacts with some of them)
- Final report of the European commission: Pharmaceutical Sector Inquiry - 8 July 2009
- WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies
- PHIS (Pharmaceutical Health Information System) database
- ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Global health care system road map

From our internal proprietary information database focused on market access.

From local experts and companies for Greece, Hungary, Poland and Portugal:

- Dr. Barbara Baroutsou, Internist /Medical Director in the Pharmaceutical industry, Greece
- George Kritsionis, Portfolio Management Director and Vassilios Katsos, President and CEO, Pharmathen S.A, Greece
- Dávid Dankó, PhD, Corvinus University of Budapest-Institute of Management, Hungary

- Jakub Adamski, Lawyer, Chief expert at the Ministry of Health, Poland
- Dr. Szymon Jarosławski, PhD, Independent Consultant, Poland
- Henrique José Duarte Limas, PharmD, Portugal

4.2 Identification of products of interest

4.2.1 Products going off-patent

To identify the range of products that will go off-patent between 2012 and 2016, as a starting point, we used the lists of patent expirations published by Pharmacy Purchasing & Products[36]: "Major patent expirations for 2010-2015" (September 2009) and by Medco "Estimated Dates of Possible First Time Generic/ Rx-to-OTC Market Entry 2012-2027"[37] and "First Time Approved Generics: 2011"[38] (January 2012). These lists provided a starting point and were further completed by additional research.

As such, we crossed several databases to identify the range of products that would go off-patent between 2012 and 2016: Datamonitor reports, PharmaVitae database, Medtrack database, Patent databases (Free access patent databases such as World Intellectual Property Organization, European Patent Office, Espacenet and Commercial online databases such as STN International/CAPADOC, Questel Orbit, Genericsweb), Pharmaceutical company websites, press releases, investor's reports and the IMS database, as well as our in-house proprietary drug information database.

We also considered data exclusivity for products that did not have intellectual propriety protection but were covered by the 10 year data exclusivity.

One of the main problems we faced was finding the accurate patent expiry dates for all countries, due to the extensive range of patents available for one product (European and National patent). Moreover, Hungary and Poland operate under a dual system before and after European Union entry and this is true for patents and marketing exclusivity. This will impact the date and number of generic entries. For example, there were some molecules that were already generics in Poland, whereas in

[36] http://www.pppmag.com/documents/V6N9GenericDrugsSupp/p8_9.pdf

[37] http://www.medcohealth.com/art/corporate/anticipatedfirsttime_generics.pdf

[38] http://www.medcohealth.com/art/corporate/firsttime_generics.pdf

Western Europe, generics for the very same molecule were not expected to reach the market for the next few years[39]. Due to sensitivity of this confidential information, there was no possibility to obtain validation for this type of information by any of the pharmaceutical unions at national or European level including EGA, nor by pharmaceutical companies themselves. The large number of patent litigations surrounding launch of generics and biosimilars is a consequence of the difficulty to appreciate the actual date of the loss of Intellectual Property (IP), and the value of some additional patents that research based companies use to reinforce their IP protection.

As the objective of the project was to assess the potential for savings related to the penetration of generic and biosimilar drugs, we also considered products that went off-patent in 2010 and 2011 regarding their potential impact on the budget of the forecasted period. Indeed in many countries the generic penetration could be slow and such products might continue to uptake market share 2 years after launch.

For biosimilar drugs, exact patent expiration dates are generally hard to be established due to the lack of centralized listing of biological patents and due to the fact that expiration dates are proprietary information to the companies. Moreover each product has formulation patents which are difficult to assess[40]. As such, significant biological expirations over the forecasted period were mainly extracted from the last publically available data from the Generics and Biosimilars Initiative (GaBi).[41] Only a European expiry date could be identified for these molecules (except for one product with a specific launch date found for United Kingdom).

[39] Examples of differences in patent expiry dates between Poland and France, Germany, United Kingdom (UK):

Drug name	Country	Patent expiry date
Zomig (Zolmitriptan)	Germany	2012/03
	France	2012/03
	UK	2012/03
	Poland	2006/06
Aricept (Donepezil)	Germany	2012/02
	France	2012/02
	UK	2012/02
	Poland	2003/09
Exelon (Rivastigmine)	Germany	2011/03
	France	2012/07
	UK	2011/03
	Poland	2001/03
Zometa (Zoledronic acid)	Germany	2013/05
	France	2012/11
	UK	2013/05
	Poland	2003/11

[40] GaBi-Generics and Biosimilars Initiative- http://www.gabionline.net/Biosimilars/Research/US-54-billion-worth-of-biosimilar-patents-expiring-before-2020

[41] GaBi-Generics and Biosimilars Initiative- http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020

It should be noted that the approval of some molecules under 'generics regulations' or 'biosimilars regulations' is not still obvious. Indeed, in July 2010, the U.S. Food and Drug Administration (FDA) approved the first generic version of the low-molecular-weight heparin (LMWH), Lovenox (enoxaparin sodium injection). LMWHs are complex sugar molecules and difficult to characterise. The FDA approved the generic enoxoparin based on criteria of identity (even if not identical) through current analytical technology and integrated multivariate data analysis[42]. Currently the European Regulatory framework states that clinical trials are required to demonstrate that two LMWHs are similar biological medicinal products. However in a concept paper released in July 2011 regarding the revision of the guideline (dated from 2009) on similar biological medicinal products containing LMWHs, the EMA discussed the substitution of clinical data by analytical data, at least for clinical efficacy.[43] . This highlights the complexity of classification of biologics in some cases.

It should also be difficult to classify the 'copy' of glatiramer acetate (Copaxone) as generic or biosimilar. Indeed, Copaxone is a complex peptide drug, a heterogeneous mixture of polypeptides, forming a random polymer (average molecular mass 6.4 kilodaltons). In 2008, there was a first attempt of 'genericization' with a submission of an abbreviated new drug application to FDA for approval of a generic version.'[44]

As such, we decided to include glatiramer acetate and LMWHs in the model 'generics'.

4.2.2 New entrant products

The range of products that would enter the market between 2012 and 2016 was assessed by cross-checking several databases: European Medicines Agency public information, Datamonitor reports, PharmaVitae database, Medtrack database, Pharmaceutical company websites and press releases, investor's reports, our in-house proprietary drug information database and study registries such as clinicaltrial.gov.

We also included products that entered into the market in 2010 and 2011 regarding their potential impact on the budget during the forecasted period.

We selected drugs according to the following criteria:

- Drugs that could be approved or were approved (for new entrants in 2010 and 2011) via the European Medicines Agency procedure, i.e. drugs for the treatment of HIV, cancer, diabetes, neurodegenerative diseases, immune dysfunctions, viral diseases, medicines derived from biotechnology processes, advanced-therapy medicines, orphan medicines or medicine considered as a significant innovation, or if its authorization would be in the interest of public health.[45]

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[42] The identity problem- Nature Biotechnology -Volume:28, Page: 877 -Year published: (2010)- http://www.nature.com/nbt/journal/v28/n9/full/nbt0910-877.html

[43] EMA website-Biosimilar- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

[44] GaBi website-Copaxone sees off generics challenge-06 July 2012- http://www.gabionline.net/Generics/News/Copaxone-sees-off-generics-challenge

[45] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp

- Only the first approval of new entities was considered. We excluded generics, renewals, variations or updates.

- In order to minimize uncertainty and be consistent with the time window considered for this project, we only considered products that had a positive phase II on the primary end point. Phase IIa were not considered as a phase II.

- We considered orphan drugs before end of phase II as being possible entrants. Indeed, due to the orphan procedures, these drugs with an ongoing phase II could potentially reach the market during the forecasted period.

4.3 Budget impact analysis

4.3.1 Budget impact calculation

We separately analyzed the budget impact of generic entries on one hand, and the impact of new approved innovative pharmaceutical products on the other, taking into account the ageing population.

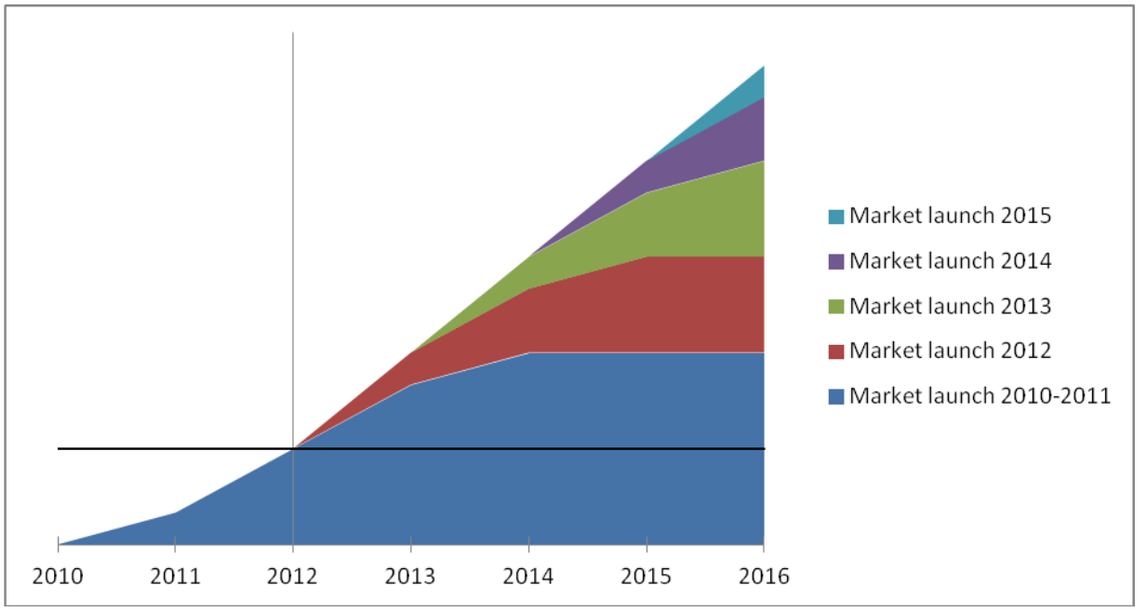
The forecast of the **Net Budget Impact** can be summed up in the following equation:

Net Budget Impact

= additional costs of new drugs entries - savings associated to generic drugs penetration

The budget impact of genericization and of new entrants is cumulative over the 2012-2016 time horizon for each Member State. The budget impact includes drugs going off-patent and new entrants from 2010 (Figure 3).

Figure 3. Illustrative cumulative budget impact assessment



The budget impact is presented from 3 perspectives:

- From the manufacturer's perspective taking into account manufacturer ex-factory sales.
- From the society perspective by integrating all sales based on retail and hospital sales irrespective of reimbursement.

- From the healthcare public payer perspective by applying the reimbursement rates in place in each Member State to public sales. This perspective will inform future policies that are targeted towards the budget impact and the efficiency within the healthcare systems in the Member States.

For reimbursement rates, a decision was made to apply one global rate per country on the total of pharmaceutical expenditures based on the mean of co-payment levels in place in each country (Table 6). Firstly, this assumption appears to be quite reasonable considering that the main pharmaceutical classes are represented in our model. As such, applying different levels of reimbursement rates is expected to lead to similar results as applying an average rate across the different therapeutic areas. Secondly, in most countries, reimbursement rates depend also on patient diseases, ages, cost of medicine, etc. We assumed that applying this reimbursement rate for all consumed medicine, including in hospitals, would not substantially affect the results of our model. In order to account for that uncertainty, we also developed a specific scenario in which, we accounted for the reimbursement rate only in the outpatient sector (Section 6.3.10).

Table 6. Reimbursement rates applied per country[46]

	UK	Germany	France	Poland	Greece	Portugal	Hungary
Reimbursement rate	100.0%	90%	69.0%	62.5%	80%	81.6%	67.0%

In Germany, private health insurance covers about 10% of the population. Therefore, the healthcare public payer perspective should exclude those 10%. However, we decided not to exclude this 10% of the population as:

- It allows for better consistency with other countries studied.
- Actually, there is no accurate picture of the drug consumption of this population, i.e, how much those 10% of the population account for pharmaceutical expenditure, and how this consumption is splitted between inpatient and outpatient pharmaceutical expenditure.Therefore, it would have been not accurate to identify the actual number and to subtract from the overall expenditure to account for only privately insured inhabitants.

Either way, taking into account this part of the population in the pharmaceutical budget estimation, would not be a serious matter, if we assume that their drug consumption represents the same level of expenditure as the remaining publicly insured patients, i.e, this would give a discount of 10%.

4.3.2 Set-up of a study board of experts

The study was conducted under the supervision and validation at each stage by a board of 6 experts, used to review and assess medicinal products, with experience in sitting on various boards of health agencies, refered below in the report as study board of experts and made up of:

- **Prof. Jean-Paul AURAY** is Doctor in Mathematics. He is Research Director at CNRS, and Professor at the University of Claude Bernard Lyon 1. He is responsible for the medico-economic decision making of the Master Sciences of Health Systems at the University of Lyon. His research areas are health economics, methods of mathematics for human sciences, and industry economics.

[46] PPRI (Pharmaceutical Pricing and Reimbursement Information) Pharma Profiles, G-BA for Germany, Local market intelligence

- **Prof. Gérard DURU** has a PhD in Mathematics, and is a former Research Director at CNRS and University of Lyon. From 1981 to 1993, he was responsible for a scientific group dedicated to Decisions Sciences and Health Policies, involving several research units addressing multidisciplinary health issues. He is a former President of the International Society for System Science in Health care, and a former President of the French Society of Health Economics. He is the author of numerous publications in the field of decision-making support applied to Health and Quality of Life.

- **Prof. Michel LAMURE** is the head of the health services research unit in ERIC, a joint research team, under the tutorship of both University Claude Bernard Lyon 1 and University Lumière Lyon 2. He has a PhD in Mathematics, and is a Professor at the University of Lyon. He was involved in different responsibilities during these last years, in particular, at a national level (such as advisor of the French Minister of Education, Chairman of the French University National Council for computer sciences). His research interest addresses mainly evaluation methods in the field of Decision Sciences and Health Policy. He is a former General Secretary of the International Society for System Science in Health care.

- **Dr. Francis MEGERLIN** has a PhD in International and Comparative Law, a HDR (Pharmaceutical Sciences) and is a Reader at the Faculty of Pharmacy at University Paris Descartes. He is a member of the Research Laboratory for Multidisciplinary Applied Researches in Health Economics (Liraes), and a Senior Fellow at the Berkeley Center for Health Technology, University of California, Berkeley. His research area focuses on assesment and pricing of health technologies, and international healthcare policy comparisons.

- **Prof. François LHOSTE** is a Professor of Clinical Pharmacology, and of Pharmaco-economics at the University Paris Descartes, co-director of the Master strategy and Management of the Health Industries of École Supérieure des Sciences Économiques et Commerciales (ESSEC), member of the Economic Committee of Health products, and delegate of Direction Générale de la Compétitivité, de l'Industrie et des Services (DGCIS).

- **Prof. Mondher TOUMI** is an M.D., M.Sc. in Biological Sciences, and a Ph.D. in Economic Sciences. After having worked in the Laboratory of Pharmacology at the University of Marseille, he joined the Public Health Department. After a career in the industry, he was appointed Professor at Lyon I University in the Department of Decision Sciences and Health Policies in February 2009, and he conducts the first European University Diploma of Market Access (www.EMAUD.org). His research area focuses on modelling decision making and international healthcare policy comparisons.

Prof. Mondher Toumi acted as a moderator for the study board of experts and is co-author of this report.

Prof. Mondher Toumi is consultant at Creativ-Ceutical and, as such, has worked for a large number of pharmaceutical companies. He does not declare any other competing interests for this specific project.

The other experts do not declare any competing interests for this specific project.

The study board of experts assessed the indirect impact of generic entries and the impact of new entrants. For this exercise, the expert's inputs were standardized in order to maximize the reproducibility of the impact assessment, and minimize the variability of appreciation across different products within the same therapeutic class or disease area.

The study board of experts defined the rules for assessment and established some principles and assumptions that are listed in following sections. The board operated under consensus reached through a deliberative process.

The study board of experts attempted as far as possible to anticipate future regulation for pricing and reimbursement in light of current trends and ongoing pricing and reimbursement reforms in many Member States of the Euroepan Union.

4.3.3 Budget impact of genericization: "drop-out analysis"

A model was developed for generics and biosimilars for each country, given the country specific health policies.

4.3.3.1 Identification of all inputs and assumptions for the model

Direct impact

The direct impact on savings corresponds to the value extrapolated from the market share evolution of the generic versus the originator.

Seven inputs were considered to calculate the direct impact:

- Sales value for 2011 of the originator (branded) drug extracted from the IMS database, including hospital and retail sales as well as manufacturer and public sales.
- Date of patent expiry crossing several databases as reported in section 4.2.1.

With the provisions of the European Union regulatory system, generic medicines can be ready to enter the market without delay upon patent expiry. Under European Union law, it is not allowed to link marketing authorisation to the patent status of the originator reference product.[47] As such, we assumed the date of patent expiry as the date of marketing authorization.

- Time to market launch after marketing authorization: it corresponds to the time delays of pricing and reimbursement status after marketing authorization.

Even if generic medicines can be ready to enter the market without delay upon patent expiry, we applied a time to market launch after marketing authorization to take into account the different time delays of pricing and reimbursement approval systems existing across the Member States under study.

The development of biosimilars is more complex than generics (developmental time for a generic medicine is around 3 years and around 6 to 9 years for a biosimilar due to the need to conduct phase I and III clinical trials[48]) and needs Health Technology Assessment, as by definition, a biosimilar is "similar" to and not the same than the biological reference. As such, we applied 6 additional months to the time to market launch after marketing authorization to account for technical assessment and related administrative burden to obtain a listed price.This is expected to reflect reality due to the complexity of achieving pricing and reimbursement for biosimilars compare to generics.

- Price reduction of the generic/biosimilar versus the originator.
- Generic/biosimilar penetration versus off-patent brands in volume.
- Time to reach generic/biosimilar peak sales.

[47] EU commission: Pharmaceutical Sector Inquiry -Final Report -8 July 2009

[48] Steven Simoens & Gilbert Verbeken & Isabelle Huy- Biosimilars and market access: a question of comparability and costs? - Targ Oncol-DOI 10.1007/s11523-011-0192-7-Published online 17JAN2012.

- Impact of generic/biosimilar entry on brand price.

These data were extracted from the sources described in section 4.1 and were validated by the study board of experts.

Indirect impact

The assessment of the indirect impact of generic entry, i.e, the level of industry competition and life cycle management strategies, was based on the inputs of the study board of experts regarding the following assumptions:

- When 4 or more generics were available for the same therapeutic area (competing for the same indication) it was considered that the generics competition will incure an additional saving that was estimated to be between 5 and 20% according the insight of the study board of experts.

- The entry of generics has in some cases been considered to displace the mix of treatments used for the same indication, as generics could become first line treatment when they have a potential to be more cost effective treatment option.

- When combos, including one product to be generic or patented reformulations of products to be generic during the study period were developed, they were considered to slow down the uptake of generics.

- When me-too drugs were developped at the same time of generic entry, they were considered to slow down the uptake of generics by shifting the mix of products used for the given indication.

As such, indirect impacts varied from -50% to 25% based on the inputs of the study board of experts depending on the country health policies, the therapeutic area and the competitive environment.

4.3.3.2 Development of the model

This model estimates a separate and combined effect of the direct and indirect impact on savings from the genericization of the market for each year in the forecasted period. We assumed that the sales grew linearly between the drug launch date and the time when the peak of sales was reached (depending on the country-specific time for off-patent drugs to reach its maximum penetration over the brand products). Then, we assumed for the period of interest that once the peak of sales was reached, that the sales remained stable overtime unless specific events that were factored by the study board of experts as indirect impact.

4.3.4 Budget impact of branded products: 'drop-in analysis'

4.3.4.1 Identification of all inputs and assumptions for the model

Five inputs were considered to calculate the potential impact of the new entrants:

- Development phase of the new entrant based on Datamonitor reports, PharmaVitae database, Medtrack database, Pharmaceutical company websites, press releases, investor's reports, and clinical trial registries such as clinical-trials.gov.

- Potential marketing authorization dates (referred to as 'EU launch date' in our model): year and quarter.

The entry date was estimated based on Datamonitor reports, PharmaVitae database, Medtrack database, Pharmaceutical company websites, press releases, and investor's reports.

These dates were often inconsistent according to the sources. They were systematically reviewed and validated by the study board of experts based on the available clinical trials performed, the initiation date of ongoing phase III trials, the recruitment progress, the disease area, and the date of filling to EMA if applicable. Those rules were modulated based on the number of patients to be recruited, the evidence of the recruitment speed based on clinical trial registries when well updated, the trial sample size, and the disease area, as the speed of running trial is not consistent across diseases.

Then, we assumed for all countries, except for Germany, that the sales of the new entrant would impact the market the year after the European Union date of marketing approval ("EU launch") due to pricing and reimbursement policies. For Germany, the impact was assumed to be the year of EU launch as companies initiate sales based on free pricing and do have one year to achieve the negotiated price should they evidence added value to the reference comparator designated by G-BA (Federal Joint Committee). In the United Kingdom, although prices are still free, NICE (National Institute for Health and Clinical Excellence) reviews usually happen about a year or more after the marketing authorization is granted. Until NICE issue a recommendation, product uptake remains minimal. In January 2014, the United Kingdom will move from free pricing to value based pricing, mirroring the French system concept which is expected to delay new product's access to the market.

- Status of the disease as rare or not rare.

In the case of rare diseases, we considered that peak sales are achieved over a year, due to the important unmet needs for therapies in these disease areas, the lack of alternative therapy in most cases and the targeted presribers who are well informed of any new treatment options for that poorly serviced population.

For other products, we considered that peak sales are reached over a period of three years.

- Total of sales value in 2011 for each of the main therapeutic areas and total of sales values in 2011 for main competitors.

These data were extracted from the IMS database following an extensive search of the actual market for each therapeutic area.

- Impact of the new entrant: our analysis approach was based on a budget impact analysis to determine if the new entrant would substantially impact the sales value of a given disease area.

We considered that, to impact the sales of a therapeutic area, a new entrant will have to bring an added clinical value. A new entrant that does not bring an added clinical value will have no impact on the sales. In principle this does not mean they will not generate sales, but the sales will only replace existing products with a similar price. This is consistent with actual regulations within European Union countries.

The assessment of the impact of new entrants was done in 3 steps:

1. First step: we built a file per therapeutic area for the forecasted period 2012-2016 including the following tables:

- Epidemiology data and status of the disease (rare or not) based on Datamonitor reports, the Orphanet website, as well as websites specialized in the considered area.

- Brand and generic market for each country: we reported the main drugs of the therapeutic area (identified via Datamonitor reports, the EMA website, National drugs databases), identified their class and we reported sales in value and volume for 2010 and 2011, as well as the market share for 2011 (extracted from the IMS database).

- New generics with patent expiries between 2012 and 2016.

- New entrants for the period 2012-2016: we reported all new entrants to be launched in the considered timeframe and we reported some key information on the drug's strengths and weaknesses etc. based on data extracted from Datamonitor reports, Medtrack database, Pharmaceutical company websites, press releases, and study registries.

2. Second step: we built a global table for drugs that entered the market in 2010 and 2011 and reported drugs' strengths and weaknesses based on data extracted from Datamonitor reports, Medtrack database, Pharmaceutical company websites, press releases, clinical trial registries, publications and Health technology assessments each time they were available for products approved in 2010 and 2011.

3. Third step: we organized several meeting with the study board of experts to determine the budgetary impact of selected new entrants. To determine if a new entrant had a budgetary impact, the study board of experts reviewed evidence in support of either efficacy or safety improvements over the available drugs to support their conclusions.

In practice we operated in the following way: the tables described earlier (Steps one and two) were projected to enable the review of evidence by the study board of experts. After this review, they either discussed or shifted toward a consensus on the potential impact, or they asked for additional information. As important background research was performed to fill in the tables, it was often possible to access the sources and provide the requested information on the spot. Should the information not be accessible on the spot, it was searched later and provided at the next meeting with the study board of experts.

The board of experts took into account the new attributes that the product would bring from the perspective of the health technology assessments in place for each country.

