

**Universidade de Lisboa**

**Faculdade de Farmácia**



**Contribute to the sustainability of the  
Portuguese healthcare system in the health  
technologies area**

**Eliana Vilhena Silva Martins**

**Mestrado Integrado em Ciências Farmacêuticas**

**2017**



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**Monografia de Mestrado Integrado em Ciências Farmacêuticas  
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**Orientador: Professor Doutor Hélder Mota Filipe**

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## I. Abstract

During the last years the pharmaceutical market went through profound modifications, and although some reasons are related with spontaneous and natural phenomena (*i.e.* demographic and disease pattern changes), most of them have a deep connection with a perspective change, which is almost the harbinger of a paradigm shift.

This work analyses the transformation and transition that healthcare systems around Europe are suffering and passing through regarding access to medicines, and particularizes the case of Portugal. Firstly, measures related with pricing and reimbursement are discussed regarding their characteristics, advantages and associated problems, and then, policies related to budget containment are also analysed. However, it is important to refer that increasingly there is a thin line between what is considered a pricing policy and a measure to control pharmaceutical expenditure. These subjects are exposed from a European Union perspective (incentives and proposals from centralised entities), Member States viewpoint (embracing measures and strategies, with relevant examples), and lastly, from the Portuguese approach. These sections that focus attention in Portugal are particularly important because, although it is not a top target country for European pharmaceutical market access, it is interestingly considered a guide for the Europe's future in control of costs with healthcare.

From this point, a brief description of a European joint negotiation and purchasing model follows, which was thought to be aligned with the European tendencies. This model is presented as being sustained by several entities as the National Competent Authorities and some EMA's branches, and by processes as the one found in the *Joint Procurement of medical countermeasures*. The centralised procurement is also analysed, and a small reflection is done about the benefits and eventual constraints of the proposal.

**Key concepts:** Pharmaceutical market, Access to medicines, Pharmaceutical policies, European healthcare systems, Joint procurements

## I. Resumo

Durante os últimos anos, o mercado farmacêutico tem sofrido alterações profundas, e, embora alguns dos motivos estejam relacionados com fenómenos naturais e espontâneos (*i.e.* modificações na demografia e no padrão de doenças), a maior parte tem uma forte conexão com uma alteração de perspetiva, que quase funciona como um prenúncio de uma mudança de paradigma.

Este trabalho analisa as transformações e transições pelas quais os sistemas de saúde europeus estão a passar em termos de acesso ao medicamento, e particulariza o caso de Portugal. Primeiramente, discutem-se medidas mais direcionadas para o preço e participação, e de seguida analisam-se políticas de redução de despesa com medicamentos, ainda que haja uma forte correlação e complementaridade entre os dois tipos. Estes assuntos são em ambos os casos expostos de uma perspetiva da União Europeia (incentivos e propostas das entidades centrais), de um ponto de vista dos Estados Membros (medidas e estratégias, com recurso a exemplos relevantes), e finalmente, segundo a abordagem portuguesa. As seções que se focam em Portugal acabam por ter uma extrema importância porque, não obstante o facto de Portugal não ser uma prioridade no que diz respeito a acesso ao mercado europeu, é considerado um “guia” para o futuro da Europa em questões de controlo de gastos com cuidados de saúde.

A partir desse ponto, parte-se para a descrição de um modelo de negociação e compra de produtos farmacêuticos de forma conjunta, por parte dos Estados Membros da União Europeia, que se julgou estar de acordo com as tendências europeias. Este modelo sustenta-se em entidades como as Autoridades Nacionais Competentes, estruturas da EMA, e em processos como o descrito para a *Joint Procurement of medical countermeasures*. A estratégia de gestão centralizada proposta é também analisada e é feita uma pequena reflexão sobre os benefícios e eventuais contras da proposta, que podem ser vistos como oportunidades de melhoria de determinados aspetos.

**Conceitos-chave:** Mercado farmacêutico, Acesso a medicamentos, Políticas do medicamento, Sistemas de saúde europeus, Acordos de cooperação

## **II. Aims**

This project arose with the aim of pointing out the current problems and the future concerns that European healthcare systems will face, with a particularization for the Portuguese one. Additionally, the idea of giving a contribute by developing a model capable of addressing part of these issues emerged, and the exposure of this ended up being the main goal.

This document is expected to provide an overlook of the pricing methodologies (related with the manner the price is set, which depends solely on the country, and not on the company), reimbursement procedures (which also depend on the country's evaluation and is based on some aspects also important for pricing decisions), and finally, strategies to reduce the public expenditure with pharmaceuticals, that embraces both pricing and reimbursement decisions, and goes beyond these. To fully understand which are the challenges and what is being done to address these challenges, a survey of these policies, from a European Union, Member States and Portuguese viewpoint was made.