For already approved products (2010-2011), the assessment of the French Health Authority (HAS) was used whenever available and the budget impact was considered only for the following ASMR (Improvement of Medical Benefit) of the new medicine based on the degree of innovation of the new medicine relative to the existing treatments): ASMR I (Major innovation), II (Important improvement) and III (Moderate improvement). We considered that there was no budget impact for ASMR IV (Minor improvement) or V (No improvement). It was complemented by the Scottish Medicine Consortium (SMC) HTA review to provide a second perspective on the incremental cost effectiveness.

It was assumed that the following new entrants would not have any budget impact:

- Combination of already approved products unless it brings a major added value in terms of efficacy or safety, versus the use of the combination of the active compounds taken separately

- Me-too drugs

- New formulations of already approved products: these new formulations might often lead toward a better compliance of the treatment but do not bring a major added value in terms of efficacy or safety (the case of an antipsychotic depot was considered as valuable in the light of the recent experience with Risperidone Depot)

Specific assumptions were adopted for the oncology area and the assessment of the impact was based on the Overall Survival. If the overall survival benefit was not available, then the product was considered as not assessable. When phase II results show overall survival, the study board of experts considered the comparator. Placebo was not considered as appropriate when

a well established treatment is approved for that indication. If the comparator was not placebo the following consideration were taken:

- If overall survival was inferior to 3 months: no budgetary impact
- If overal survival was between 3 and 6 months: medium impact
- If overall survival was above 6 months: important impact

The impact was then quantified by the study board of experts case by case, based on the current price of existing alternative treatments, the magnitude of overall survival, severity of the condition, the existence of effective therapies, etc.

For the small countries, Poland, Hungary, Greece and Portugal, it was noticeable that the penetration of new oncology products was quite low compared to France and Germany. This therapeutic class is thought to incur the largest budget increase over the coming decade, and as such, is under close scrutiny by payers. The current increased focus on Member State budget deficits makes the payers unlikely to adopt a more open attitude toward oncology drugs. We therefore implemented a different methodology for oncology forecasts in the small countries. We considered that the ratio of penetration between France and those countries would remain stable during 2012-2016. We generated the forecast for oncology products in France and simulated the forecast for small countries.

4.3.4.2 Development of the model

This model estimates the value of sales and the progression of market share in a competitive environment. The additional expenditure is initially calculated based on the forecast for each product in each country. Then the results are combined to provide the total expected forecasts in each year.

This model takes into account the risk of failure regarding the development of the drug. We are using the results from a study conducted by DiMasi *et al*. [49] that utilized a large dataset of clinical trial (n=1225) approval rates in the United States to estimate clinical phase transition and clinical approval probabilities for drugs. It should be noted that even if the regulatory drug approval processes are quite different between Europe and the United-States, the risk of failure will remain close. It was reported that the estimated clinical approval success rate and phase transition probabilities diverged significantly by therapeutic class. Another outcome was the substantial differences in clinical approval success rates by product type, i.e; large versus small molecules.

We decided to consider the risk of failure per therapeutic class instead of per product type (small versus large molecule) to fit with our budget impact analysis orientated per therapeutic area/class. One of the reasons for the variability of the risk of failure between therapeutic classes could be the different regulatory standards applied for each class of medicines, but also the predictive value of preclinical models. As such, clinical approval rates can vary from 24% for systemic anti-infective to 8% for central nervous system drugs (Table 7).

[49] DiMasi J.A. et al. Trends in risks associated with new drug development: success rates for investigational drugs. *Clinical Pharmacology & Therapeutics* 87, 272-277 (March 2010)

Table 7. Phase transition and clinical approval probabilities by therapeutic class[50]

Therapeutic class	Phase I to Phase II	Phase II to Phase III	Phase III to regulatory submission	Regulatory submission to approval	Clinical approval success rate
Antineoplastic/immunologic	71.8%	49.0%	55.3%	100%	19.4%
Cardiovascular	62.9%	32.4%	64.3%	66.7%	8.7%
Central nervous system	59.6%	33.0%	46.4%	90.0%	8.2%
Gastrointestinal/metabolism	67.5%	34.9%	50.0%	80.0%	9.4%
Musculoskeletal	72.4%	35.2%	80.0%	100%	20.4%
Respiratory	72.5%	20.0%	85.7%	80.0%	9.9%
Systemic anti-infective	58.2%	52.2%	78.6%	100%	23.9%
Miscellaneous	62.8%	48.7%	69.8%	91.3%	19.5%

4.3.5 Accounting for an ageing population

Ageing was taken into account in two ways, either directly in inputs parameters of the model, or indirectly for prevalences calculation purpose, using the evolution of the population structure (average evolution from 2012 to 2016 derived from the 2012 ageing report[51]). These data are expected to be very robust as anticipating ageing of a population for the next five year is a very well define process with very little uncertainty. Based on the high level of certainty of ageing over a five year period, this was not implemented in the sensitivity analysis.

Prevalence data was mainly extracted from Datamonitor epidemiology reports. When no prevalence data was available in Datamonitor reports, various public sources were searched including Medline and Embase, but also web sources (especially Orphanet for rare diseases), and either prevalence for one country was used as an estimate for other countries, or global average prevalence for all countries, still taking ageing into account using evolution of the population structure (2012-2016) derived from the 2012 ageing report[52] .

[50] DiMasi J.A. et al. Trends in risks associated with new drug development: success rates for investigational drugs. *Clinical Pharmacology & Therapeutics* 87, 272-277 (March 2010)

[51] The 2012 ageing report- Economic and budgetary projections for the 27 EU Member States (2010-2060)- EURopEAn EconoMy 2|2012 (provisional version)

[52] The 2012 ageing report- Economic and budgetary projections for the 27 EU Member States (2010-2060)- EURopEAn EconoMy 2|2012 (provisional version)

4.3.6 Uncertainty surrounding the estimations

The intrinsic uncertainty surrounding the estimations was addressed in two ways:

- Deterministic one-way sensitivity analysis to identify drivers of the model outputs.
- Probabilistic sensitivity analysis to quantify the robustness of the model outputs.

4.3.6.1 Deterministic one-way sensitivity analysis

Deterministic one-way sensitivity analysis allows us to assess the impact that changes in a given parameter will have on the model's outputs. For each parameter assessed, the model was run with two sets of parameters. For each parameter we defined an upper limit and a lower limit. The model computed the outputs for each parameter separately. It provided the output values for the upper and lower limit of each variable integrated within the one- way deterministic sensitivity analysis. The results of the deterministic one-way sensitivity analysis on the pharmaceutical net budget impact are presented in the form of a 'Tornado diagram', representing the range of variation of the pharmaceutical net budget impact for alternative values of several parameters.

Parameters of the generic and new entrant model included in the one-way sensitivity analysis were based on the collection of healthcare policy in place for the pricing and reimbursement of generic and branded products for each country. The results of the collection of these data are presented in Section 5.1 and Appendix 0.

We ran two one-way deterministic sensitivity analyses. One assuming a standard magnitude of relative change for all variables to define the upper and lower limit, and the second, following specific boundaries defined by the experts.

In the first case, all parameters were increased and decreased by 30% of their original value, in order not to overweigh a parameters' variation compared to the others (Table 8). Therefore, it allows us to see which parameter is a key driver of the model without bias. The drawback of this method is that some parameters exceed realistic ranges. For instance, a percentage may exceed 100%. Depending on the base case values of a given country, the parameters listed in Table 9 are likely to exceed a realistic range.

As such, a second one-way deterministic sensitivity analysis was run with specific high and low values defined by the study board of experts, to complement this analysis. The upper and lower limits were defined, to provide a good estimate of the impact of each parameter allowing, for example, asymmetric ranges (e.g. when prices of generics are high, it would be more relevant to have a large range for price decrease, and a smaller range for price increase). The drawback of this method is that it overweighs some parameters' variations compared to the others. The upper and lower limits used for one-way deterministic sensitivity analysis are listed in Appendix 8.3 and the results of this second one-way deterministic sensitivity analysis are provided in Appendix 8.4.

Table 8. Parameters taken into account in the deterministic one-way sensitivity analysis

Model inputs	Range (+/-)
Model "New entrants"	
Time to market for the new entrant after marketing approval	± 30%
Time to reach peak of sales for new entrants for treatment of non rare diseases (months)	± 30%
Time to reach peak of sales for new entrants for treatment of rare diseases (months)	± 30%
Model "Generics"	
SMH - Time to market launch (days)	± 30%
SMH - Price reduction of the generic (%)	± 30%
SMH - Generic penetration (generics/off-patent brands)	± 30%
SMH - Time to reach maximum of generic penetration (months)	± 30%
SMH - Impact of generic entry on brand price (%)	± 30%
SMR - Time to market launch (days)	± 30%
SMR - Price reduction of the generic (%)	± 30%
SMR - Generic penetration (generics/off-patent brands)	± 30%
SMR - Time to reach maximum of generic penetration (months)	± 30%
SMR - Impact of generic entry on brand price (%)	± 30%
BH - Time to market launch (days)	± 30%
BH - Price reduction of the biosimilar (%)	± 30%
BH - Biosimilar penetration (biosimilars/off-patent brands)	± 30%
BH - Time to reach maximum of biosimilar penetration (months)	± 30%
BH - Impact of biosimilar entry on brand price (%)	± 30%
BR - Time to market launch (days)	± 30%
BR - Price reduction of the biosimilar (%)	± 30%
BR - Biosimilar penetration (biosimilars/off-patent brands)	± 30%
BR - Time to reach maximum of biosimilar penetration (months)	± 30%
BR - Impact of biosimilar entry on brand price (%)	± 30%
Healthcare Public Payer	
Reimbursement rate	± 30%

Table 9. Parameters of the model likely to exceed realistic ranges under the deterministic one-way sensitivity analysis

Model "Generics"
Small molecule hospital - Price reduction of the generic (%)
Small molecule hospital - Generic penetration (generics/off-patent brands)
Small molecule retail - Price reduction of the generic (%)
Small molecule retail - Generic penetration (generics/off-patent brands)
Biosimilar hospital - Price reduction of the biosimilar (%)
Biosimilar hospital - Biosimilar penetration (biosimilars/off-patent brands)

4.3.6.2 Probabilistic sensitivity analysis

Deterministic one-way sensitivity analysis and tornado diagrams are useful to analyze impact of one parameter varying in the model, but do not represent the confidence in model's inputs and the consistency of the model. For this purpose, a probabilistic sensitivity analysis was conducted.

In probabilistic sensitivity analysis, a distribution is assigned to each parameter of the model rather than assigning a single value. Then, the model is run a large number of times with random inputs, generated according to distributions assigned to the parameters. The uncertainty existing around the model inputs is therefore reflected by the results of this sensitivity analysis.

As data are quite specific to drugs and therapeutic areas, it may be difficult to represent them with complex distributions like Log-Normal, Weibull or Beta distributions. A uniform distribution was used for each parameter of the model and a distance was assigned according to the base case value. This allows for each value between the bounds of the range to have the same probability to be generated. This means that uncertainty is reflected without any (a priori) assumptions. The bounds of the range were computed by adding or subtracting the distance to the base case value (corresponding in this case to the median of the distribution). For some values the bound obtained in this way was not realistic (e.g. higher than 100 or lower than 0 for a percentage, lower than 0 for a positive value). In this case, realistic bounds were used.

The model was subsequently run a large number of times (1000 times), using the inputs listed in Table 10. Each simulation is a particular case of the budget impact model. The aggregated results of each simulated model for each country and each perspective were saved and plotted, and basic statistics were computed (mean, standard error, median, minimum, maximum, first (25%) and third (75%) quartiles).

The probabilistic sensitivity analysis provides two charts:

- The cumulative distribution of the simulated budget impacts, informing on the probability to obtain a budget impact lower than or equal to a chosen value,
- The scatter plot of the 'Savings' according to the 'Additional costs' of each simulation, showing the spread of the simulations.

Table 10. Inputs used for the probabilistic sensitivity analysis

Model inputs	Distribution law	Range (+/-)
Model "New entrants"		
Input on drug price and prevalence - Drug price variation in %	Uniform	± 10%
Input on drug price and prevalence - Prevalence's variation in %	Uniform	± 10%
Input on % of the drug's revenue - Variation in value of the %	Uniform	± 10 points
Input on country specific coefficient for sales - Coefficient's variation in %	Uniform	± 10%
Time to market for the new entrant after marketing approval	Uniform	± 3 month
Time to reach peak of sales for new entrants for treatment of non rare diseases (months)	Uniform	± 6 month
Time to reach peak of sales for new entrants for treatment of rare diseases (months)	Uniform	± 3 month
Model "Generics"		
Time to market launch after marketing authorization (days)	Uniform	± 180 days
Time to reach maximum of generic penetration (months)	Uniform	± 6 months
Price reduction of the generic (%)	Uniform	± 10 points
Generic penetration (generics/off-patent brands)-Volume uptake (%)	Uniform	± 10 points
Impact of generic entry on brand price (%)	Uniform	± 10 points
Healthcare Public Payer		
Reimbursement rate	Uniform	± 5 points

4.3.7 Overall analysis

The analysis of the net budget impact follows the equation depicted in section 4.3.1. The results are presented in terms of the annual impacts over the 2012-2016 time horizon for each Member State. The results are presented in 2011 Euros, as the forecasts are based on the sales in value for 2011.

Figure 4 presents the different characteristics of the model outputs.

- The model is presented according to the three perspectives: the healthcare public payer perspective, the society perspective (sometimes referred as public perspective) as well as the manufacturer's perspective.

- The model allows us to distinguish between several types of distribution chain: retail, hospital, and combined retail and hospital.

- The model presents several outcomes: savings due to products going off-patent, additional costs due to new entrants products and net budget impact

  To summarize, this means that for each country, 27 tables of results were developped accounting for a total of 189 tables for the 7 countries. As too many results would affect the reading flow of the report, the healthcare public payer perspective was selected as the base case and all other results are presented in Appendices.

Figure 4. Description of model characteristics

5. Results

5.1 Collection of information regarding specific pharmaceutical policies in place in each country

Healthcare policies in place for the pricing and reimbursement of generic and branded products were collected for each country and are summed up in Appendix 0.

Far-reaching changes were seen in the drug market access environment in most of the Members States under study:

- In France, the new drug safety law voted in 2011 will reinforce the economic assessments of health products as well as the provision of real world data to support the benefit/risk ratio of drugs.
- In Germany, the new health bill AMNOG (known as Arzneimittelmarkt-Neuordnungsgesetz) approved at the end of 2010, represents a significant change for the introduction of drugs in Germany, introducing the concept of benefit/cost assessments of drugs.
- In the United Kingdom, value-based pricing will be introduced in 2014, replacing free pricing, price cuts, price freezes and profit controls with both pre- and post-launch price reviews, to reflect any changes in a drug's value as a result of new evidence.
- In Poland, the new reform on Pricing and Reimbursement from January 2012 introduced Health Technology Assessment and price negotiation.
- In Greece, pharmaceutical expenditure containment measures were introduced in 2011, including the merge of the health insurance function to create a single body, the National Health Services Organization (EOPYY), as well as pricing reductions, increasing generic medication use, hospital cost reduction, etc.

We detected wide variability between countries concerning generics entry policy. Generics are available from their market approval date up to 180-270 days after. Generics prices range from the same price to 60% lower than the branded product at time of entry. In some countries, the generics entries impact the price of the whole class by regulatory rules, while it may be company free decision in others. In Hungary, brands are excluded from the market at generic entry. Besides, discounts on brands vary from 0 to 50%. Generic substitution is driven by either local mandatory requirements, or financial pharmacist incentives. As a consequence, the generic market share varies between 25 to almost 100% in volume, and 20 to 70% in value.

Regarding the biosimilar market, the European Union is a global leader, accounting for 80% of global spending on these molecules.[53] Indeed, the European Union was first to establish an approval pathway for biosimilars with the publication of the Guideline on Similar Biological Medicinal Products (CHMP/437/04) in October 2005 (in revision with draft revised guideline that should be released for consultation in the first semester of 2012). Moreover, product-specific biosimilar guidelines were developed. To date, guidelines were adopted for 7 products (recombinant human insulin, somatropin, recombinant granulocyte-colony stimulating factor, recombinant interferon alpha, low- molecular-weight heparins, recombinant

[53] IMS Health- Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape.December 2011.

erythropoetins, and monoclonal antibodies (effective in December 2012)) and there are guidelines in development for 2 products (recombinant follicle stimulation hormone and recombinant interferon beta). Since 2005, EMA has approved 14 biosimilars within the product classes of human growth hormone, granulocyte stimulating factor and erythropoietin.[54]

In terms of national pricing and reimbursement policies on biosimilars, little information was available despite the fact that Europe is the market with the greatest number of pipeline and marketed biosimilar products, totaling 67 (32 molecules) as of December 2011[55]. Some data about biosimilar penetration were only found for France and Germany (these 2 countries account for half the biosimilars market by value with a 34% and 17% share respectively across Europe[56]), and some policies about prices were reported for Hungary.

For hospital, as it is a tender market, there is a strong competition among products. Even branded products will substantially discount their prices to maintain their position in hospitals. The hospital market is therefore affected by a large discount practice and could be considered de facto as 100% generic market.

Based on the data collected and the experts' inputs, we defined the parameters to feed the generic/biosimilar model (Table 11).

[54] EMA website- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

[55] Datamonitor- Biosimilars: Pipeline Trends - 00149-002/Published 12/2011

[56] IMS Health- Shaping the biosimilars opportunity:A global perspective on the evolving biosimilars landscape.December 2011.

Table 11. Generic/Biosimilar model parameters

	UK	Germany	France	Poland	Greece	Portugal	Hungary
Generic model parameters - Small molecules RETAIL							
Time to market launch after marketing authorization (days)	0[57]	0[57]	60[58]	180[59]	270[60]	149[61]	45[62]
Price reduction of the generic (%)	75[63]	55[64]	60[65]	45[66]	60[60]	60[67]	55[60]
Generic penetration (generics/off-patent brands)-Volume uptake (%)	80[63]	85[68]	80[69]	85[70]	25[71]	25[72]	100[60]
Time to reach maximum of generic penetration (months)	12[63]	12[64]	36[69]	24[60]	36[60]	30[60]	18[60]
Impact of generic entry on brand price (%)	0[63]	0[64]	20[73]	25[66]	50[60]	0[60]	0[60]
Generic model parameters - Small molecules/Biosimilars HOSPITAL[60]							
Time to market launch after marketing authorization (days)	0	0	0	0	0	0	0
Price reduction of the generic/biosimilar (%)	80	80	80	80	80	80	80
Generic penetration (generics-biosimilar/off-patent brands)-Volume	100	100	100	100	100	100	100
Time to reach maximum of generic/biosimilar penetration (months)	0	0	0	0	0	0	0
Impact of generic/biosimilar entry on brand price (%)	0	0	0	0	0	0	0
Generic model parameters - Biosimilars RETAIL[74]							
Time to market launch after marketing authorization (days)	180	180	469	540	450	529	580
Price reduction of the biosimilar (%)	25	25	30	45	25	30	50
Biosimilar penetration (generics/off-patent brands)-Volume uptake (%)	15	25	15	25	5	15	100
Time to reach maximum of biosimilar penetration (months)	12	12	36	24	36	30	18
Impact of biosimilar entry on brand price (%)	0	0	10	12	25	0	0

[57] EGA Report-2009-How to increase patient access to generic medicines in European healthcare systems
[58] EGA- 2011 Market Review (Part 1)-The European Generic-Medicines Markets - Price and Reimbursement Systems-April 2011./Article L5121-10 Public health code
[59] EGA- 2011 Market Review (Part 1)-The European Generic-Medicines Markets - Price and Reimbursement Systems-April 2011.
[60] Experts' insight
[61] Data provided by the Portuguese Generic Medicines Association, Apogen
[62] Experts' insight-Act XCVIII/2006 and MoH decree 32/2004 (IV.26.)
[63] Experts' insight based on Datamonitor, UK Pharmaceutical Market Overview DMHC2608, June 2010
[64] Experts' insight based on IGES report: "Generika in Deutschland: Wettbewerb fördern – Wirtschaftlichkeit stärken, Oktober 2011, Berlin;" http://www.progenerika.de/de/publik/gutachten.2011.html
[65] GEMME website accessed in 2012 (http://www.medicamentsgeneriques.info/son-cadre-reglementaire-et-sanitaire/prix-et-admission-au-remboursement/)
[66] Experts' insight - Act of 12 May 2011 on reimbursement of drugs, foodstuffs for particular nutricional use and medical devices
[67] Experts' insigh based on Data provided by the Portuguese Generic Medicines Association, Apogen
[68] Experts' insight based on Pro Generika Market Data 2011, IMS Pharmascope ; http://www.progenerika.de/de/publik/broschueredaten.html and IGES report: "Generika in Deutschland: Wettbewerb fördern – Wirtschaftlichkeit stärken, Oktober 2011, Berlin;" http://www.progenerika.de/de/publik/gutachten.2011.html
[69] Experts' insight based on LEEM Report 2011 (http://www.leem.org/les-entreprises-du-medicament-en-france-elements-chiffres-edition-2011) and Senat website accessed in 2012-http://www.senat.fr/rap/r07-427/r07-42728.html and http://www.senat.fr/rap/l11-074-2/l11-074-23.html)/(National Assembly website accessed in 2012-http://questions.assemblee-nationale.fr/q13/13-120139QE.htm)
[70] http://www.pharma.focusreports.net/index.php#state=InterviewDetail&id=1216 (interview of president of PZPPF=polish association of pharma industry employers)
[71] Calculated from retail drugs sales in Greece for 2011
[72] INFARMED Database-April 2012
[73] National Assembly website accessed in 2012-http://questions.assemblee-nationale.fr/q13/13-120139QE.htm
[74] Experts'insight. For France: Expertise report of Afssaps on biosimilars-July 2011 (http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Des-medicaments-issus-des-biotechnologies-aux-medicaments-biosimilaires-etat-des-lieux-Point-d-information). For time to market launch after marketing authorization, based on data for brands with 6 additional months.

5.2 Identification of products of interests

5.2.1 Products going off-patent

5.2.1.1 Generics

We identified 202 generics during the period 2012-2016 and 71 products that went off-patent during 2010 and 2011. Generic products were classified per ATC code[75] (Level 4) (Appendix 8.6). From the perspective of the budget impact analysis of generics and the match with budget impact analysis of new entrants, we then classified the generics into 24 therapeutic areas, gathered under 10 classes (Table 12). These therapeutic areas refer either to a specific disease, or to a pharmacotherapeutic class of drug when it covers several indications. All products that didn't fit in the therapeutic areas/classes were grouped under 'others'.

Table 12. Classification of generics per ATC codes, therapeutic areas and classes

Class	Therapeutic area	ATC code	
ANTI-INFECTIVES	ANTIBIOTICS	J01X	OTHER ANTIBACTERIALS
ANTI-INFECTIVES	ANTIBIOTICS	J01G	AMINOGLYCOSIDE ANTIBACTERIALS
ANTI-INFECTIVES	ANTIBIOTICS	J01M	QUINOLONE ANTIBACTERIALS
ANTI-INFECTIVES	ANTIBIOTICS	J01F	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
ANTI-INFECTIVES	ANTIBIOTICS	J01D	OTHER BETA-LACTAM ANTIBACTERIALS
ANTI-INFECTIVES	ANTIBIOTICS	J01A	TETRACYCLINES
ANTI-INFECTIVES	ANTIVIRALS	J05A	DIRECT ACTING ANTIVIRALS
CARDIOVASCULAR	DYSLIPIDEMIA	C10A	LIPID MODIFYING AGENTS, PLAIN
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION	C09D	ANGIOTENSIN II ANTAGONISTS, COMBINATIONS
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION	C09C	ANGIOTENSIN II ANTAGONISTS, PLAIN
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION	C09B	ACE INHIBITORS, COMBINATIONS
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION	C08C	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION	C07B	BETA BLOCKING AGENTS AND THIAZIDES
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION	C09X	OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
CARDIOVASCULAR	ANTICOAGULANTS-THROMBOLYTICS	B01A	ANTITHROMBOTIC AGENTS
CENTRAL NERVOUS SYSTEM	ALZHEIMER	N06D	ANTI-DEMENTIA DRUGS
CENTRAL NERVOUS SYSTEM	DEPRESSION	N06A	ANTIDEPRESSANTS
CENTRAL NERVOUS SYSTEM	EPILEPSY	N03A	ANTIEPILEPTICS
CENTRAL NERVOUS SYSTEM	MIGRAINE	N02C	ANTIMIGRAINE PREPARATIONS
CENTRAL NERVOUS SYSTEM	MULTIPLE SCLEROSIS	L03A	IMMUNOSTIMULANTS
CENTRAL NERVOUS SYSTEM	PAIN	N02A	OPIOIDS
CENTRAL NERVOUS SYSTEM	PAIN	N02B	OTHER ANALGESICS AND ANTIPYRETICS
CENTRAL NERVOUS SYSTEM	PARKINSON	N04B	DOPAMINERGIQUES
CENTRAL NERVOUS SYSTEM	ANTISPYCHOTICS	N05A	ANTIPSYCHOTICS
CENTRAL NERVOUS SYSTEM	INSOMNIA	N05C	HYPNOTICS AND SEDATIVES
ENDOCRINOLOGY	DIABETES_NON INSULINS	A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
GENITO-URINARY	BENIGN PROSTATIC HYPERTROPHY	G04C	DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY

[75] ATC index 2012- http://www.whocc.no/atc_ddd_index/

Class	Therapeutic area	ATC code	
GENITO-URINARY	GENITO-URINARY	G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE
GENITO-URINARY	GENITO-URINARY	G02C	OTHER GYNECOLOGICALS
GENITO-URINARY	GENITO-URINARY	G02B	CONTRACEPTIVES FOR TOPICAL USE
GENITO-URINARY	GENITO-URINARY	G03F	PROGESTOGENS AND ESTROGENS IN COMBINATION
GENITO-URINARY	GENITO-URINARY	G03C	ESTROGENS
GENITO-URINARY	GENITO-URINARY	G03D	PROGESTOGENS
GENITO-URINARY	GENITO-URINARY	G04B	OTHER UROLOGICALS, INCL. ANTISPASMODICS
GENITO-URINARY	GENITO-URINARY	G03B	ANDROGENS
IMMUNOLOGY AND INFLAMMATION	PSORIASIS	D05A	ANTIPSORIATICS FOR TOPICAL USE
MUSCULOSKELETAL	OSTEOPOROSIS	M05B	DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION
MUSCULOSKELETAL	OSTEOPOROSIS	G03X	OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
ONCOLOGY	ONCOLOGY	L02B	HORMONE ANTAGONISTS AND RELATED AGENTS
ONCOLOGY	ONCOLOGY	L01C	PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS
ONCOLOGY	ONCOLOGY	L01D	CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES
ONCOLOGY	ONCOLOGY	L01X	OTHER ANTINEOPLASTIC AGENTS
ONCOLOGY	ONCOLOGY	L01A	ALKYLATING AGENTS
ONCOLOGY	ONCOLOGY	L01B	ANTIMETABOLITES
ONCOLOGY	ONCOLOGY	V10X	VARIOUS PAIN PALLIATION RADIOPHARMACEUTICALS
OTHER	AMYOTROPHIC LATERAL SCLEROSIS	N07X	OTHER NERVOUS SYSTEM DRUGS
OTHER	OTHERS	A06A	LAXATIVES
OTHER	OTHERS	A08A	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
OTHER	OTHERS	A02B	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE
OTHER	OTHERS	C01E	OTHER CARDIAC PREPARATIONS
OTHER	OTHERS	C03D	POTASSIUM-SPARING AGENTS
OTHER	OTHERS	A04A	ANTIEMETICS AND ANTINAUSEANTS
OTHER	OTHERS	H01B	POSTERIOR PITUITARY LOBE HORMONES
OTHER	OTHERS	H01C	HYPOTHALAMIC HORMONES
OTHER	OTHERS	L04A	IMMUNOSUPPRESSANTS
OTHER	OTHERS	N06B	PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
OTHER	OTHERS	S01E	ANTIGLAUCOMA PREPARATIONS AND MIOTICS
OTHER	OTHERS	S01L	OCULAR VASCULAR DISORDER AGENTS
OTHER	OTHERS	V03A	ALL OTHER THERAPEUTIC PRODUCTS
OTHER	OTHERS	P01B	ANTIMALARIALS
OTHER	OTHERS	J02A	ANTIMYCOTICS FOR SYSTEMIC USE
OTHER	OTHERS	D11A	OTHER DERMATOLOGICAL PREPARATIONS
OTHER	OTHERS	A16A	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
OTHER	OTHERS	C02K	OTHER ANTIHYPERTENSIVES
OTHER	OTHERS	D07C	CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS
OTHER	OTHERS	N07B	DRUGS USED IN ADDICTIVE DISORDERS
OTHER	OTHERS	S01B	ANTIINFLAMMATORY AGENTS
OTHER	OTHERS	B06A	OTHER HEMATOLOGICAL AGENTS
OTHER	OTHERS	C01C	CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES
OTHER	OTHERS	D06B	CHEMOTHERAPEUTICS FOR TOPICAL USE
OTHER	OTHERS	H01A	ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES
OTHER	OTHERS	M03A	MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS
OTHER	OTHERS	M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
OTHER	OTHERS	N01A	ANESTHETICS, GENERAL
OTHER	OTHERS	N01B	ANESTHETICS, LOCAL
RESPIRATORY	ALLERGIC RHINITIS	S01G	DECONGESTANTS AND ANTIALLERGICS
RESPIRATORY	ALLERGIC RHINITIS	R01A	DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE
RESPIRATORY	ALLERGIC RHINITIS	R06A	ANTIHISTAMINES FOR SYSTEMIC USE
RESPIRATORY	ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

Class	Therapeutic area	ATC code	
RESPIRATORY	ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
RESPIRATORY	ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	R03A	ADRENERGICS, INHALANTS

5.2.1.2 Biosimilars

We identified 10 major biosimilars during the period 2012-2016. Biosimilars were classified per ATC code[76] (Level 4) (Table 13).

For Pegfilgastrim, the year of patent expiry is estimated between 2015 and 2017 (internal source). As such it was decided to include this molecule in the list.

Table 13. List of biological products going off-patent during the period 2012-2016

ATC code		Generic Name	Expiry month	Expiry year	Country
L01X	OTHER ANTINEOPLASTIC AGENTS	Trastuzumab	7	2014	UK
L01X	OTHER ANTINEOPLASTIC AGENTS	Trastuzumab	8	2015	All countries except UK
J06B	IMMUNOGLOBULINS	Palivizumab	8	2015	All countries
L01X	OTHER ANTINEOPLASTIC AGENTS	Cetuximab	6	2014	All countries
L04A	IMMUNOSUPPRESSANTS	Etanercept	2	2015	All countries
L04A	IMMUNOSUPPRESSANTS	Infliximab	8	2014	All countries
L01X	OTHER ANTINEOPLASTIC AGENTS	Rituximab	11	2013	All countries
L03A	IMMUNOSTIMULANTS	Pegfilgastrim	?	2015	All countries
L03A	IMMUNOSTIMULANTS	Interferon beta 1a	?	2015	All countries
B03X	OTHER ANTIANEMIC PREPARATIONS	Darbepoetin alfa	7	2016	All countries
A10A	INSULINS AND ANALOGUES	Insulin glargine	?	2014	All countries

5.2.2 New entrant products

We identified 254 new entrants that are expected to enter the market during the period 2012-2016 with some of them in several indications (Appendix 8.7) and 66 new entrants approved in 2010 and 2011 including 3 new entrants marketed under 2 different names (same pharmaceutical company), one new entrant developed by 2 companies, and one new entrant developed in 2 indications with 2 separate marketing authorizations (Appendix 8.8).

From the perspective of budget impact analysis, we then classified the new entrants into 37 therapeutic areas, gathered under 10 classes (Table 14). These therapeutic areas refer either to a

[76] ATC index 2012- http://www.whocc.no/atc_ddd_index/

specific disease or to a pharmacotherapeutic class of drug when it covers several indications. All products that didn't fit in the therapeutic areas/classes were grouped under 'others'.

Table 14. Classification of new entrants per therapeutic areas and classes

Class	Therapeutic area
ANTI-INFECTIVES	ANTIBIOTICS
ANTI-INFECTIVES	HIV (Human Immunodeficiency Virus)
ANTI-INFECTIVES	HCV (Hepatitis C Virus)
CARDIOVASCULAR	ANTICOAGULANTS-THROMBOLYTICS
CARDIOVASCULAR	CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION
CARDIOVASCULAR	DYSLIPIDEMIA
CENTRAL NERVOUS SYSTEM	ALZHEIMER
CENTRAL NERVOUS SYSTEM	ANTIPSYCHOTICS
CENTRAL NERVOUS SYSTEM	DEPRESSION
CENTRAL NERVOUS SYSTEM	EPILEPSY
CENTRAL NERVOUS SYSTEM	INSOMNIA
CENTRAL NERVOUS SYSTEM	MIGRAINE
CENTRAL NERVOUS SYSTEM	MULTIPLE SCLEROSIS
CENTRAL NERVOUS SYSTEM	PAIN
CENTRAL NERVOUS SYSTEM	PARKINSON
ENDOCRINOLOGY	DIABETES_INSULINS
ENDOCRINOLOGY	DIABETES_NON INSULINS
GENITO-URINARY	BENIGN PROSTATIC HYPERTROPHY
GENITO-URINARY	CONTRACEPTION
GENITO-URINARY	ENDOMETRIOSIS
GENITO-URINARY	HYPOGONADISM IN MEN
GENITO-URINARY	MENOPAUSE
GENITO-URINARY	OVERACTIVE BLADDER
IMMUNOLOGY AND INFLAMMATION	INFLAMMATORY BOWEL DISEASE
IMMUNOLOGY AND INFLAMMATION	LUPUS
IMMUNOLOGY AND INFLAMMATION	PSORIASIS
IMMUNOLOGY AND INFLAMMATION	RHEUMATOID ARTHRITIS
MUSCULOSKELETAL	OSTEOPOROSIS
ONCOLOGY	ONCOLOGY
OTHER	PULMONARY ARTERIAL HYPERTENSION
OTHER	AMYOTROPHIC LATERAL SCLEROSIS
OTHER	GAUCHER DISEASE
OTHER	HEMOPHILIA
OTHER	ANEMIA
OTHER	OTHER DISEASES
RESPIRATORY	ALLERGIC RHINITIS
RESPIRATORY	ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

The number of new entrants per year is illustrated in Table 15.

Table 15. Number of new entrants per year

	2010	2011	2012	2013	2014	2015	2016	Total
Number of new entrants	19	47	39	74	56	56	29	320

This table lists the number of new entrants per year assuming that all of them will be approved. In reality some of them will see their development discontinued and a risk failure factor was taken into account in the model for such discontinuation.

5.3 Budget impact analysis

5.3.1 2011 pharmaceutical budget

Table 16 presents the global pharmaceutical market from the society perspective for 2011 per country and split retail and hospital distribution chain. For Greece, no hospital data are available and therefore the hospital market accounts for 0. As a general reference, it should be observed that for the 6 remaining countries in the panel, hospital budgets range from 9.6% to 36.1% of overall pharmaceutical expenditure. Hospital pharmaceutical expenditure is rather low in Germany with 9.6% of total market, while quite high in the United Kingdom as it accounts for 36.1%. The structure of pharmaceutical expenditures (retail/hospital) will have a dramatic impact on forecasting. Hospitals will operate through tenders and when biosimilars or generics are available, they do benefit from increased discount. Hospital products do have minimal impact on distribution cost while retail sales are impacted by more or less important distribution costs. Finally, new generics or biosimilars once approved could enter into hospital tenders from day 1 in most countries. This contributes to speed up the generic savings.

The drug expenditure per capita ranges from €138 per capita in Poland to €608 per capita in France. It is interesting to notice that Greek and Portuguese pharmaceutical expenditure per capita are higher than for the United Kingdom, at €446, €377 and €339 respectively. The newest Member States still are behind the remaining part of European Union, with pharmaceutical expenditure per capita up to one third that of France.

Table 16. Total pharmaceutical sales in 2011 per country from the society perspective

Country	Retail pharmaceutical sales		Hospital pharmaceutical sales		Total pharmaceutical sales (million euros)	Total population	Total pharmaceutical sales per capita (thousand euros)
	Million euros	% of total	Million euros	% of total			
United Kingdom	13,592	63.9	7,679	36.1	21,271	62,761,350	0.339
Germany	36,322	90.4	3,852	9.6	40,174	82,852,470	0.485
France	30,431	79.8	7,709	20.2	38,140	62,747,780	0.608
Poland	4,303	82.6	910	17.5	5,212	37,725,210	0.138
Greece	5,048	100.0	-	0.0	5,048	11,312,160	0.446
Portugal	2,967	73.6	1,062	26.4	4,029	10,684,970	0.377
Hungary	1,679	82.8	349	17.2	2,028	9,993,116	0.203

Table 17 presents the global pharmaceutical market for 2011 from the healthcare public payer perspective per country and split retail and hospital distribution chain.

Table 17. Total pharmaceutical sales in 2011 per country from the healthcare public payer perspective

Country	Retail pharmaceutical sales		Hospital pharmaceutical sales		Total pharmaceutical sales (million euros)	Total population	Total pharmaceutical sales per capita (thousand euros)
	Million euros	% of total	Million euros	% of total			
United Kingdom	13,592	63.90	7,679	36.10	21,271	62,761,350	0.339
Germany	32,690	90.41	3,467	9.59	36,157	82,852,470	0.436
France	20,997	79.79	5,319	20.21	26,317	62,747,780	0.419
Poland	2,689	82.54	569	17.46	3,258	37,725,210	0.086
Greece	4,038	100.00	-	-	4,038	11,312,160	0.357
Portugal	2,421	73.64	867	26.36	3,288	10,684,970	0.308
Hungary	1,125	82.79	234	17.21	1,359	9,993,116	0.136

When considering the healthcare public payer perspective, it is interesting to notice that France becomes second to Germany despite the public expenditure being about 150% that of Germany. This highlights the low reimbursement level in France compared to Germany.

5.3.2 Franchise to be generics

Table 18 presents the healthcare public payer perspective of total pharmaceutical sales exposed to generic competition per year and per country and Table 19 and Table 20 provide the detail per distribution chain. These tables represent the actual sales in 2011 of products that will become generics during the period of interest and the data are not cumulative.

Table 18. Total (Retail+Hospital) of sales in value (2011 euros) of products going off-patent per country and per year of patent expiry (million euros) from the healthcare public payer perspective

Country	2012	2013	2014	2015	2016	Total
United Kingdom	1,717	448	394	614	294	**3,466**
Germany	1,669	1,069	1,061	1,378	810	**5,987**
France	1,914	782	835	677	460	**4,670**
Poland	4	11	9	33	11	**68**
Greece	213	112	156	88	58	**626**
Portugal	113	87	111	91	58	**459**
Hungary	14	2	19	9	30	**74**

Although in 2012, a turnover of € 1.717 billion is expected to be genericised in the United Kingdom for example, it should be noted that in reality, some products will fall in the public domain at the beginning of the year while others at the end of the year (exact date of patent expiry is available in Appendix 8.6). As such, not all the yearly turnover will be accessible to the generic sales. But this will be the case for the following years.

The franchise to become generics during the period of interest has the highest value in Germany, followed by the United Kingdom and France. Poland displays the smallest value.

Table 19. Retail sales in value (2011 euros) of products going off-patent per country and per year of patent expiry (million euros) from the healthcare public payer perspective

Country	2012	2013	2014	2015	2016	Total
United Kingdom	1,616	291	308	492	94	**2,801**
Germany	1,641	1,028	1,011	1,301	700	**5,680**
France	1,848	744	797	559	351	**4,299**
Poland	3	4	4	29	5	**44**
Greece	213	112	156	88	58	**626**
Portugal	102	54	104	64	23	**346**
Hungary	13	1	18	9	24	**66**

Table 20. Hospital sales in value (2011 euros) of products going off-patent per country and per year of patent expiry (million euros) from the healthcare public payer perspective

Country	2012	2013	2014	2015	2016	Total
United Kingdom	101	157	86	121	201	**666**
Germany	27	41	50	78	110	**307**
France	67	39	38	118	109	**371**
Poland	1	7	6	4	6	**23**
Greece	NA	NA	NA	NA	NA	**NA**
Portugal	11	34	7	26	34	**113**
Hungary	0	1	1	1	6	**8**

For all countries, the largest proportion of franchise to be genericised is obviously originated from retail sales. However, the proportion varies from one country to another. As expected, the United Kingdom displays the largest hospital opportunity for generic franchises of about twice that of France and Germany, while it is the reverse situation on the retail market.

5.3.3 Net pharmaceutical budget impact during 2012-2016 by perspective

Table 21 presents the output of the forecast project during 2012-2016 from the 3 perspectives: manufacturer, society and healthcare public payer.

Table 21. Net pharmaceutical budget impact during 2012-2016 per country and by perspective (million euros)

Country	Manufacturer	Society	Healthcare public payer
United Kingdom	-6,149	- 9,367	-9,367
Germany	-529	- 923	-831
France	-5,009	- 8,100	- 5,589
Poland	55	66	41
Greece	- 657	-1,010	-808
Portugal	- 262	- 298	-243
Hungary	- 96	- 125	-84

Almost all countries will experience drug budget reduction with the exception of Poland which will experience increases. Savings appear to be among the highest for the United Kingdom from all perspectives. This is driven by, on one hand, a high level of savings related to speed and magnitude of generic penetration, and on the other, tight criteria from the National Health Service (NHS) to recommend new entrants that will impact the NHS budget.

This table highlights the very high level of savings in the United Kingdom, followed by France and far behind, at the same level, by Greece and Germany.

The difference between manufacturer prices and public prices is the reflection of, on one side, the pharmaceutical distribution margin, and on the other, the proportion of hospital market share.

It is noticeable that the ratio of ex-factory to public price is among the highest in Germany, France, the United Kingdom, Greece (about 30%) and among the lowest in Hungary (about 14%) (Table 22). This highlights an opportunity for savings, should the health care organization and distribution chain be revisited.

Table 22. Average ratio per country of manufacturer to public price based on global manufacturer and public pharmaceutical sales for 2011

Country	Ratio public/manufacturer price		
	Retail	Hospital	Average
United Kingdom	32%	32%	32%
Germany	39%	0%	35%
France	40%	0%	32%
Poland	26%	24%	25%
Greece	34%	-	34%
Portugal	32%	0%	24%
Hungary	16%	4%	14%

As the model is presented according to three perspectives (healthcare public payer, society and manufacturer), several types of distribution chain (retail, hospital, combined retail and hospital) and several outcomes (savings due to products going off-patent, additional costs due to new entrants products and net budget impact), the results provided an important number of tables, i.e, 27 tables per country accounting for a total of 189 tables for the 7 countries. As such, the healthcare public payer perspective was selected as the base case. All tables and figures related to the pharmaceutical budget impact analysis according to the 3 perspectives for all countries are available in Appendix 8.10.

5.3.4 Net pharmaceutical budget impact per year during 2012-2016 from healthcare public payer perspective

Table 23 (Figure 5) presents the cumulative net budget impact per year and per country for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective.

Table 23. Cumulative net budget impact per year (2011 euros) and per country for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

Country	Budget Impact 2012	Budget Impact 2013	Budget Impact 2014	Budget Impact 2015	Budget Impact 2016
United Kingdom	- 920	- 2,751	-4,961	-7,270	-9,367
Germany	- 402	- 963	-1,376	-1,550	-831
France	- 451	- 1,370	-2,634	-4,145	-5,589
Poland	- 4	5	11	17	41
Greece	- 68	-202	-366	-587	-808
Portugal	- 7	-28	-75	-154	-243
Hungary	-27	-58	-78	- 85	- 84

Figure 5. Cumulative net budget impact per year (2011 euros) and per country for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

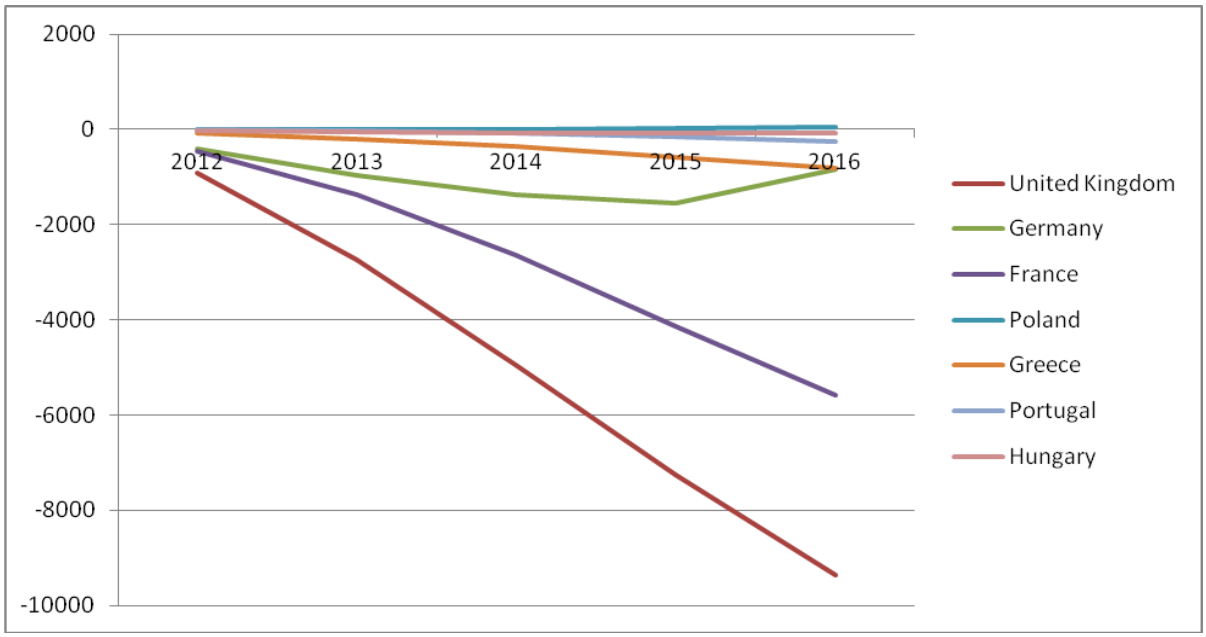


Figure 6, Figure 7, Figure 8, Figure 9, Figure 10, Figure 11 and Figure 12 present the cumulative savings and additional costs for each country for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective.