Another important premise of this work is the fact that European Union has little involvement in Member States health matter, and that is why the Union was not only focused during the pricing, reimbursement and cost saving policies, but also in the proposal chapter. The “contribution for the sustainability” of access to medicines as we know, or even the improvement of the access, is based in two objectives – the necessity of modifying and resolve the access issue, and the deepening of the involvement of the EU on healthcare subjects.

### **III. Acknowledgments**

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## VI. List of abbreviations

ABPI - Association of the British Pharmaceutical Industry	Ecphin - European Community Pharmaceutical Information Network
ACSS - Central Administration of the Health System	EE - Estonia
AT - Austria	EL - Greece
ATC - Anatomical Therapeutic Chemical	EMA - European Medicines Agency
BE - Belgium	EPR - External Price Referencing
BG - Bulgaria	ES - Spain
CAPR - Competent Authorities for Pharmaceutical Pricing and Reimbursement	ESHI - Etatist Social Health Insurance
CATS - Health Technologies Assessment Commission	EU - European Union
CBA - Cost-benefit Analysis	Eudranet - European Human and Veterinary Pharmaceuticals Telecommunication Network
CEA - Cost-effectiveness Analysis (CEA)	EUnetHTA - European Network on Health Technology Assessment
CED - Coverage with Evidence Development	Euripid - European Integrated Price Information Database
CH - Switzerland	FI - Finland
CHMP - Committee for Medicinal Products for Human Use	FNM - National Medicines Formulary
CMA - Cost-minimization Analysis	FR - France
CNFT - National Pharmacy and Therapeutic Commission	GCC/GPP - Gulf Cooperation Council Group Purchasing Program
COI - Cost-of-illness	GDF - Global TB Drug Facility
CP - Centralised Procedure	GDP - Gross Domestic Product
CUA - Cost-utility Analysis	GNI - Gross National Income
CY - Cyprus	HIV - Human Immunodeficiency Virus
CZ - Czech Republic	HR - Croatia
DDD - Defined Daily Dose	HTA - Health Technology Assessment
DH - Department of Health	HTAN – Health Technology Assessment Network
DK - Denmark	HU - Hungary
DP - Differential Pricing	IC - Iceland
DPP-4 - Dipeptidyl peptidase 4	IE - Ireland
EC – European Commission	INN - International
ECDC - European Centre for Disease Prevention and Control	IPR - Internal Price Referencing

IT - Italy	PPRS - Pharmaceutical Price Regulation Scheme
JA - Joint Action	PRP - Pharmacy Retail Prices
JPA - Joint Procurement Agreement	PT - Portugal
LT - Lithuania	PVA - Price-volume Agreements
LU - Luxembourg	QOL - Quality of Life
LV - Latvia	R&D - Research and Development
M - Millions	RO - Romania
MAH - Market Authorization Holder	ROP – Ramsey’s Optimal Pricing
MEA - Managed-entry Agreements	SARS - Severe acute respiratory syndrome
MERS - Middle East Respiratory Syndrome	SE - Sweden
MoU - Memorandum of Understanding	SHI - Social Health Insurance
MS - Member State(s)	SI - Slovenia
MT - Malta	SiATS - Health Technologies Assessment Information System
NCA - National Competent Authority	SiNATS - National System for Health Technology Assessment
NHI - National Health Insurance	SK - Slovakia
NHS - National Health Service	SNS - (Portuguese) National Health Service
NICE - National Institute for Health and Care Excellence	SPMS - Shared Services of the Ministry of Health
NL - Netherlands	TB - Tuberculosis
NO - Norway	TFEU - Treaty on the Functioning of the European Union
OECS/PPS - Organization of Eastern Caribbean States/Pharmaceutical Procurement Service	UK - United Kingdom
OOP - Out-of-pocket	VAT - Value-added Tax
OTC - Over-the-counter	VBP - Value-based Pricing
PAHO RF - Pan American Health Organization vaccine revolving fund	VHI - Voluntary Health Insurance
PL - Poland	WHO - World Health Organisation
PPP - Purchasing Power Parity	YoY - Year over Year

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## 1. Introduction

### 1.1. National and Global responsibilities for health

In ancient times, health was seen as an individual good, based on a Doctor-Patient relationship, which promotion and preservation was not a public responsibility. However, soon people started to realize the importance of considering health as a subject with public relevance, and from this point, the State became the figure responsible for its maintenance and administration. Later, in the XX century, a new concept was born – *Welfare state*, and this modified the action field of the State in health matters, from a management point of view, to the provision of healthcare, through an organized service, available to every citizen (1).