Figure 6. UNITED KINGDOM-Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

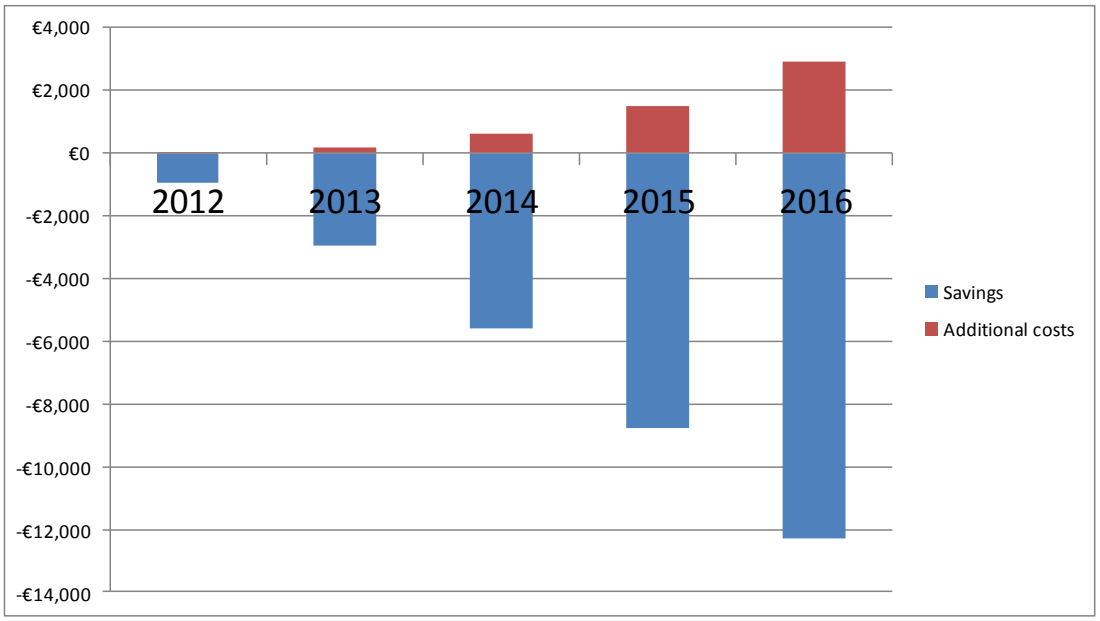


Figure 7. GERMANY-Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

Figure 8. FRANCE- Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

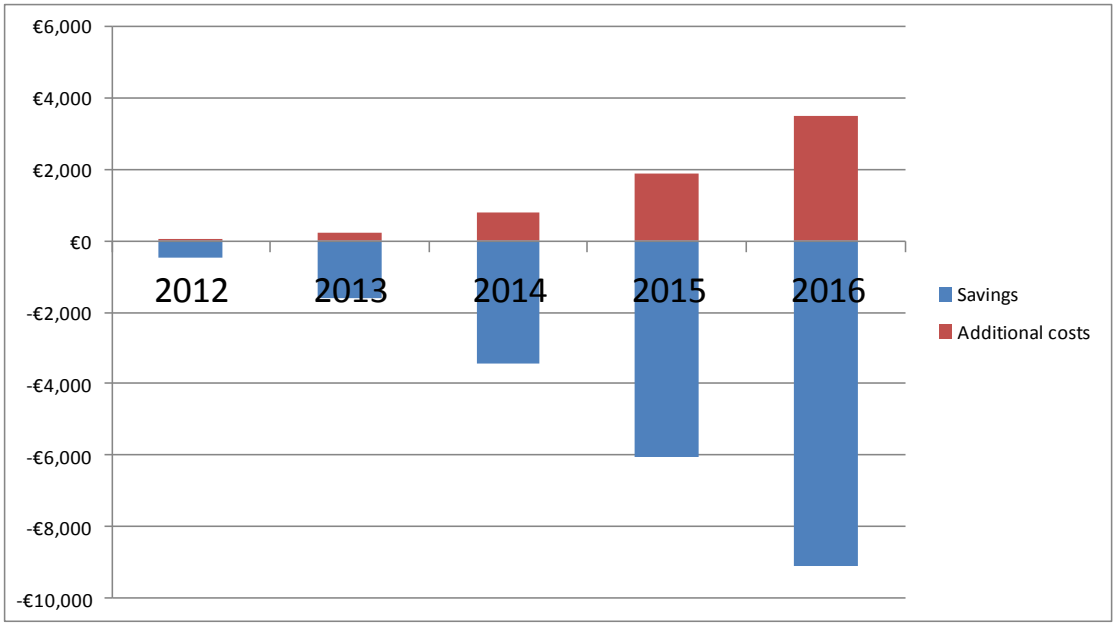


Figure 9.POLAND-Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

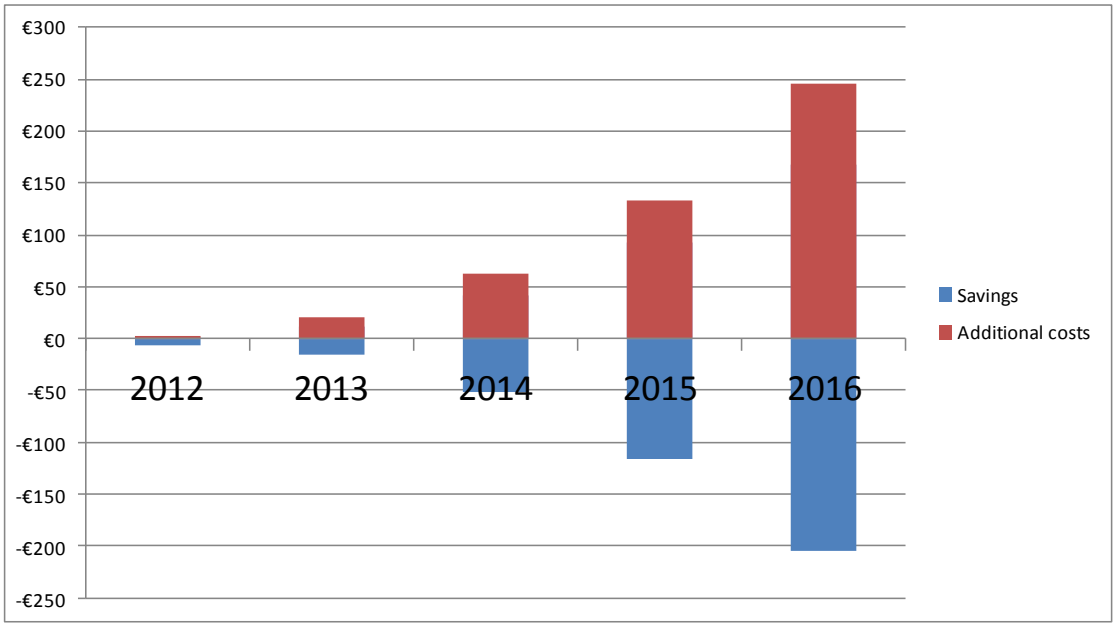


Figure 10.GREECE-Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

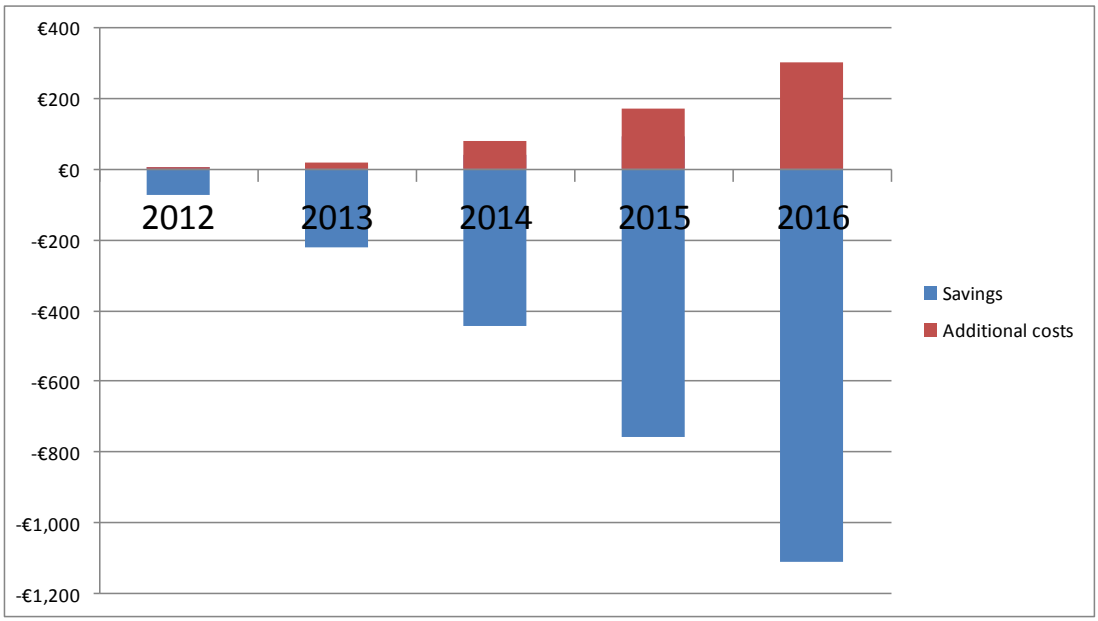


Figure 11.PORTUGAL- Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

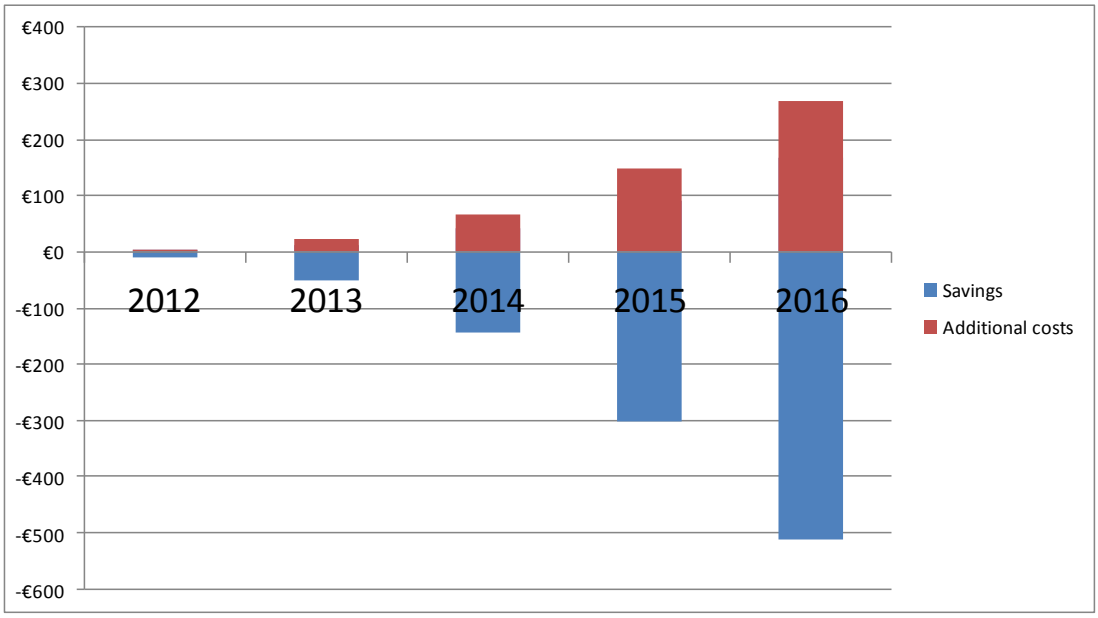
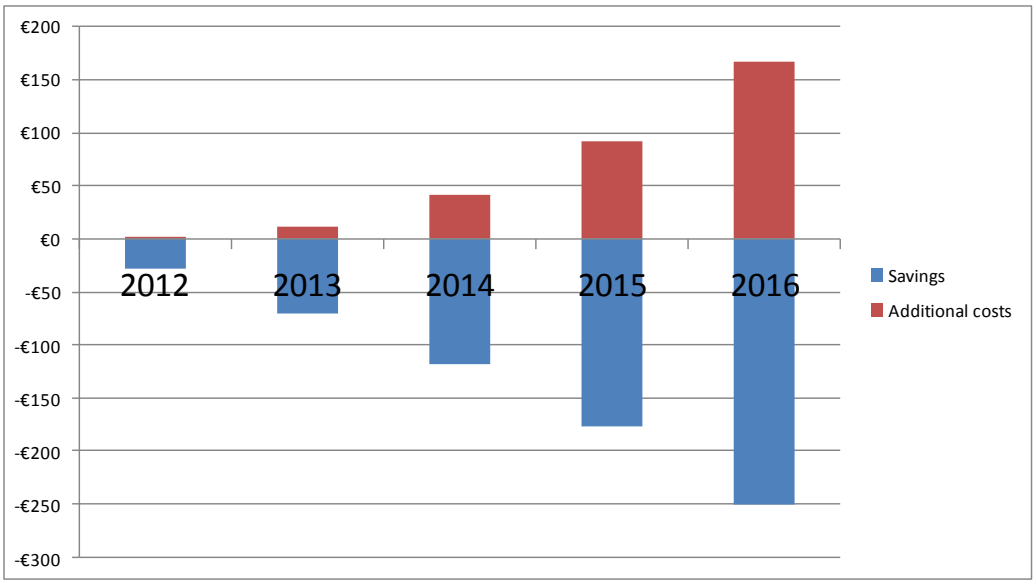


Figure 12. HUNGARY- Cumulative savings and additional costs per year (2011 euros) for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)



When comparing the small countries, one could see that the introduction of new regulation in Greece will have an impact over the coming years with a continuous increase of savings overtime. Portugal, Hungary and Poland undergo few regulation processes to manage the pharmaceutical market and operate under strict cost containment at the level of the medicine price negotiations with the drug agencies. As such, those countries will see the impact on savings becoming smaller over time. In mitigation, one should also acknowledge the very low generic penetration in the Greek market. This would allow room for higher savings when incitative policies are set up to encourage generic uptake.

Table 24 presents the net budget impact per year for retail and hospital pharmaceutical expenditures expressed as percentage of total 2011 pharmaceutical sales from the healthcare public payer perspective.

Table 24. Net budget impact per year and per country for retail and hospital pharmaceutical expenditures expressed as percentage of total 2011 pharmaceutical sales from the healthcare public payer perspective

Country	Budget Impact 2012	Budget Impact 2013	Budget Impact 2014	Budget Impact 2015	Budget Impact 2016
United Kingdom	-4%	-9%	-10%	-11%	-10%
Germany	-1%	-2%	-1%	0%	2%
France	-2%	-3%	-5%	-6%	-5%
Poland	0%	0%	0%	0%	1%
Greece	-2%	-3%	-4%	-5%	-5%
Portugal	0%	-1%	-1%	-2%	-3%
Hungary	-2%	-2%	-1%	-1%	0%

Overall the trends are for a reduction of drugs expenditure overtime except for Poland. The United Kingdom showed the largest savings as it benefits, as explained earlier, from a large hospital market, a high and speedy generic penetration and very stringent criteria for recommendation for use of new branded entrants within the NHS. Germany has a low level of savings as new entrants will continue to enjoy a free pricing for the first year and therefore the access for new branded products will not be delayed. Time to market of new branded products is a critical factor for budget impact.

Table 25(Figure 13,Figure 14), Table 26 and Table 27 present the net pharmaceutical budget impact on the overall period 2012-2016 per country and per therapeutic class from the healthcare public payer perspective for total pharmaceutical expenditures (Hospital+retail), retail pharmaceutical expenditure and hospital pharmaceutical expenditures respectively.

Table 25. Net budget impact during 2012-2016 (2011 euros) per country and per therapeutic class for retail and hospital pharmaceutical expenditures from the healthcare public payer perspective (million euros)

	UK	Germany	France	Poland	Greece	Portugal	Hungary
Anti-infectives	-9	423	413	-15	-11	-43	0.73
Cardiovascular	-3,102	-2,737	-2,850	-8	-457	-75	-70
Central nervous system	-2,137	-1,105	-1,252	38	-262	-6	-14
Endocrinology	-167	-39	-19	-0.02	-41	-4	-0.12
Genito-urinary	-593	-457	-213	-2	-17	-6	-10
Immunology and inflammation	657	1,952	474	58	69	47	37
Musculoskeletal	-229	-521	-412	-0.02	-11	-22	-20
Oncology	939	2,714	839	90	90	60	78
Others	-610	489	-712	9	-57	30	3
Respiratory	-2,093	-535	-729	-2	-96	-3	-68
Biosimilar	-2,023	-1,014	-1,127	-125	-15	-222	-19
Total	**-9,367**	**-831**	**-5,589**	**41**	**-808**	**-243**	**-84**

Figure 13. Net pharmaceutical budget impact during 2012-2016 (2011 euros) per therapeutic class for retail and hospital expenditures from the healthcare public payer perspective for UK, Germany and France (million euros)

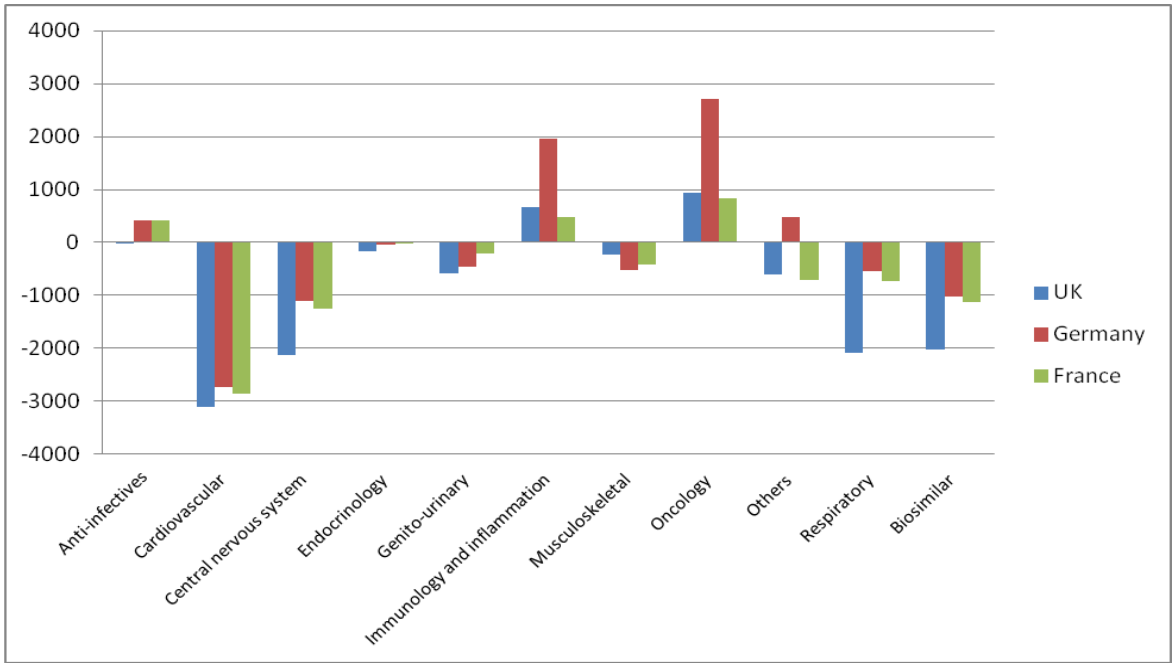
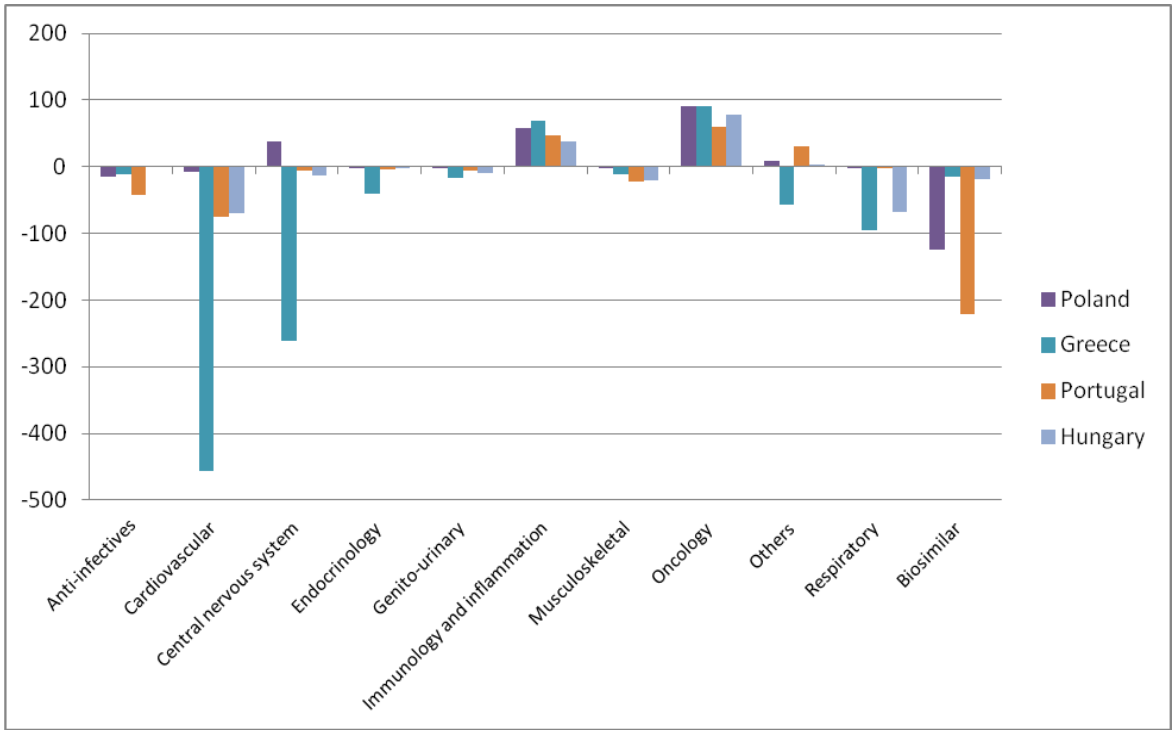


Figure 14. Net pharmaceutical budget impact during 2012-2016 (2011 euros) per therapeutic class for retail and hospital expenditures from the healthcare public payer perspective for Poland, Greece, Portugal and Hungary (million euros)



The cardiovascular and central nervous system areas, followed by the respiratory area and biosimilar entry, account for the most important savings. The impact of biosimilar savings is critically affected by the proportion of hospital distribution. The hospital market allows, through tenders, dramatic price discount while the discount remains fixed and limited through the retail distribution. This was, for example, the case for erythropoietin and filgrastim, which saw their prices going down dramatically at hospital level to an 85% discount on brand price, while such products only enjoy an average of a 30% discount on the retail market. In the United Kingdom, biosimilars will generate twice as much in savings than in France and Germany.

On the other hand, we can see the oncology area being the leading source for additional costs, followed far behind by the immunology and inflammation therapeutic class. This doesn't come as a surprise as these disease areas are the ones where new biologic entities to enter the market with substantial clinical benefits are the largest.

Table 26. Net pharmaceutical budget impact during 2012-2016 (2011 euros) per country and per therapeutic class from the healthcare public payer perspective for the retail expenditure (million euros)

	UK	Germany	France	Poland	Greece	Portugal	Hungary
Anti-infectives	-8	355	92	-1	-11	-3	-0.45
Cardiovascular	-2,699	-2,687	-2,745	-3	-457	-47	-58
Central nervous system	-2,003	-1,059	-1,156	18	-262	-37	-13
Endocrinology	-167	-39	-19	-0.02	-41	-4	-0.12
Genito-urinary	-511	-360	-177	-2	-17	-4	-10
Immunology and inflammation	132	1,694	301	19	69	9	36
Musculoskeletal	-91	-452	-368	-0.02	-11	-3	-20
Oncology	-7	2,041	340	35	90	3	51
Others	-617	240	-812	4	-57	-3	-7
Respiratory	-2,016	-509	-720	-2	-96	-3	-68
Biosimilar	-10	-87	-21	-0.005	-15	-0.76	-4
Total	**-7,997**	**-862**	**-5,284**	**68**	**-808**	**-93**	**- 95**

Table 27. Net pharmaceutical budget impact during 2012-2016 (2011 euros) per country and per therapeutic class from the healthcare public payer perspective for hospital expenditure (million euros)

	UK	Germany	France	Poland	Greece	Portugal	Hungary
Anti-infectives	-0.3	68	320	-14	-	-40	1
Cardiovascular	-404	-50	-105	-5	-	-28	-12
Central nervous system	-133	-46	-96	19	-	31	-0.5
Endocrinology	-0.38	-0.02	-0.023	0	-	0	-0.0003
Genito-urinary	-83	-97	-37	-0.003	-	-2	-0.04
Immunology and inflammation	525	258	172	39	-	38	1
Musculoskeletal	-138	-70	-44	0	-	-18	-0.038
Oncology	946	672	499	55	-	57	26
Others	7	249	100	5	-	33	10
Respiratory	-77	-26	-9	-0.046	-	-0.003	-0.3
Biosimilar	-2,013	-928	-1,106	-125	-	-221	-15
Total	**-1,370**	**31**	**- 305**	**- 27**	**-**	**-151**	**11**

6. Sensitivity analysis

6.1 Deterministic one-way sensitivity analysis

The results of the one-way sensitivity analysis (with all parameters increased and decreased by 30%) are illustrated per country on the tornado diagrams from the healthcare public payer perspective (Figure 15,

Figure **16**, Figure 17,Figure 18, Figure 19,Figure 20 and Figure 21). Tables of results and results from the two other perspectives are available in Appendix 8.2. Overall, apart from Portugal and Poland, two parameters will have the greatest influence on the results of the model: the price reduction of the generics of small molecules versus branded products and the penetration rate of these generics via the retail chain distribution.

In the United Kingdom and in France, 3 parameters have an important impact: the price reduction of the generics of small molecules versus branded products and the penetration rate of these generics via the retail chain distribution but also the reimbursement rate. For the United Kingdom, the other parameters of notes are the penetration rate of biosimilars and the price reduction of the biosimilar versus branded products via the hospital chain distribution. For France, the parameters which follow are the time to reach peak of sales for new entrants used to treat non rare diseases and time to market for the new entrant after marketing approval.

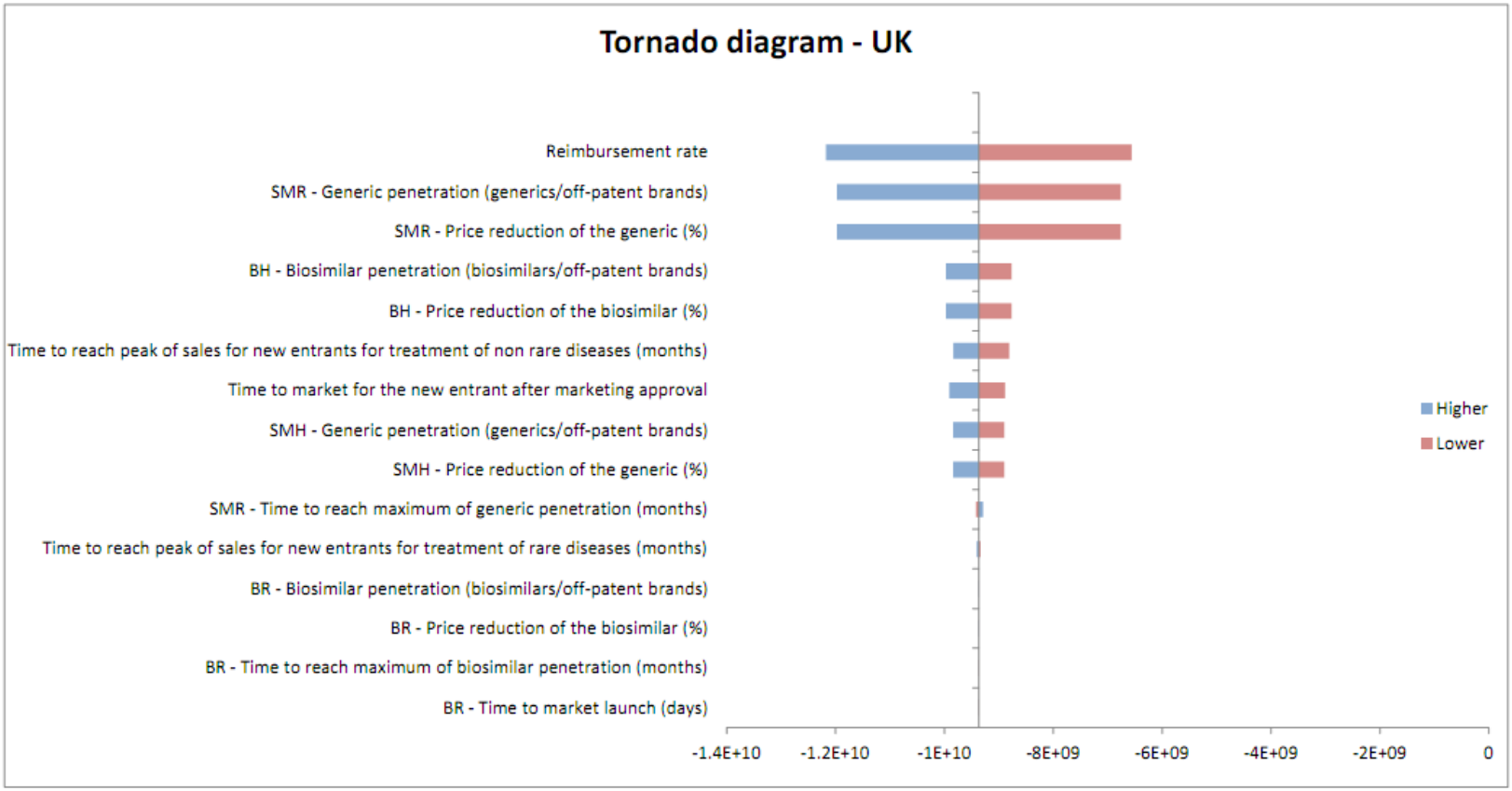
In Germany, the price reduction of the generics of small molecules versus branded products and the penetration rates of these generics via the retail chain distribution are also the main factors impacting the results of the model. The time to reach peak of sales for new entrants used to treat non rare diseases is also an important factor.

In Portugal and Poland, the model is much more sensitive to the variations. We can report the important variation on the hospital distribution chain parameters, first, on the price reduction and penetration rate of biosimilars and then, on the price reduction and penetration rate of generics of small molecules, as critical factors that influence the model outputs.

In Greece, the most important parameters influencing the model are the impact of the entry of the generics of small molecules on the brand price and the reimbursement rate followed, by the price reduction of the generics of small molecules versus branded products via the retail chain distribution.

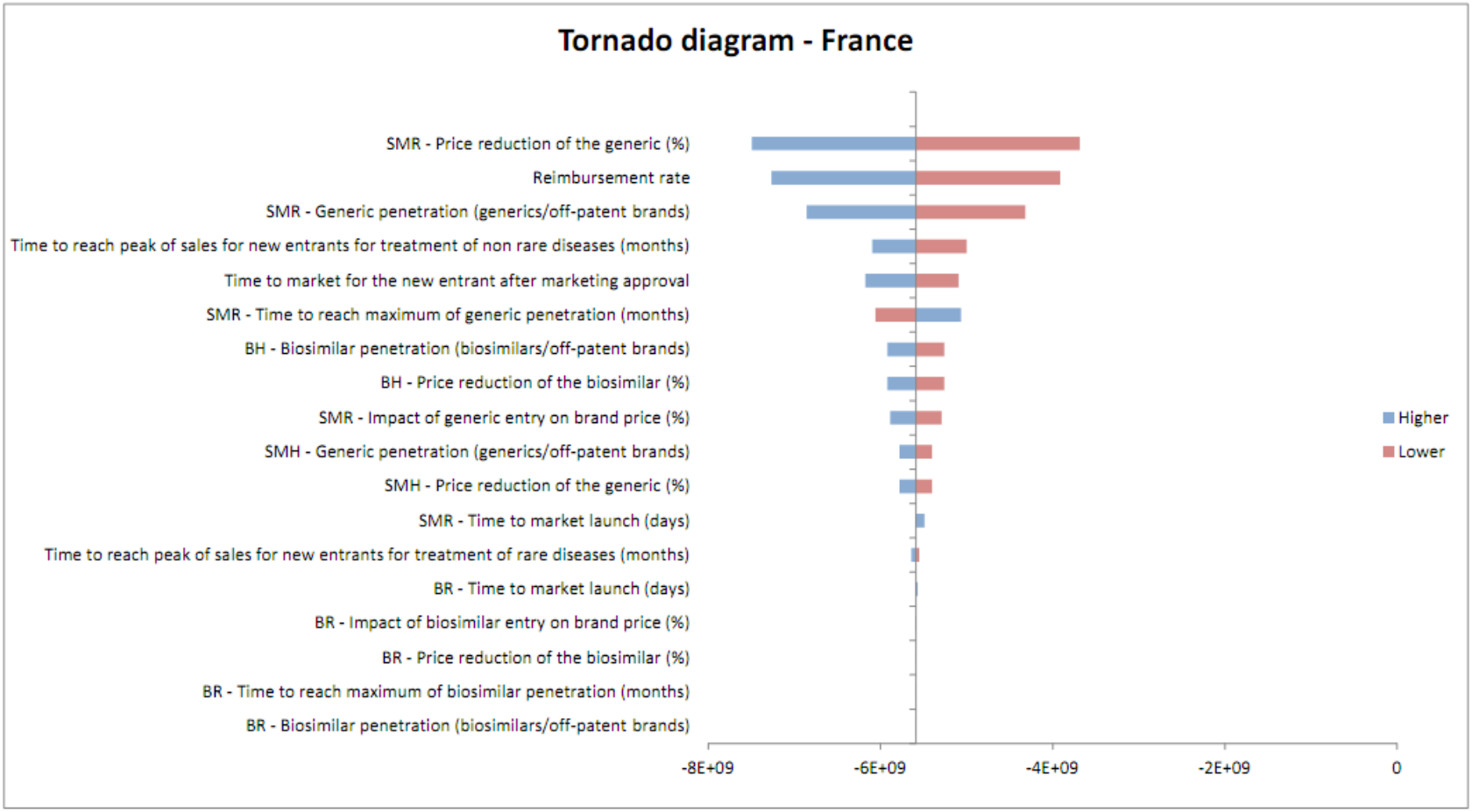
In Hungary, the price reduction of the generics of small molecules versus branded products and the penetration rates of these generics via the retail chain distribution are again the main factors impacting the results of the model.The reimbursement rate is also an important factor.

Figure 15. UNITED KINGDOM-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



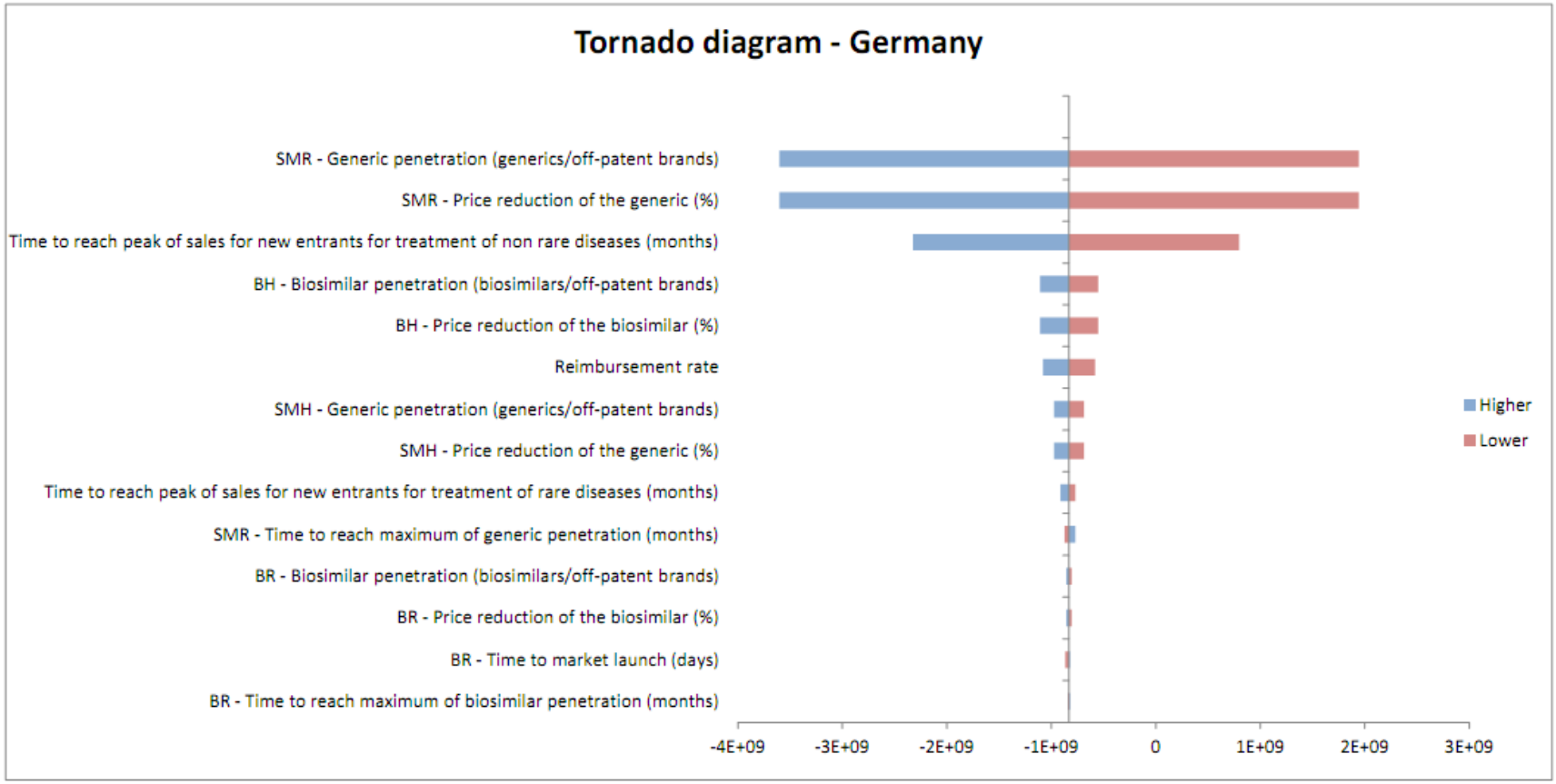
SMR=Small Molecule RetailBH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

Figure 16. FRANCE-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



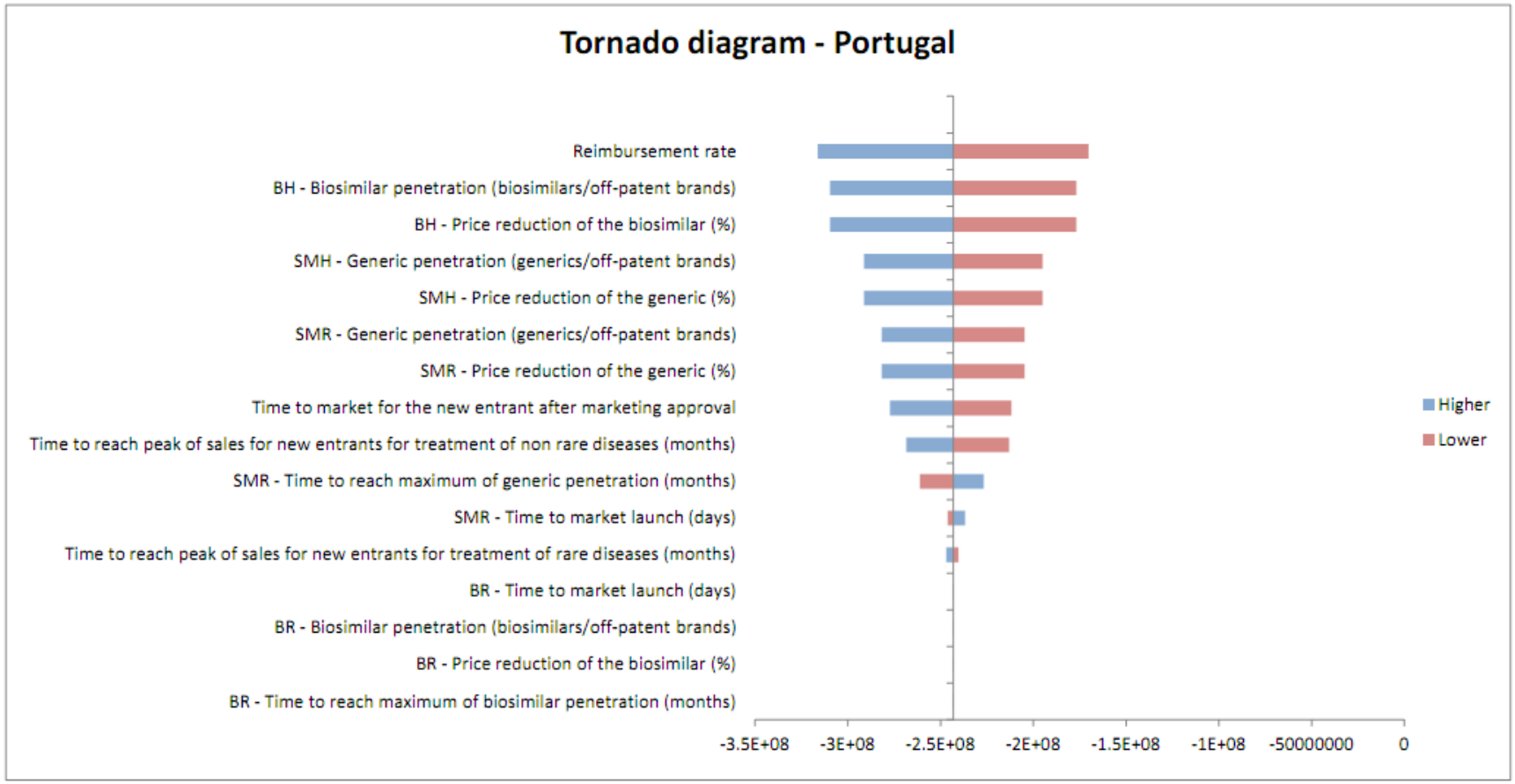
SMR=Small Molecule Retail/BH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

Figure 17. GERMANY-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



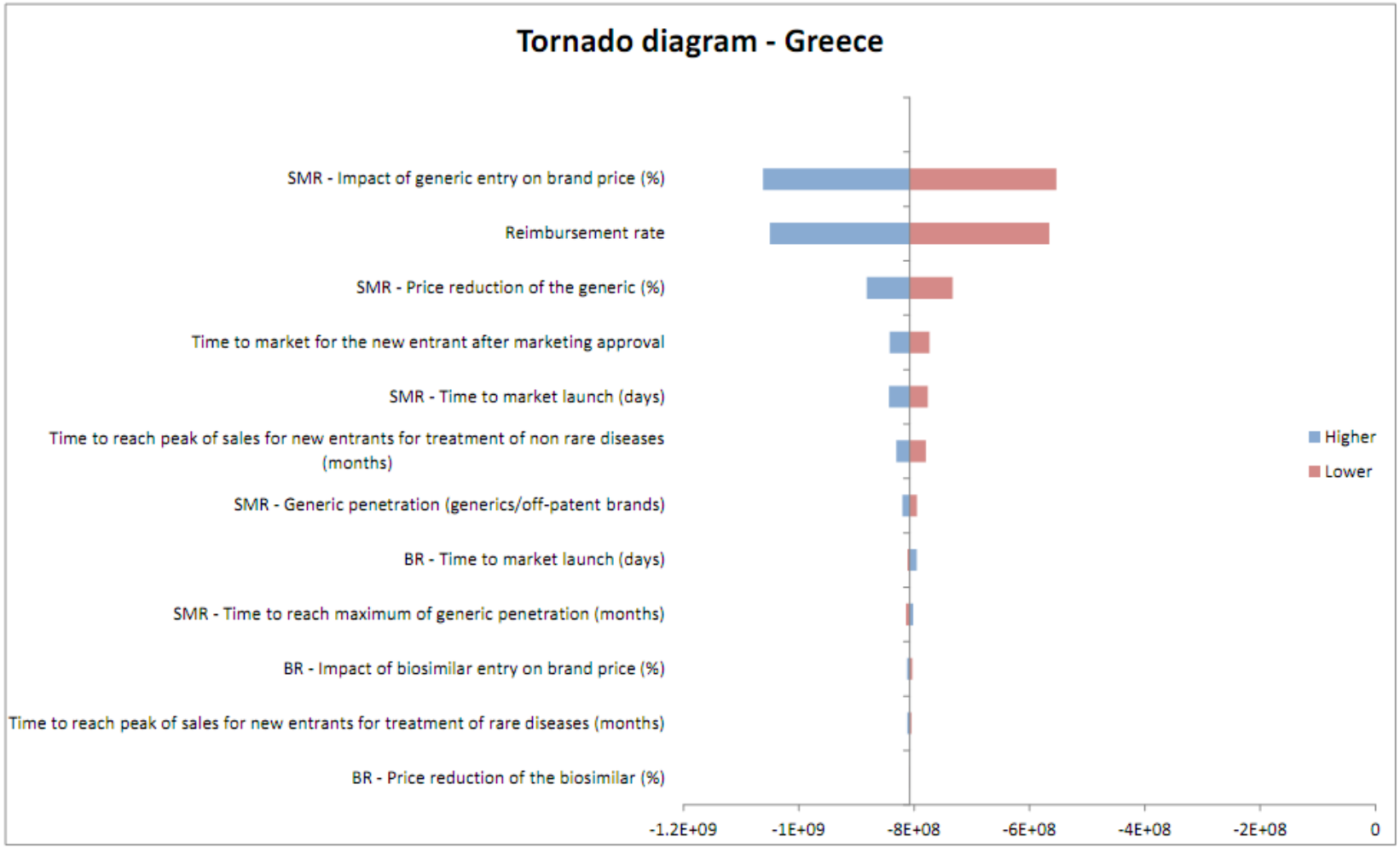
SMR=Small Molecule Retail /BH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

Figure 18. PORTUGAL-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



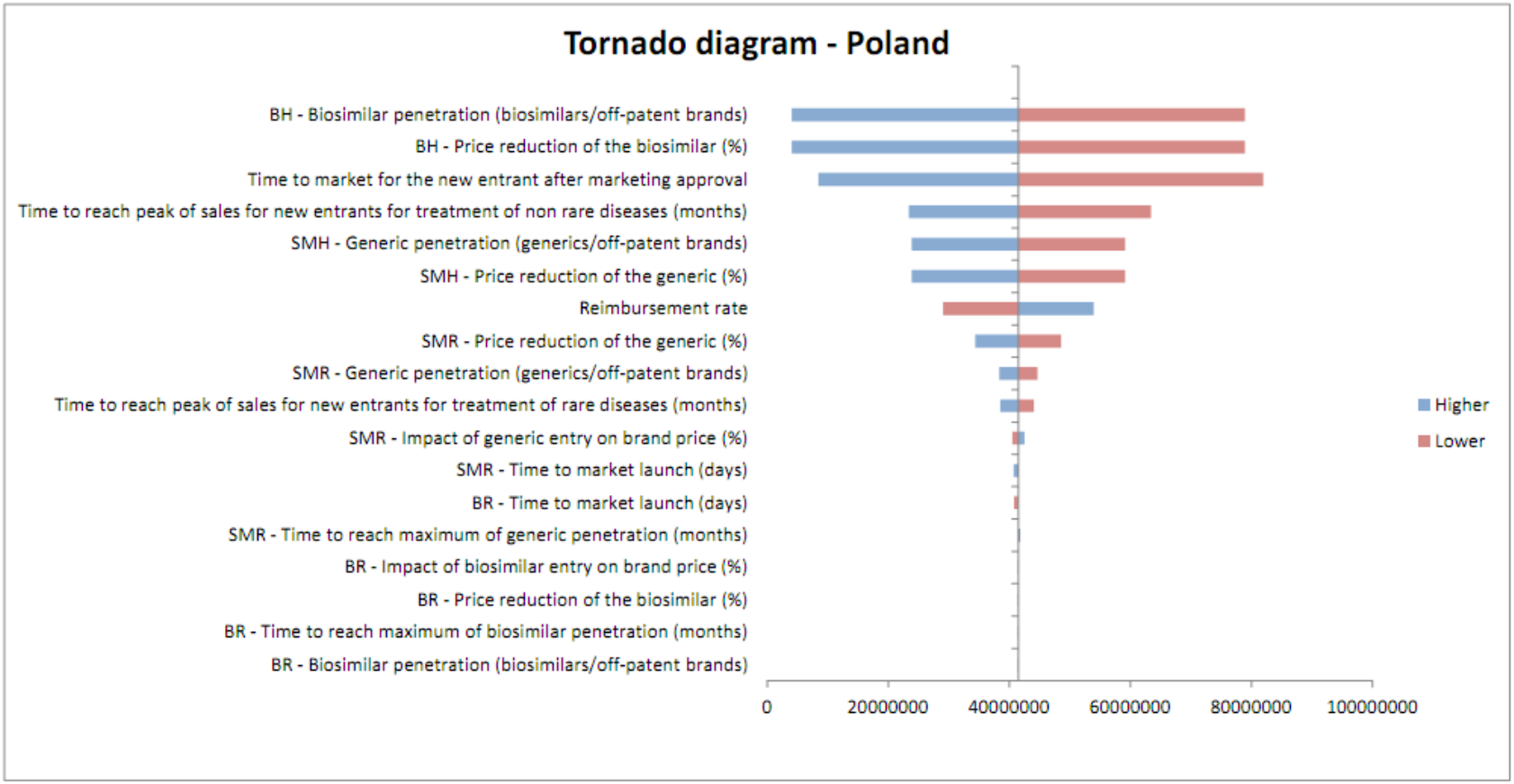
SMR=Small Molecule Retail/ BH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