From a broader perspective to the specific plan of pharmaceuticals, the State has the responsibility to “*promote and assure access of every citizen to healthcare services within the limits of the available human, technical and financial resources.*” (2). Nowadays, the financial factor is becoming more important and there is an urge to find consistent alternatives to the current paradigm.

### 1.2. Current challenges and pharmaceutical expenditure

The pharmaceutical sector is dealing with a pattern changing, and although the global financial crisis has had a huge impact on this, there are a lot of other factors:

- a) *New (high-cost) health technologies.* What was for decades considered as a “trend” of the pharmaceutical industry – relatively cheap medicines for a broad market, does not apply anymore to the reality we are living. Most of the drugs in the pipeline are directed for a narrow market, and the expected values to have access to those are way superior to the ones we were used to. This is more evident in hospital medicines (oncologic, antiviral...), known for its high prices and high margins (3), but the ambulatory market is also showing some changes with the new high-priced oral anticoagulants and antidiabetics (4).
- b) *Biological and Biosimilar medicines.* Most of the pharmaceutical firms are turning to biologics market, because, besides the effectivity success, the costly development of these drugs (from 200 to 2 000 M €), the global annual sales figures

are approximately 200 000 M € (prediction for 2017) (5). These medicines figure a major part of the companies' pipelines, and they will bring some troubles to governmental budgetary compliance, since the development of biosimilars is also expensive, and the price reduction is much more limited (when compared to branded/generic medicines). Besides this, there are some barriers to the market entry of biosimilars, which discourage the investment in these therapeutic agents (6).

- c) *Personalized medicines*. The vision of “right drug, right patient, right time” is already being adopted by some pharmaceutical companies, and in fact this perspective reveals an interesting method to avoid unnecessary and ineffective treatments. But on the other hand, to achieve the requisite return on investment in such a small market, these drugs will most likely demand an increase in public expenditure (7).
- d) *Population ageing, chronic/noncommunicable diseases*. Ageing is usually considered to be the main reason for the increase in health expenditure (mainly in countries as Portugal), but the statistics in which we rely to assume this, ignore the time profile that shows that the biggest share of expenses in health matters come in the final two years of life, proving that ageing just transfers the expense to a later time (8). On the other hand, ageing is associated with long-term conditions and noncommunicable diseases, and these are in fact the greatest health burden the world is facing. The health technologies used in these diseases are expensive and most of the times help to control rather than treat (9).
- e) *Infectious diseases*. On the one side, the increasing globalization has proven to be responsible for the spreading of new or endemic infectious diseases – MERS, SARS, Ebola, on the other, old diseases, as TB, are becoming drug-resistant. Altogether, these phenomena create additional social pressure upon the agents responsible for developing therapeutic solutions (9).
- f) *Tighter health budgets*. Several European countries, mostly the ones heavily affected by crisis, reported cuts on public spending on health, of which pharmaceuticals constitute a relevant share (10). Although some policies generated savings and enhanced efficiency (use of international non-proprietary name and greater use of generic alternatives), others may have achieved savings but



undermined efficiency (lower drug prices). Surprisingly, most of the measures did not bring saving, at least immediately, but generated efficiency gains – strengthening policies to promote health or prevent diseases and greater use of HTA to support decisions (11).

- g) *Higher expectations from society.* Citizens are becoming consumers of health information and are challenging their healthcare providers in an active way (12). An Era of patient-centred medicine is rising, and not only are these aware of their options, but are also taking part of the decision in terms price/effectiveness, quality of life/life expectancy, treatment/adverse effects, and this is leading the governments and other healthcare providers to pursue more information and make better evaluations of the health technologies available (13).

To deal properly with these modifications the health sector and the pharmaceutical market are facing, it is necessary to know what is being done to control the pharmaceutical public expenditure, so, the next chapter is a literature review of pharmaceutical pricing policies.

## 2. Review and analysis of pharmaceutical policies

### 2.1. Pharmaceutical Pricing and Reimbursement Policies

#### 2.1.1. European Union Framework

European Directives set out only minimum requirements and fundamental principles in healthcare matters, and although it is clear that each and every country must provide universal coverage, structural differences can be found, starting from the basic organization of the healthcare system (14). This ends up influencing health policies in general, and pharmaceutical practices in particular. According to the typology developed by Rothgang et al. (15) and Wendt et al. (16) there are four types of health systems: the *National Health Service* (NHS), *National Health Insurance* (NHI), *Social Health Insurance* (SHI) and the *Etatist Social Health Insurance* (ESHI). This four types differ in three dimensions – financing, service provision and regulation, each one dominated either by state, societal (*i.e.* NGO’s, consultancy agencies or research institutes), or private actors (17,18) (see **Table 1.**).