Figure 19. GREECE-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



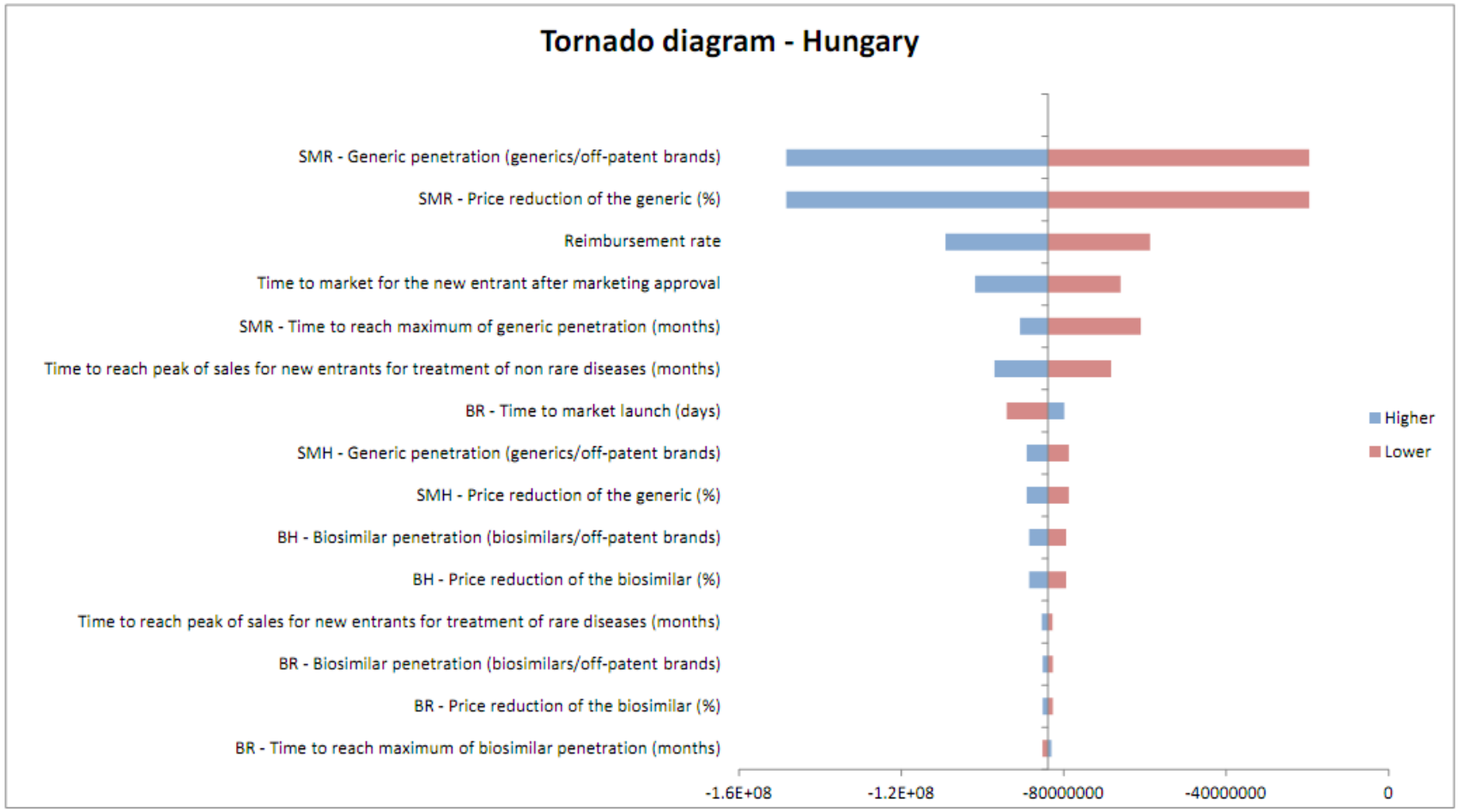
SMR=Small Molecule Retail/BH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

Figure 20. POLAND-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



SMR=Small Molecule Retail/ BH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

Figure 21. HUNGARY-Tornado diagram (with all parameters increased and decreased by 30%)-Change in pharmaceutical budget impact from the healthcare public payer perspective (euros)



SMR=Small Molecule Retail/ BH=Biosimilar Hospital/SMH=Small Molecule Retail/BR=Biosimilar Retail

6.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses were performed, in which the results of 1,000 iterations of the model were averaged to give an estimate of savings, of additional costs and, of net budget impact. The results of the probabilistic sensitivity analyses for additional costs and savings were illustrated per country, by percentage cumulative curves and scatter plots. The percentage cumulative curves show the probability of achieving at least a specific level of net budget impact.

It is important to note that results of a probabilistic sensitivity analysis are very sensitive to laws and ranges of variation chosen. For this analysis, we implemented uniform laws with quite large uncertainties, even on well-known parameters, to cover a large scope of scenarios.

In Germany (Table 28, Figure 24 and Figure 25), probabilistic sensitivity analysis showed a very low net budget impact compared to the base case. In fact, half of the simulations were between €-3,203 and €-1,116 million with a base case at €-831 million. It is due to the fact that time to market for the new entrant after marketing approval was fixed to zero in the base case that the only evolution of this parameter in the sensitivity analyses was an increased time. This provides an asymmetric variation in one signle direction as time to market could not be negative.Moreover, it was shown that this parameter is a key driver of the results; it could be interesting to performed the sensitivity analysis without this parameter.

In France, the 75th percentile of the net budget impact distribution was approximately €-4,883 million (Table 28, Figure 26 and Figure 27) from the healthcare payer perspective, i.e., according to our distributions, France has 75% chance of performing at least €-4,883 million. Half of the simulations were between €-6,252 and €-4,883 million. The projected net budget impact for France was not altered with variations in parameters. Similar results are presented for other countries in Table 28 and Figure 22,

Figure 23, Figure 28, Figure 29, Figure 30, Figure 31, Figure 32, Figure 33, Figure 34 and Figure 35.

Table 28. Summary of results of the probabilistic sensitivity analysis- Budget impact (Euros) by perspective

		Budget Impact (Euros)		
		Society	Manufacturer	Healthcare public payer
United Kingdom	Mean	-9,514,558,303	-6,241,813,897	-9,274,550,903
	Median	-9,471,510,547	-6,213,886,871	-9,193,337,688
	Q1 ; Q3	-10,393,444,163 ; -8,584,715,360	-6,825,052,931 ; -5,626,898,010	-10,133,934,500 ; -8,359,360,816
Germany	Mean	-2,390,632,787	-1,449,510,286	-2,153,160,796
	Median	-2,371,904,560	-1,433,942,695	-2,113,031,908
	Q1 ; Q3	-3,474,014,049 ; -1,234,612,586	-2,175,511,686 ; -716,205,201	-3,203,238,727 ; -1,116,275,428
France	Mean	-8,116,938,653	-4,996,765,442	-5,590,275,131
	Median	-8,044,568,982	-4,957,955,439	-5,511,270,453
	Q1 ; Q3	-9,030,178,949 ; -7,128,169,893	-5,589,573,792 ; -4,375,290,995	-6,251,750,586 ; -4,883,272,318
Poland	Mean	81,543,514	66,700,070	50,999,972
	Median	83,300,144	68,117,139	52,064,941
	Q1 ; Q3	49,015,414 ; 112,270,659	41,944,579 ; 90,040,851	29,791,461 ; 71,459,409
Greece	Mean	-1,050,058,033	-683,385,295	-840,017,660
	Median	-1,046,185,687	-680,130,103	-836,503,588
	Q1 ; Q3	-1,165,450,815 ; -942,831,488	-758,434,472 ; -613,649,598	-923,458,403 ; -751,333,082
Portugal	Mean	-348,781,518	-281,851,214	-284,706,536
	Median	-344,125,197	-276,511,541	-280,252,414
	Q1 ; Q3	-418,386,208 ; -275,178,836	-340,813,791 ; -221,174,290	-341,609,301 ; -224,143,837
Hungary	Mean	-145,243,460	-111,639,443	-97,342,729
	Median	-142,700,796	-109,216,470	-95,216,498
	Q1 ; Q3	-183,158,536 ; -104,230,652	-143,921,701 ; -76,960,493	-123,141,017 ; -69,602,671

Figure 22. UNITED KINGDOM- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

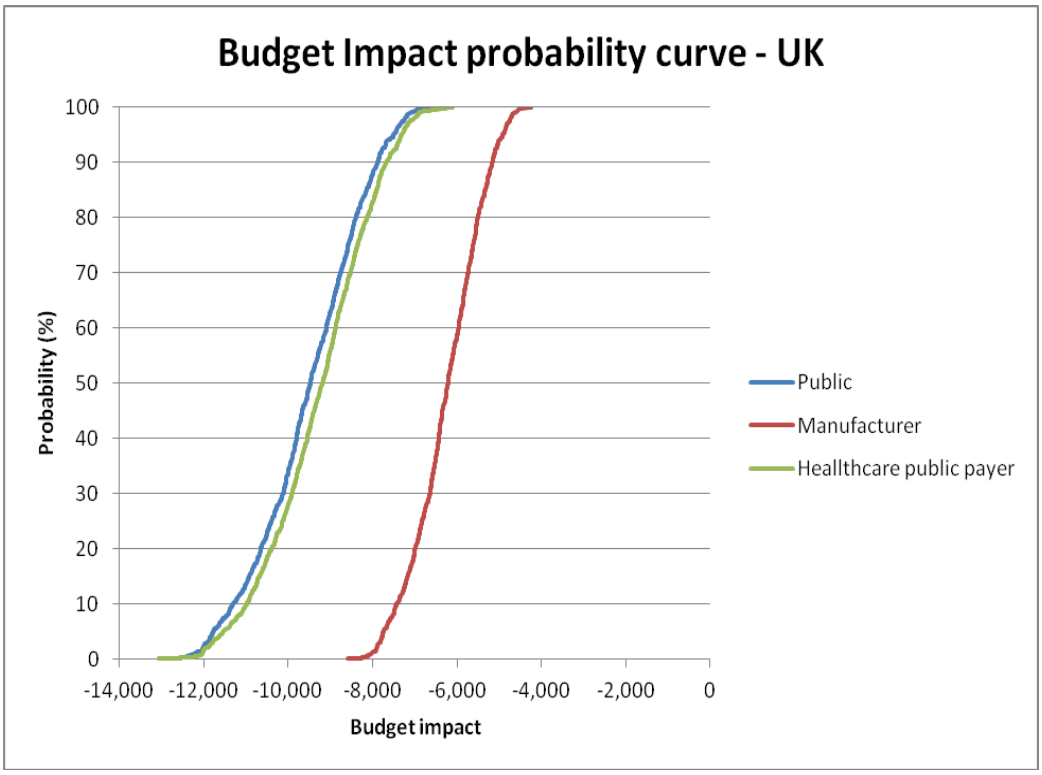


Figure 23. UNITED KINGDOM- Probabilistic sensitivity analysis-Scatter plot (million euros)

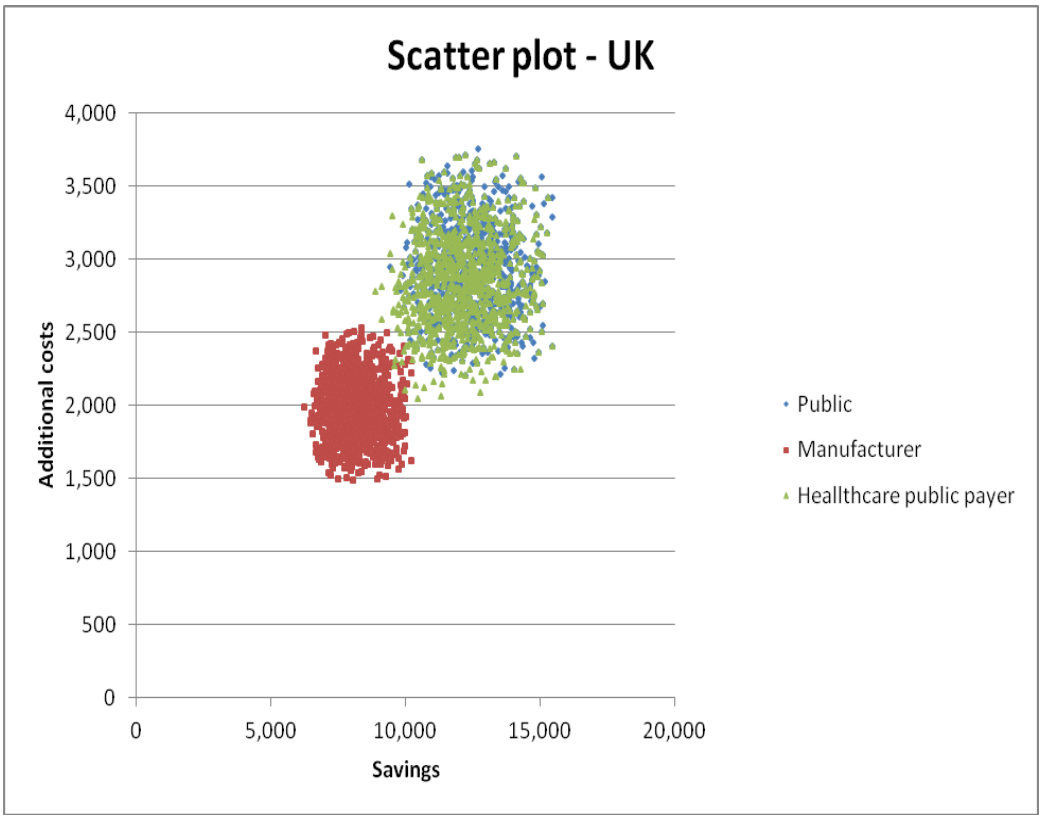


Figure 24.GERMANY- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

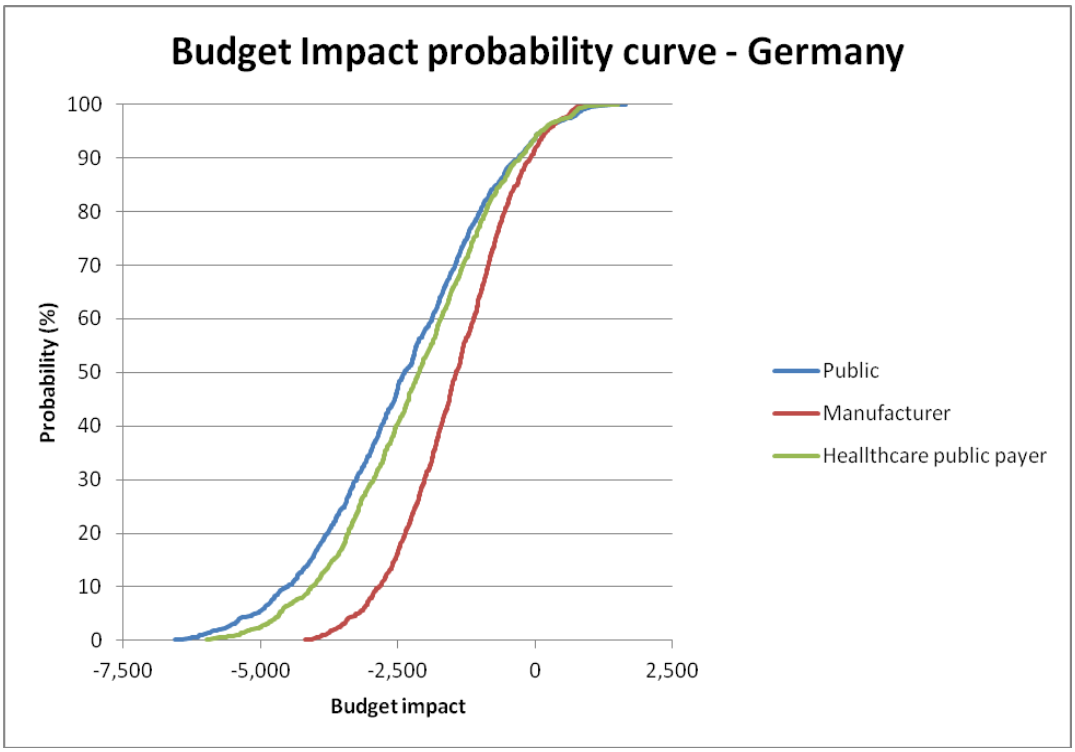


Figure 25. GERMANY- Probabilistic sensitivity analysis-Scatter plot (million euros)

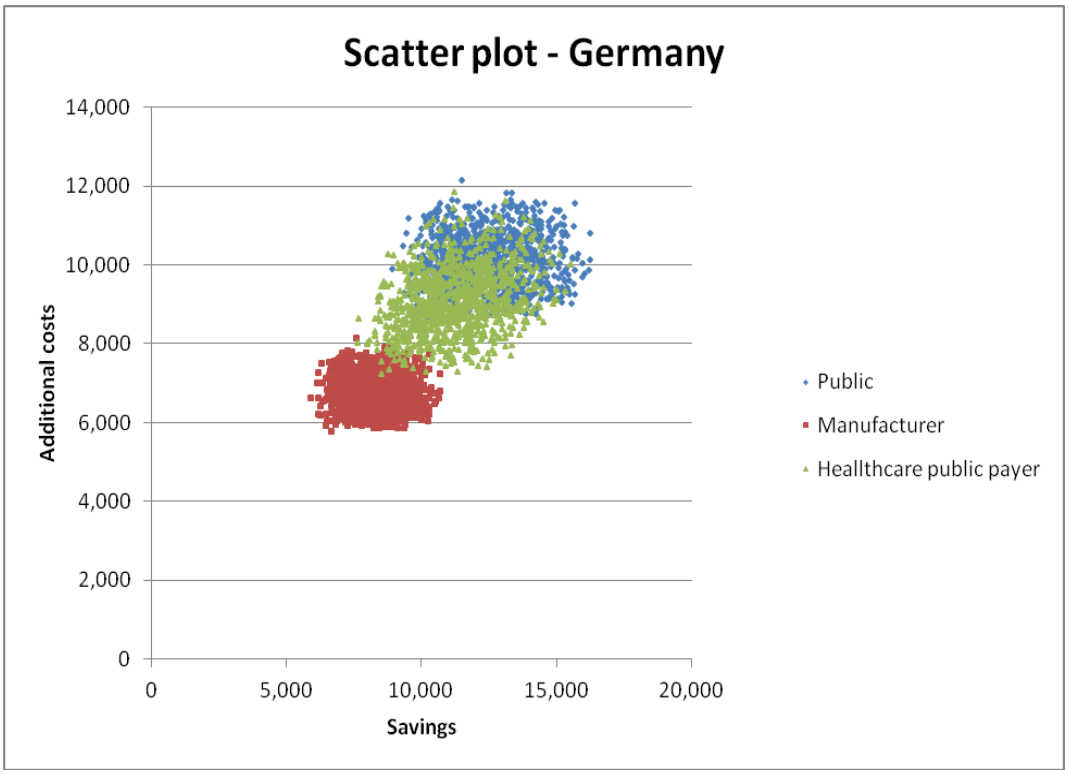


Figure 26. FRANCE- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

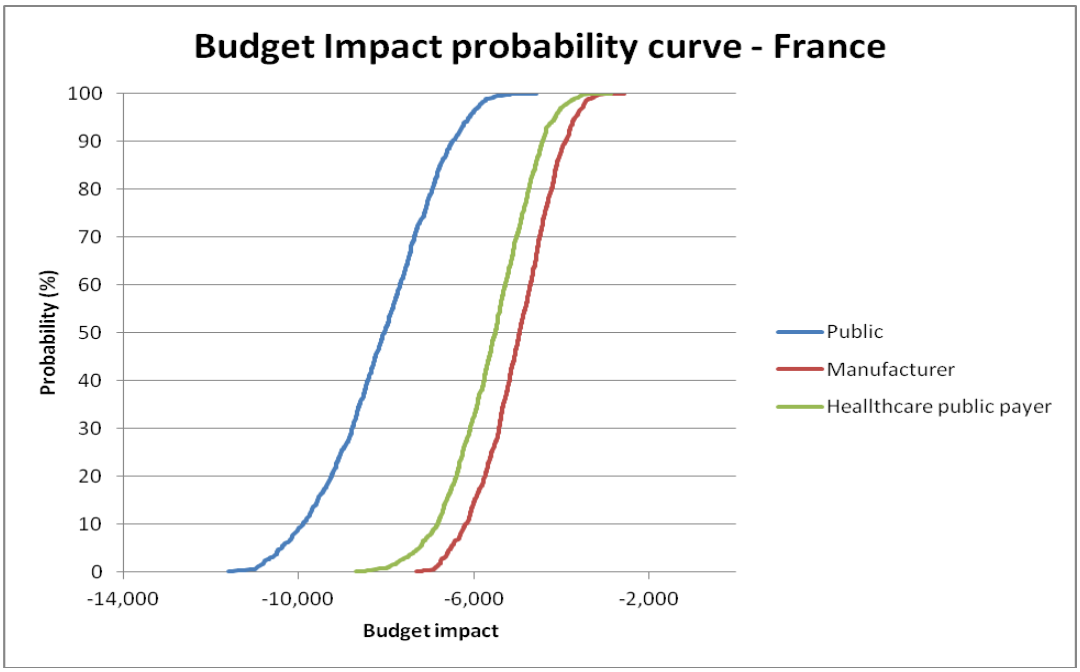


Figure 27. FRANCE- Probabilistic sensitivity analysis-Scatter plot (million euros)

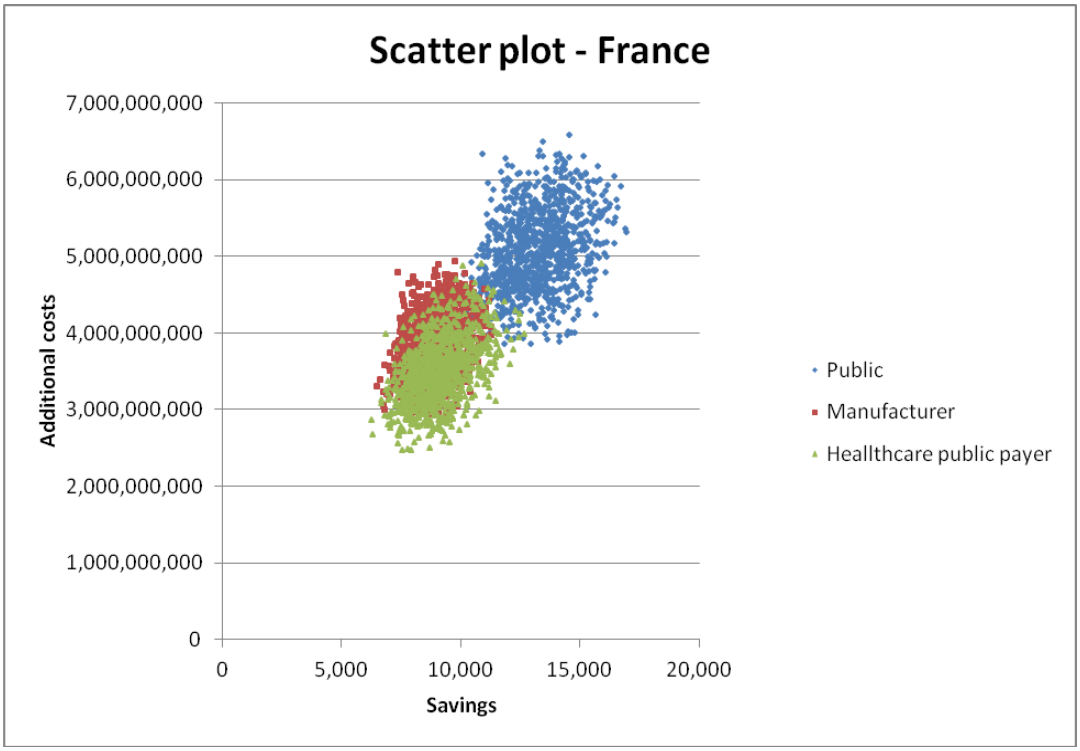


Figure 28. POLAND- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

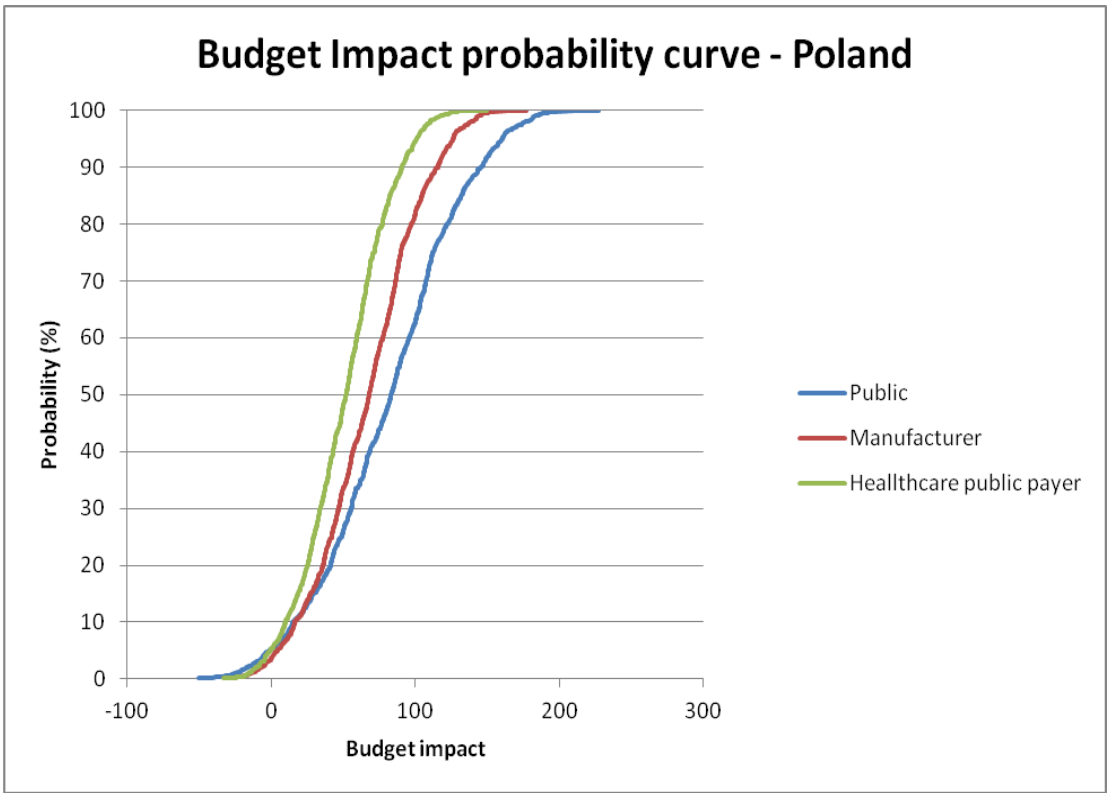


Figure 29.POLAND- Probabilistic sensitivity analysis-Scatter plot (million euros)

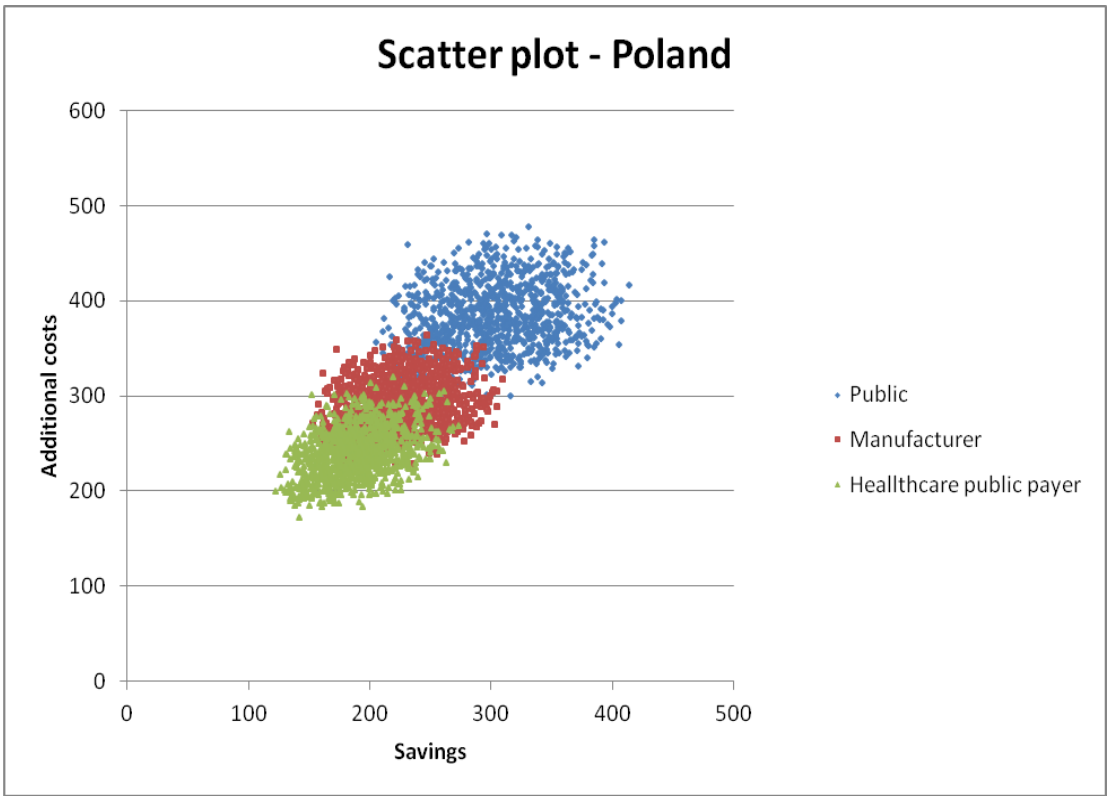


Figure 30. GREECE- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

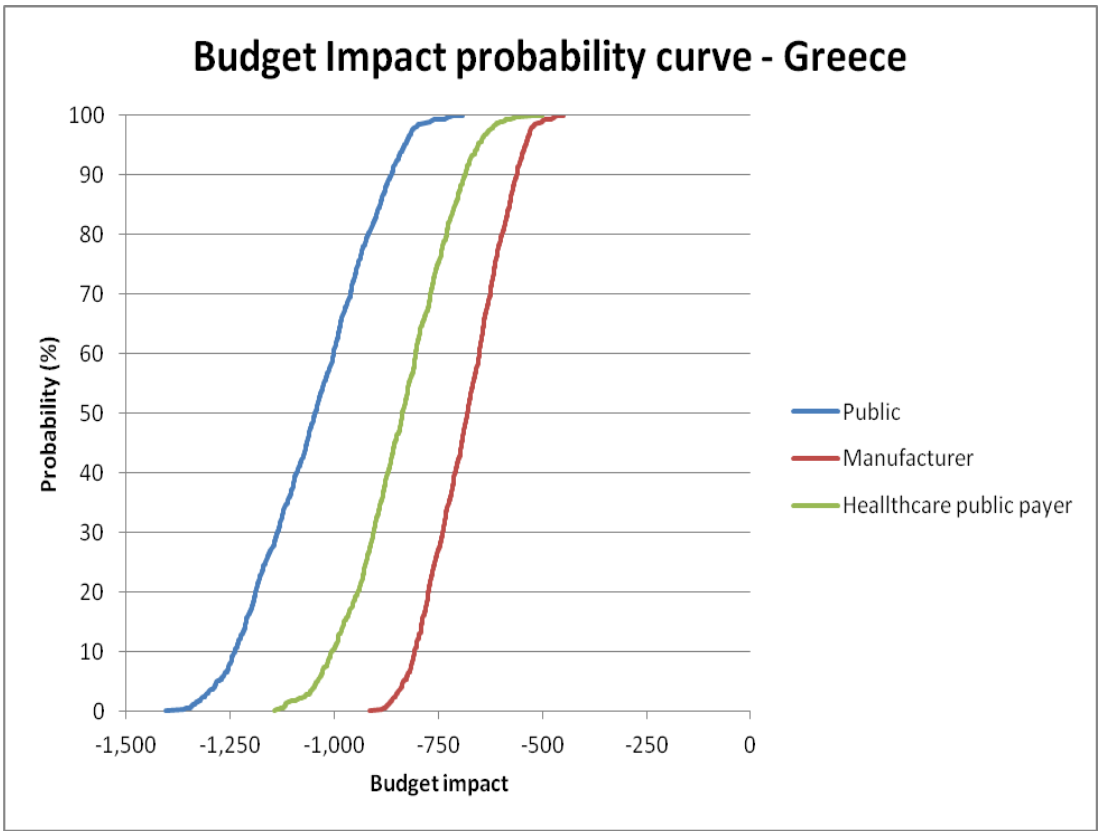


Figure 31. GREECE- Probabilistic sensitivity analysis-Scatter plot (million euros)

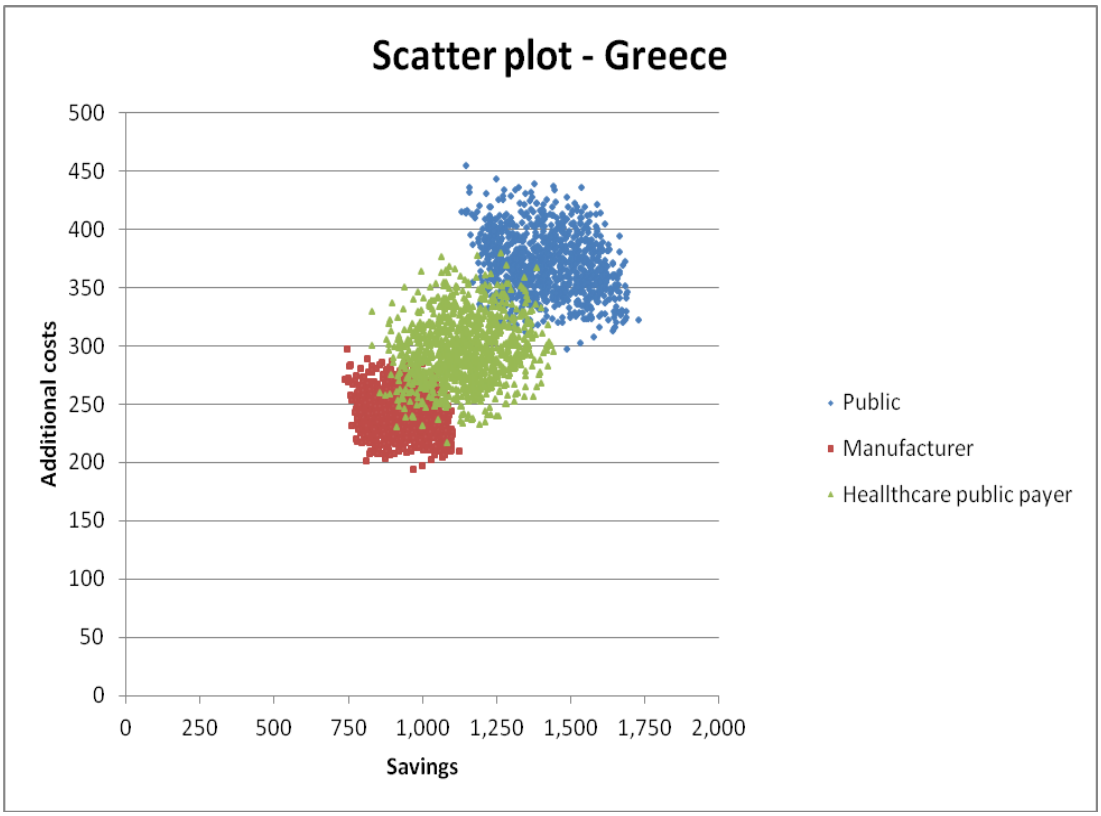


Figure 32. PORTUGAL- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

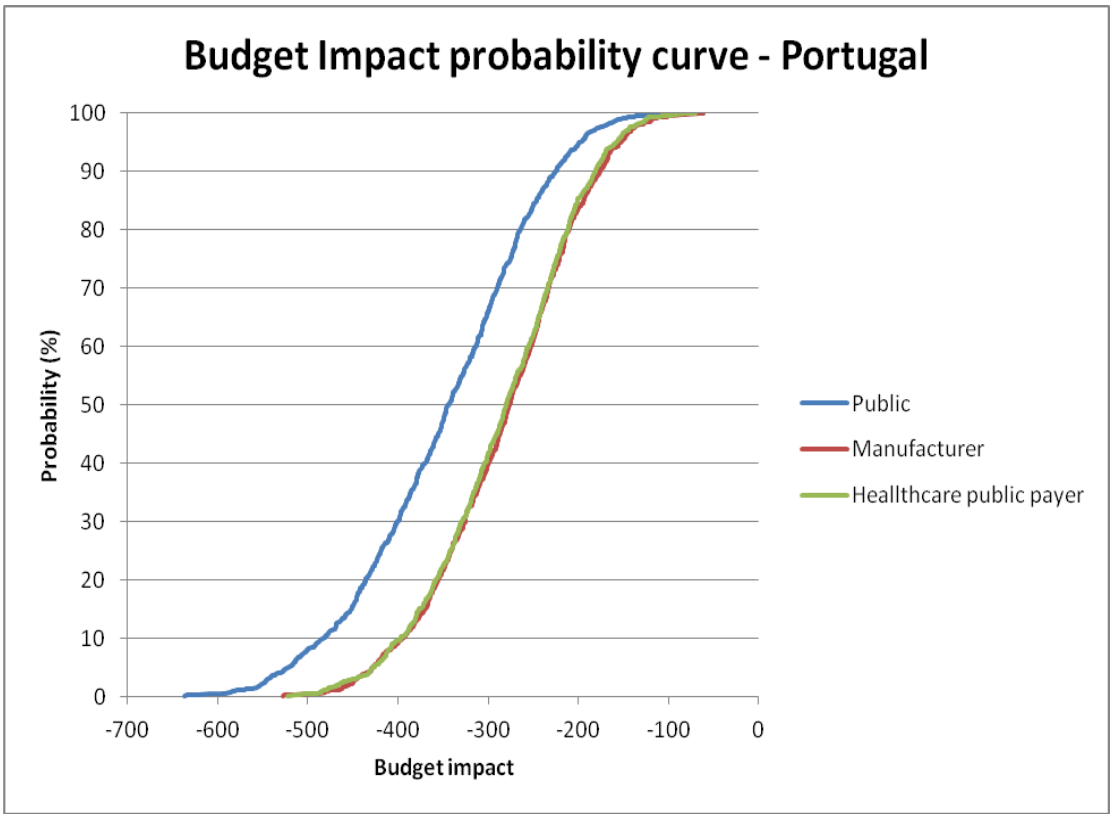


Figure 33. PORTUGAL- Probabilistic sensitivity analysis-Scatter plot (million euros)

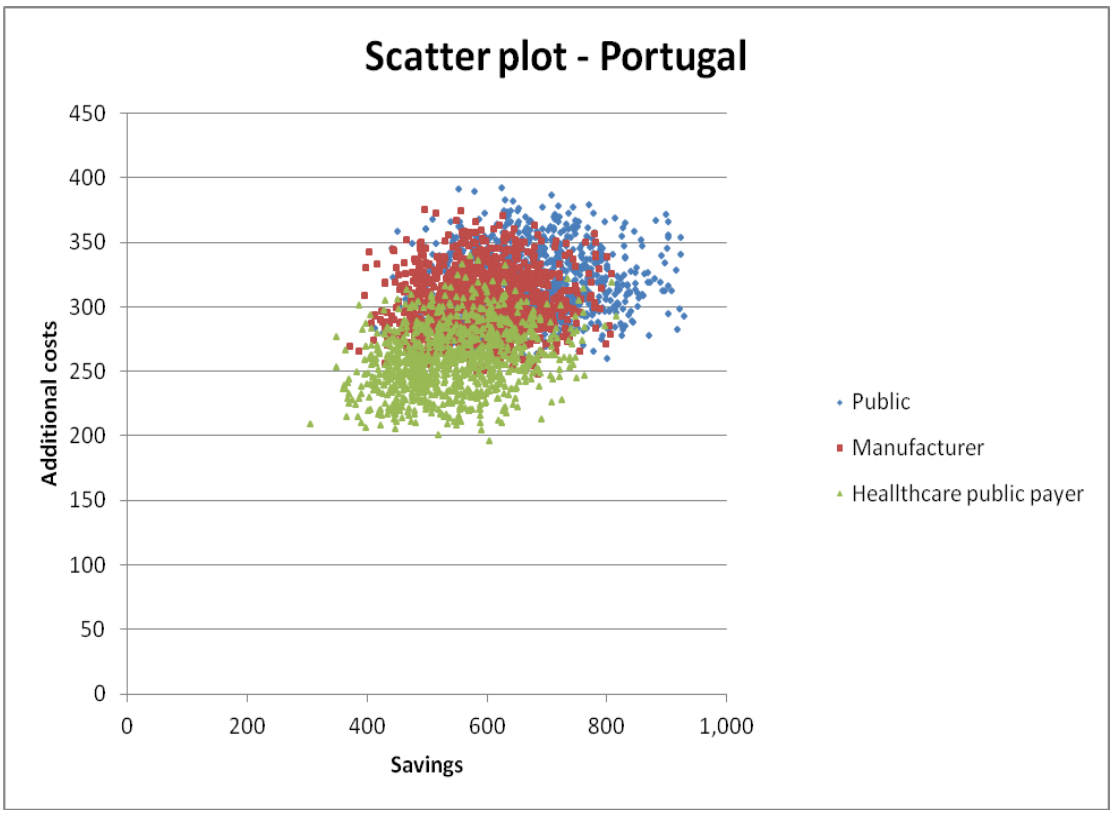


Figure 34. HUNGARY- Probabilistic sensitivity analysis-Budget impact probability curve (million euros)

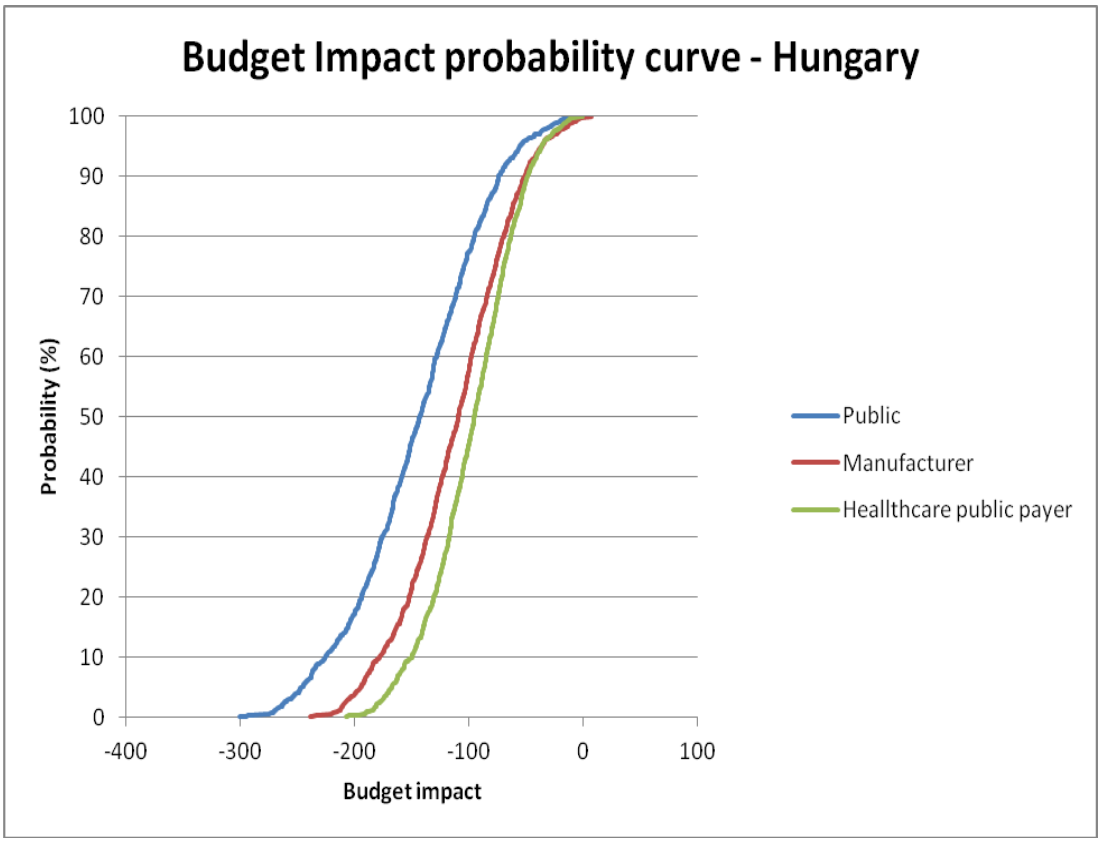
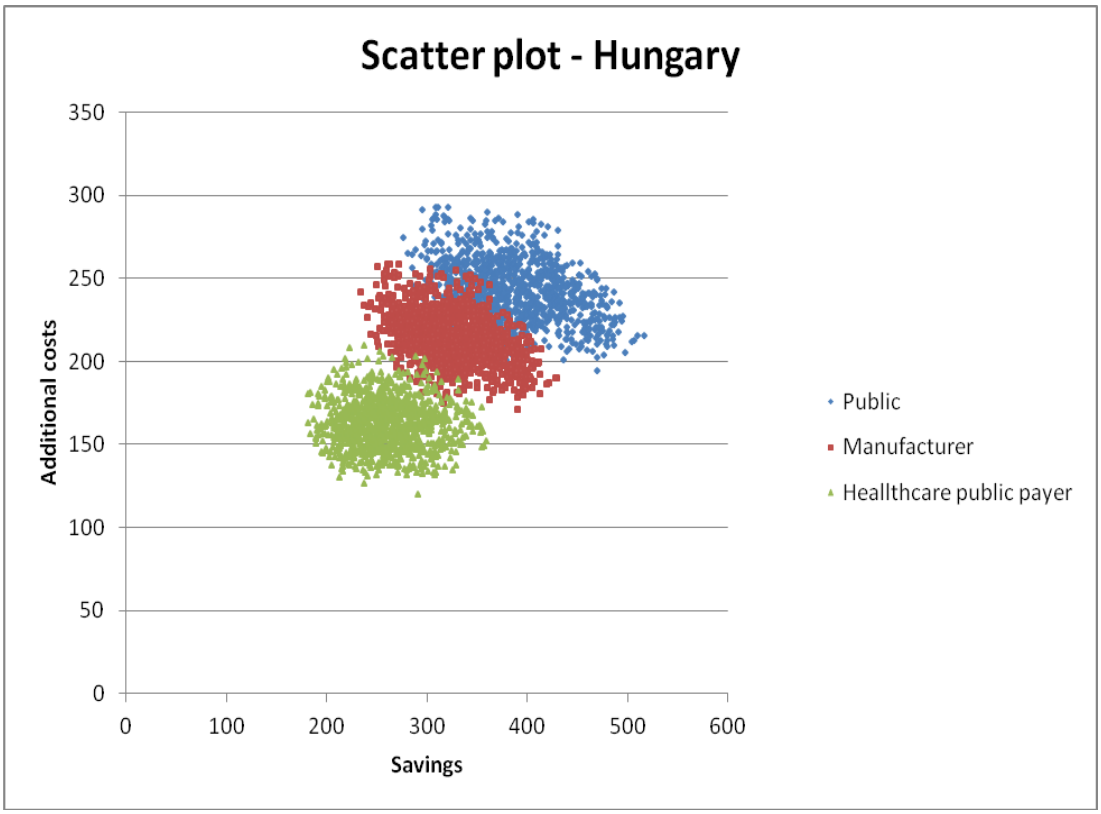


Figure 35. HUNGARY- Probabilistic sensitivity analysis-Scatter plot (million euros)



6.3 Impact of Pharmaceutical policies' changes

In order to inform policy decision makers we have built a number of scenarios that were reviewed and amended by the study board of experts. The scenarios are presented below.

6.3.1 Scenario 1-Pharmaceutical policies of the United Kingdom applied to all other countries

Table 29-Scenario 1- Pharmaceutical policies of the United Kingdom applied to all other countries- Net budget impact 2012-2016 (2011 euros) and per country for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 1
United Kingdom	-9,367	-9,367
Germany	-831	- 8,445
France	-5,589	-10,796
Poland	41	42
Greece	-808	-1,199
Portugal	-243	- 951
Hungary	- 84	- 76

It was not unexpected that Germany would experience the widest changes under this scenario, with up to 10 times more savings. Germany and the United Kingdom are on the opposite sides of each other in terms of health policies and health care systems. France and Portugal would also enjoy substantial additional savings under this scenario. Those savings are mainly driven by the increase in generic and biosimilar policies while the new entrants have a lesser impact to explain the changes except for Germany, as delayed entry is an important driver.