**TABLE 1.** Organization of the healthcare systems in Europe (adapted from Wind et al., 2016 (19)).

	<b>NHS</b>	<b>NHI</b>	<b>SHI</b>	<b>ESHI</b>
<b>Financing</b>	State	State	Societal actors	Societal actors
<b>Service provision</b>	State	Private	Private	Private
<b>Regulation</b>	State	State	Societal Actors	State
<b>EU Member States</b>	CY, DK, EL, ES, FI, MT*, SE, PT, UK	IT, IE, RO	AT, DE, HR, LU, LV*, SI**	BE, BG, CZ, EE, FR, HU, LT, NL, PL, SK

\* Malta and Latvia have mixed public/private service provision

\*\* Slovenia is evolving into a SHI, however service provision is still in the hands of state actors

Having this in mind, it is easy to understand why EU has so little action in pricing and reimbursement of pharmaceuticals – the variations between systems, at least by now, do not allow harmonization of procedures/strategies. However, under EU coordination, MS are focused on achieving “1) *timely and equitable access to pharmaceuticals for patients all in the EU, 2) control of pharmaceutical expenditure for Member States, and 3) reward for valuable innovation within a competitive and dynamic market that also encourages Research & Development*” (20).

Also, as an attempt to move towards a better coordination and to facilitate single market in the field of pharmaceutical, there is the *Transparency Directive* (4). This secondary legislation requires national authorities to deliberate prices and reimbursement within specific time limits, to publish price lists, including price increases, price freezes, and to publish negative lists with justification (medicinal products excluded from coverage of its insurance systems) (21).

Following the previous Directive, in 2004, also with the goal of improving the sharing of medicinal products' information and to promote comparisons, there was created a *National Register*, containing prices, expenditure, utilization and clinical properties, with validated ATC codes and DDD values (22).

In recent years, following the economic crisis, EU has taken several actions to support MS by improving the *effectiveness, accessibility* and *resiliency* of its health systems. Some of the provided guidelines and tools focus pharmaceutical policies, in particular pricing policies: 1) promotion and discussion of *quality of care*, including patient safety, 2) enhancement the cost-effective use of medicines, with increased *transparency and cooperation*, 3) creation of *networks* to allow patients with low prevalence, complex or rare diseases to access high quality care, and 4) implementation of HTA (*Health Technology Assessment*) strategies and mechanisms, and a platform to cooperate and share those – *HTA network* (23-25).

Even the EMA, which plays a key role both in terms of linking Member States' pharmaceutical policies and sustaining a common platform to share information and knowledge, does not have any action in pricing and reimbursement decisions. However, over the last years, a gradual convergence of pricing policies and strategies was seen throughout the MS, despite their different national contexts, having as a main goal the access of their citizens to safe, effective and high quality health technologies (14).

### **2.1.2. Procedures in pricing decisions**

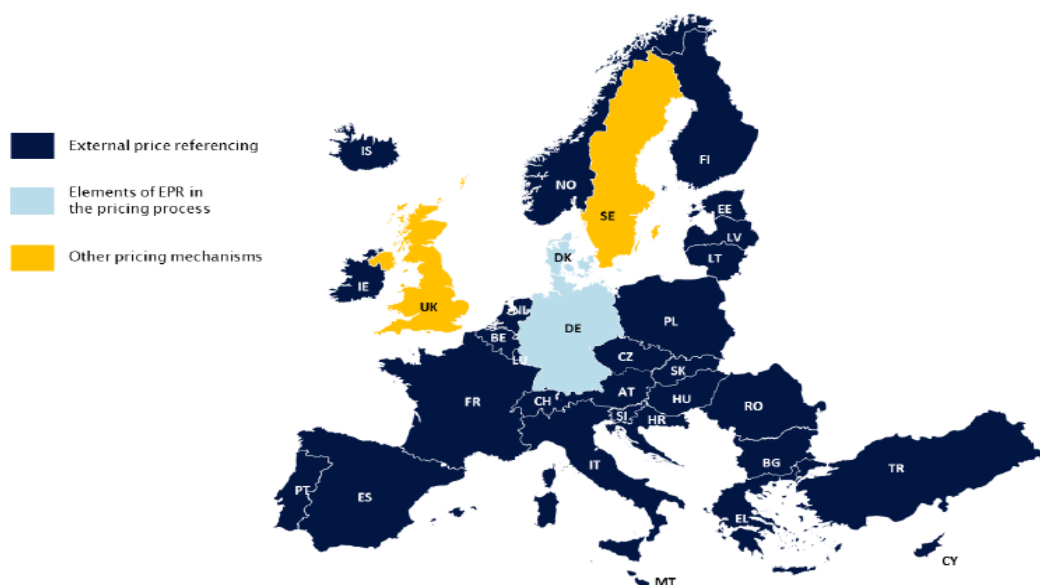
Policy-makers have at their disposal different policies to determine medicine prices, and to explain these procedures it is important to classify them as procedures for *in-patient medicines* or *off-patient medicines and generics* (26).