6.3.2 Scenario 2- Change in time to market for the new entrant after marketing approval for Germany to one year

Table 30. Scenario 2- Change in time to market for the new entrant after marketing approval for Germany to one year- Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 2
Germany	-831	- 5,016

This scenario exemplifies the importance of the time to market for new entrants. Indeed, an immediate entry of a new drug accounts for an important benefit to patients as they will get access to new products from the date of the marketing authorization, while it is dramatically delayed in other European Union countries including the United Kingdom.

It is questionable how important it is to get access to new drugs from day one; it is certainly important for new breakthrough medicines, but questionable for me-too drugs.

6.3.3 Scenario 3- Change in time to market for the new entrant after marketing approval for all countries to 6 months

Table 31. Scenario 3 -Change in time to market for the new entrant after marketing approval for all countries to 6 months- Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 3
United Kingdom	-9,367	-8,339
Germany	-831	-3,099
France	-5,589	-4,554
Poland	41	163
Greece	-808	-705
Portugal	-243	-155
Hungary	- 84	-25

Scenario 3 replicates the European Union transparency directive that aims at a 6 month-process for pricing and reimbursement. Therefore, we thought that it would be interesting to assess the potential impact of enforcing that directive on the Member States selected for our project. Except for Germany, which will increase savings, all Member States will experience a substantial reduction of their potential savings.

6.3.4 Scenario 4- Change in time to market for the new entrant after marketing approval for all countries to 0 months

Table 32. Scenario 4 -Change in time to market for the new entrant after marketing approval for all countries to 0 months- Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 4
United Kingdom	-9,367	-7,083
Germany	-831	-831
France	-5,589	-3,363
Poland	41	337
Greece	-808	-575
Portugal	-243	-49
Hungary	- 84	49

These pieces of data evidence the large impact of time to access of new branded products on the net pharmaceutical budget impact.

6.3.5 Scenario 5-Change in the level of reimbursement rate for all countries to 100%

Table 33. Scenario 5 -Change in the level of reimbursement rate of all countries to 100%- Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 5
United Kingdom	-9,367	-9,367
Germany	-831	-923
France	-5,589	-8,100
Poland	41	66
Greece	-808	-1,010
Portugal	-243	-298
Hungary	- 84	-125

This scenario is complex to interpret as it has two dimensions:

On one side, the proportion of expenditure will dramatically increased in all countries except in the United Kingdom. Indeed, healthcare public payers will have to pay, as per 2011, the proportion not paid today when the reimbursement rate is below 100%. This means that healthcare public payers and the society perspective become equal. The current model ignores that information and provides counter intuitive results, which could only be clarified if the reimbursement rate is applied to the whole expenditure and not only the difference.

The other dimension is the increased savings. As most of the countries experience savings, we expect the net balance to increase by the proportion that becomes reimbursed.

6.3.6 Scenario 6- Change in the price reduction of generics (through retail chain) for all countries to 75%

Table 34. Scenario 6-Change in the price reduction of generics (through retail chain) for all countries to 75%-Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 6
United Kingdom	-9,367	-9,367
Germany	-831	-4,191
France	-5,589	-7,176
Poland	41	26
Greece	-808	-870
Portugal	-243	-275
Hungary	- 84	-162

This scenario shows the high sensitivity of the savings to the generic price. Generic price reductions offer a very robust leverage to increase savings.

6.3.7 Scenario 7- Change in the price reduction of generics (through retail chain) for all countries to 85%

Table 35. Scenario 7-Change in the price reduction of generics (through retail chain) for all countries to 85%-Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 7
United Kingdom	-9,367	-10,526
Germany	-831	-5,871
France	-5,589	-8,234
Poland	41	20
Greece	-808	-912
Portugal	-243	-297
Hungary	- 84	-201

This scenario again shows the high sensitivity of the savings to the generic price.

6.3.8 Scenario 8-Change in the generic penetration rate (through retail chain) for all countries to 100%

Table 36. Scenario 8-Change in the generic penetration rate (through retail chain) for all countries to 100%-Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 8
United Kingdom	-9,367	-11,540
Germany	-831	-2,461
France	-5,589	-6,647
Poland	41	40
Greece	-808	-932
Portugal	-243	-628
Hungary	- 84	-84

This scenario also shows the high sensitivity of the savings to the generic penetration rate, except for Poland. Indeed, with an initial penetration rate of 85%, Poland would experience few additional savings with a 100% generic penetration rate.

6.3.9 Scenario 9-Change in the distribution chain of biosimilars for all countries restricted to hospital

Table 37. Scenario 9-Change in the distribution chain of biosimilars for all countries restricted to hospital-Total savings linked to biosimilars 2012-2016 (2011 euros) from healthcare public payer perspective (million euros)

Country	Savings biosimilars 2012-2016 Base case	Savings biosimilars 2012-2016 Scenario 9
United Kingdom	2,023	2,376
Germany	1,127	4,519
France	1,634	3,318
Poland	200	237
Greece	19	225
Portugal	272	337
Hungary	29	205

This information is also very useful for health policy decision makers. Indeed, it shows that the savings could be dramatically boosted by introducing a new regulation on the distribution chains of biosimilars. Some countries have already implemented some measures on the distribution chain to generate savings. As an example, to stimulate price competition on expensive products, the Netherlands has decided to go through the hospital distribution chain for all expensive products[77]. It will allow a reduction to drug expenditure, whilst not affecting patient access.

6.3.10 Scenario 10-Reimbursement rate applied only for retail chain for all countries

Table 38. Scenario 10- Reimbursement rate applied only for retail chain for all countries.Net budget impact 2012-2016 (2011 euros) for retail and hospital pharmaceutical expenditures from healthcare public payer perspective (million euros)

Country	Budget Impact 2012-2016 Base case	Budget Impact 2012-2016 Scenario 10
United Kingdom	-9,367	-9,367
Germany	-831	-827
France	-5,589	-5,727
Poland	41	26
Greece	-808	-808
Portugal	-243	-277
Hungary	- 84	-79

This scenario evidence that applying the reimbursement rate on the total pharmaceutical expenditure has a low impact on the budget.

[77] Source:Nza (Dutch Health Authorities)- Policy BR/CU-2068 and circulated document n°CI/12/75c12D0019919: Transition measures expensive drugs and adjustement substance list 29 May 2012.

7. Discussion

7.1 Geographical scope and timeframe

Seven European countries were selected in the scope of this project. Those countries were very heterogenous in terms of level of pharmaceutical expenditures, generic market penetration rates and public policy approaches towards the price regulation of branded and off-patent pharmaceutical products. They were also different from the health care services organization and funding policies for health care. This allowed us to capture a broader perspective of the net budget impact of different country profiles and the associated drivers.This selection would allow for extending the results to the other European countries through some qualitative projections.

The most difficult part of such a forecasting exercise is to manage the right balance between undertainty and usefulness. A shorter forecasting period is associated with higher certainty, but a longer forecasting period will provide higher interest for long term planning. The 5-year timeframe was long enough to inform decisions for better planning and short enough to make reasonable forecasts. Moreover the deterministic and probabilistic sensitivity analysis that were performed, allowed managing the uncertainty inherent to any forecasting exercise.

7.2 Collection of information/data

To get the most consistent data, several sources were confronted and when contradictions appeared the study board of experts reviewed and validated the most appropriate information to be retained.

Several sources were used to get an exhaustive list of products going off-patent and new entrants. All products that would be going off-patent between 2012 and 2016 were included. Products that went off-patent in 2010 and 2011 were also taken into account, as time to peak sale is about 3 years, and they are expected to incur additional savings during 2012 and 2013 that need to be accounted for as impact of generic entry. For the similar reason, new entrant products that were approved in 2010 or 2011 were included in the forecasting study. The potential new entrant products not already approved should gather the following criteria to be included: be a drug that could be approved via the EMA procedure and have a positive phase II. It was considered unlikely that a product with no phase II results would reach the market and generate significant sales before December 2016. We estimated that it would take about 3 years to implement and complete a phase III, one year for obtaining approval and half a year to one year before market access depending on the countries. However, even with negative phase II, some pharmaceutical companies launch a phase III study with new phase II study in parallel. In this case, some drugs not selected in the study might get access to the market during the study period. Although the assumptions look reasonable, it might be that some products for which the clinical trial program is aggressive will reach the market in that period. We anticipate this situation to be quite rare, as the risk of failure without a positive failure remains high, and very few products are experiencing a parallel phase II/III development.

To be sure to be as exhaustive as possible in the list of the potential new entrant products between 2012 and 2016, a specific criterion for orphan drugs was defined. As orphan drugs could reach the market faster than the other drugs, they were considered as possible entrants before end of phase II. We believe this again is a reasonable assumption.

After investigation, no new and important vaccines were considered to have a significant budget impact in the 5-year period of interest. This hypothesis is fair but a vaccine with an important breakthrough might be possible although highly unlikely in light of the development time required for new vaccines mainly driven by the very large sample size needed for vaccine development. However some vaccines not initially recommended and already marketed could be recommended within the period of interest and therefore generate sales. Although no major new vaccines were identified, many upgraded forms of existing vaccines are ongoing such as the flu vaccine, or children combined vaccines. This could be considered as a limitation. The study expert group is fully aware of such a limitation, and carefully considered it before making the decision of not including the vaccine impact at that stage for upgraded vaccines. The study expert group considered the vaccine recommendation bodies (National Immunization Technical Advisory Groups –NITAG-) to be, in most cases, quite unpredictable and operating under long timelines during the decision process, making it difficult to anticipate their decisions.

The study board of experts acknowledged the need for country specific qualified advisors that were identified and provided inputs at various stages of the project. Therefore, the Member States' specificities were taken into account as far as possible in the forecasting model.

The study board of experts did validate a number of assumptions through the input of local experts, to secure the integration of local perspectives. Those who accepted their contribution to be explicitely mentioned were namely acknowledged in the report.

Sales data sources were initially collected through the various national sources often directly from national health insurance (health care public payers). It happens that the level of accuracy of information is inconsistent across countries, as there are substantial differences on how the data are computed and aggregated. Finally, sales data sources were not available for hospital sales in a number of countries. Following the recommendation of the study board of experts, the IMS sales data were acquired to ensure consistency across countries and access to ex-factory and public sales, as well as pharmacy retail and hospital sales. It is important to notice that no reliable sources for hospital sales are available for Greece. However, most drugs are acquired through the retail chain in Greece, including for example oncology products. The ratio of ex-factory to retail sales is a rough aggregated estimate that is not actually representative of the detailed retail operating cost. In most countries, the cost of distribution chain is a complex calculation that depends on multiple parameters and should not be considered as a simple proportion. However from an overall budget impact, it is an acceptable option to use such an overall ratio.

The health policy information used to feed the model was mainly collected from country specific policy documents and publications. However some figures were derived from experts' interviews and validated by the study board of experts. Especially very little information was available for biosimilars.

Ageing was accounted for in the study in two ways. When epidemiological data were available and accounted for ageing, they were just implemented as such. In most cases they were obtained from Datamonitor reports. When such figures were not available, we used the current epidemiology data retrieved in the literature and adjusted for population ageing during that period. As the population age structure carries very little uncertainty over the five years period unless dramatic unexpected events, we didn t carry sensitivity analysis on the population ageing.

7.3 Hypotheses for the budget impact model

7.3.1 Products going off-patent

The evolution of the sales of generic/biosimilar product between the market access and the peak sales was assumed to be linear whereas it is not the case in real life. This assumption was quite acceptable according to the objective of the study because the largest budget impact happened after peak sales and not before. Therefore the shape of the uptake curve will have limited impact. This is not the case for hospital products but in that case we assumed peak sales are reached at day one as hospital will optimize their purchaser position through tenders.

When a generic/biosimilar version of a drug is available, it was assumed that the hospital used exclusively generic/biosimilar products. It is not really the case as hospitals could use branded drugs but only if their price is lower than or equal to the generic/biosimilar product price. For that reason the hypothesis made had no consequence on the reliability of the model outputs.

Several potential indirect impacts were taken into account according the study board of experts. When 4 or more generics were available in the same therapeutic class, it was assumed that they incurred more savings as a synergetic impact. Indeed, when several generics are available on the market for the same indication, they became competitors and the prices tend to decrease. This additional savings was estimated case by case by the study board of experts. The potential change in recommendation following an entry of a new generic and its consequences on sales as well as the slow down of the uptake of generics caused by the development of combos “generic-patented drugs”, patented reformulation of generics or me-too drugs were also evaluated by the study board of experts. These experts’ input accounts for the indirect impact in the model.

7.3.2 New entrant products

The risks of failure in the development of the new entrant drugs were estimated by therapeutic area. As they were quite different between each area, this choice was relevant. Moreover, it fits with our budget impact analysis that was oriented per therapeutic area. The clinical approval success rates appeared to also differ according to the product type i.e. large versus small molecules but no data were available for the clinical approval success rate according to both therapeutic area and product type. De facto more small molecules are expected to reach the market in that period. Therefore, using development risk for therapeutic areas was considered more relevant. It would be noted also that the large molecules are among the products leading to the high budget impact.

For new entrants already approved in 2010 and 2011, their budget impacts were estimated by the study board of experts according to the sales already generated and to the assessment of the ASMR (Amélioration du Service Médical Rendu/Improvement of Medical Benefit) of the new medicine by the French Health Authority (HAS) complemented by the Scottish Medicines Consortium (SMC) review. It was assumed that the recommandations would be close in the seven countries although it was not certain that it would be the case but the HAS and the SMC are the only health authorities to provide a comprehensive and argumented review of all products reaching the market at the time surrounding launch. Both use different methodologies as the SMC rely on cost effectiveness ratios while the HAS relies on clinical efficacy and effectiveness. Therefore, we considered that this method provided a good view on the product potential market value to be used for the forecasting exercise.

For new entrant drugs not already approved, we used the clinical results of the phase II study to assess the potential clinical benefit. Although extensive results were not always publicly available, we considered that good outcomes were expected to be shared at an early stage when available. Most companies involved in the launch of new entrants are listed companies and have to disclose available information. We reviewed all related press releases, company websites, trial registries, conference abstracts and analyst reports to assess the potential value of new products. For new entrant drugs such as a combination of an already approved product, me-too drugs and new formulations of already approved products with no additional major clinical value were considered to have no budget impact. Having no budget impact does not mean not to have any sales. In fact nowadays, with the increased pressure on Member States' budget, it is unexpected that marginal innovation or non innovative products will be allowed to impact drug expenditure budget. It is likely that such products will generate substantial sales, but by shifting budget from older to new products. Health Technology Assessment regulation at national level or health insurances has shown a substantial strengthening trend that is making it more and more difficult for such products to impact the drug budget.

The study board of experts applied severe criteria, projecting onto the next years the decision of the HAS, the National Institute for Health and Clinical Excellence (NICE), the SMC and the Institute for quality and efficiency in Health Care (IQWIG) which were currently quite stricter than in the previous years. This allowed us to free ourselves from the historical decisions which were the main basis of forecasting in most exercises. Such methods represent the benefit of simplicity and clarity. They are quite reliable when changes are happening progressively. Today, we observe quite a disruption over most countries in the value appreciation of new drugs that is making the historical benchmark less reliable. There were two options to factor such trend disruptions. One was to use historical benchmarks and factor a negative impact on the overall results to account for more stringent entry criteria. The other option was to look individually at new entrants and to assess their clinical potential and translate it in commercial potential. The latest option was selected for this project. The limitation of that option was the amount of work it does incur to complete the analysis. Sometimes, the paucity of available information made it difficult to have an objective view of clinical benefit. In that case the study board of experts, looked at time from study completion, size of company, importance of the study (sample size duration etc) and decided consistently that, when the information has not been made available, this would suggest the results are not appealing toward a robust benefit. However, it is expected that the methodology used for the study was more evidence based and more accurate than a more global management methodology. Such a method also involves expert judgement that also carries some pluses and minuses. Expert judgement allows for a

case by case specific assessment, but it does rely on the experts' capability and judgement. In our case, the number of experts involved in the study board supported by local experts provides reassurance on such limitations.

An exception was made for oncology as this therapeutic area was clearly identified in the literature to be the one with the largest unmet clinical need. It was also well identified as the one to incure the highest impact on future drug expenditures. First, in France, the United Kingdom and Germany, the budget impact was assessed case by case by the study board of experts according to the magnitude of overall survival, severity of the condition, the existence of effective alternative therapies, etc. Secondly, for Hungary, Poland, Greece and Portugal analysis, we made the assumption that the new entrant drugs would not have an important development in those countries because they would be very expensive. To estimate the penetration rate evolution in those countries, the ratio of the penetration rate for oncology drugs in each of those countries was compared to France in 2011. This ratio was expected to be stable during the study period. As for the results, the penetration rate for each of those countries in oncology is calculated according to the penetration rate in France and the ratio observed in 2011. To check the reliability of France as a reference country, the same procedure was processed with the German data and the results were stable. Those differences in the access to drugs would result in an important impact in terms of public health. In a way, for those countries for oncology, we did apply the benchmarking method described above, as the first option. Except for Poland that seems to enjoy a substantial growth of GDP, most countries are experiencing a tight overall budget and might have difficulties to find new revenue to fund additional expensive treatment options. Therefore, we considered our method to provide a reasonable estimate of oncology drugs impact in those countries.

For the new entrant products, peak sales were considered to be reached over a period of three years. This period is short compared to the average used in forecasting, where it was usually achieved over five years. However in our case, we considered that only innovative products would affect the drug budget. It is not unexpected that breakthroughs have a faster uptake.

7.4 Results discussion

The part of the hospital pharmaceutical public sales among the total pharmaceutical public sales varied from 9.6% for Germany to 36.1% for the United Kingdom. The proportion of retail sales versus hospital sales widely impacts the forecasts, as hospitals benefit from a better discount for generic or biosimilar as well as for branded products when they compete as me-too drugs.

There was a large disparity observed in the total public sales in 2011 between countries. In the United Kingdom, Germany and France, the total public sales were higher than €20 billion, whereas Portugal, Greece, Poland and Hungary spent less than €6 billion. As those countries are not comparable in terms of number of inhabitants, it seems more relevant to focus on the total public sales per capita, in order to be aware of the level of health care system of each country. France spent the highest costs with €608 per inhabitant in 2011, whereas the United Kingdom spent only €339. Germany was in second position with €485 spent per inhabitant. Portugal and Greece spent more money per capita than the United Kingdom with €337 and €446 respectively. Far behind, Poland and Hungary respectively spent in 2011, €138 and €203. The Polish and Hungarian markets are still far from mature and will certainly, in the future, increase their investment to secure patient access to

innovative products. In the current project, we didn't assume an increase in GDP per capita that might open the development of access of innovative molecules at a faster pace than it is today. In the five other countries, the market is quite mature and with a thinner margin of progression. Moreover, Portugal and Greece are today widely impacted by the economic crisis and that will be a brake to a potential progression of the market. The study board of experts took a stringent attitude for market access to reflect the current and future trends. Although neither the authors nor the study board of experts express any judgement on the appropriateness of increased hurdles for access to new drugs, they foresee an increase in pressure on pharmaceuticals to evidence additional clinical or economical benefit to achieve access. Such increased pressure has been integrated in the forecasting exercise.

This study highlights the question of equity across Europe in terms of patient access. It is especially the case for oncology as it is a therapeutic area with many new products with a good efficacy with between 3 and 6 months, or even above 6 months, of overall survival. These new products are unlikely to be widely available for Portugese, Greek, Polish and Hungarian patients. To date, no robust data evidenced the benefit of a wider access to oncology products like in Germany and France, versus a more restricted access like in the United Kingdom, Poland or Hungary. This is a major public health question to identify impact on patients overall survival in real life practice of a wider access to new oncology therapy.

The initial objective of this project was to assess net budget impact associated with generic entry and new brand entry over the period 2012-2016. We accounted for recently launched product by integrating in the forecast the product approved in 2010 and 2011. Such products have not achieved their peak sales and would have substantial sales impact over the considered period. It would have been a serious limitation if they had not been included.

On the opposite, we did not review market development of products launched before 2010 and not expected to become generic in the considered period. Such products are likely to have some impact by increasing or decreasing their market share according to various events succeptible to happen. This is obviously a limitation of this study that was considered by the study board of expert to be limited as the impact is going in both directions toward increases and decrease of budget impact and should be close to neutral.

Except in Poland where the market is in development, the drug market is likely to decrease due to several factors.

- First, even if the phenomenon of the genericization tends to slow down around the end of 2016, it will be progressively replaced by the arrival of the biosimilars. It will be a very interesting point because the biosimilars will probably incur huge savings on the global drug budget in Europe beyond 2016.

- Secondly, the criteria to assess the added value of the new entrant products were progressively more and more severe in the recent years, but in 2011 and 2012, we could see a disruption, with an acceleration of this trend that is unlikely to reverse in a short future. This trend will likely escalate in the future. This actually raises the issue about reward of innovation and incentive for developing new products.

- A third reason is the reduction of approval of new entities that bring additional benefit to existing alternative. This trend is likely to change with the development of biologics that are expected to reach the market in the medium to long term.

During the study period, the therapeutic areas that will be the drivers of the health expenditures are oncology, and immunology and inflammation. Other important areas substantially impacting the budget are cardiovascular, central nervous system and respiratory areas, with a negative overall net budget impact, as more savings will occur in relation to generic entry than additional cost related to new brands.

While savings related to generics are decreasing over the period of interest, we observe the savings associated with biosimilars taking over.

Uncertainty on the savings associated to biosimilars relies on the wide development of new biological entities that, in fact, are just slightly modified biologics such as a pegylated formulation and often refered to as analogues. The example of erythropoetin analogues shows the large potential for development of such analogues. The regulation of generics was adjusted to secure that slight changes like new salts, new crystals, isomers, new formulations, etc. are considered as generics unless they proof improved clinical benefit. Payers are currently struggling to adopt rules for coping with those challenges. There would be a need for a clear regulation to define what would be considering as a new entity and how to define a clinical improvement. Without such evolution, the risk is high that such products could arbitrarily be included or excluded from the biosimilar status.

This question is important for products available on the retail market, but of less importance on the hospital market as tenders will adjust for gaps between additional price and added value.

7.5 Conclusion

Forecasting pharmaceutical expenditure over the 5 year period (2012-2016) is a critical exercice to inform policy decision makers and help them foreseeing the potential risk of ending outside their approved budget by their parliament.

A specific model was built for the purpose of this project. A new methodology was applied to compute the impact of new branded products reaching the market based on product specific future turnover rather than using historical market drivers.

The results of this forecast project showed a consistent, but variable in magnitude, reduction in pharmaceutical expenditure in all countries with the exception of Poland.

The model developed in this study has been used to generate impact of changes in pharmaceutical policies. Obviously, implementing the pharmaceutical policies of the United Kingdom to all Member States selected in this study will have important impact in terms of savings. However, it is also important to consider that such dramatic changes might not necessarily fit the culture and health care organization of other countries and therefore might not be the best way forward.

The most important leverages that were identified are driven by generic and biosmilar prices and distribution. Reducing, even slightly, the prices of generics will have a major impact. The reduction of generic prices, the distribution of biosimilars through hospital chain and increased share of generics are among the best options to boost savings.

8. Appendices

All appendices are provided in a separate file.

8.1 Information regarding specific pharmaceutical policies in place for each country

8.2 Results of the deterministic one-way sensitivity analysis with parameters increased and decreased by 30%

8.3 Upper and lower values of the parameters defined by the study board of experts and used for the deterministic one-way sensitivity analysis

8.4 Results of the deterministic one-way sensitivity analysis with specific high and low values of parameters defined by the study board of experts

8.5 Results of the probabilistic sensitivity analysis

8.6 List of generics products over the period 2010-2016

8.7 List of new entrants over the period 2012-2016

8.8 List of new entrants over the period 2010-2011

8.9 Generic Model: Indirect Impact

8.10 Budget impact analysis