### 2.1.2.1. In-patient medicines

As seen before, the variety of health systems in the EU lead to the lack of harmonization in pricing policies, mainly when the aim is to reduce the expense. However, when it comes to deciding about prices for new pharmaceuticals, the scenario is much more standardized. *Innovation* is a key concept in this type of decisions, and HTA, specifically economic evaluation, is increasingly playing an important role in defining innovative medicines (27). Although it seems a relatively simple notion, innovation has three blurry concepts associated – commercial concept that refers to any *newly marketed* product, technological concept that means any *industrial innovation*, and, the one that truly concerns health professionals, the *therapeutic advance* (28).

Nevertheless, a state-of-the-art evidence-based assessment is still not covering all pricing decisions, at least directly, and it is important to have an overview of the procedures used in pricing decisions for both in-patient and out-patient sectors.

- a) *External price referencing*. Also referred to as international price benchmark/comparison, EPR is defined as “*the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for purposes of setting or negotiating the price of the product in a given country*” (29). In Europe, out of the 29 countries that apply EPR (in 24 out of 28 EU Member States), 20 use EPR as the sole or main pricing policy (30) (see **Figure 1**). Some countries have EPR based on statutory regulations or legislated pricing

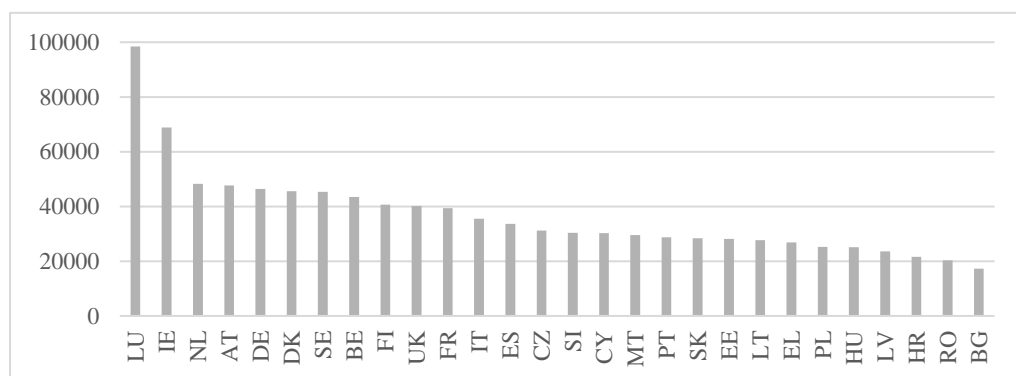


**FIGURE 1.** Use of EPR in European countries (from European Commission, 2015 (4)).

rules, with very accurate methodologies to make the calculations (*i.e.* Portugal and Austria), while in others, rules are considerably less detailed (*i.e.* Germany and Estonia), however, in almost every case, the country baskets are defined using as main criteria economic comparability (30,31). Countries compare both ex-factory prices, pharmacy purchasing prices and pharmacy retail prices (PRP), and the main method is the calculation of the average price, although some countries use also the lowest price among all the reference countries (31).

Despite the fact that EPR is a seemingly useful mechanism, it has some serious consequences in terms of negotiation with pharmaceutical companies because: 1) a low price granted to one country, *undermines the price the firm can obtain* in another country, causing access restriction to countries where potential sales volume is small, and 2) the harmonization in terms of dosages, pack sizes, labelling etc. (mainly because of market authorization centralized procedure) of first-in-class products, which do not have similar products already on the market as benchmark for regulating price, together with the existence of parallel trade, creates *spillovers* from low-pricing to higher-pricing countries, leading to access limitations, and decreased willingness to invest in R&D (31,32). In addition, the official compared prices usually do not include the *discounts and rebates*, which can provide a false sense of security to payers, leading to financial losses (4,33).

- b) *Differential pricing*. Based on Ramsey pricing principles, DP, also known as Tiered Pricing, is reported as a win-win approach to address access issues, where prices differ across markets according to the *demand elasticity* and *GDP per capita* (see **Figure 2.**) – less price sensitive (and richer) countries compensate the lower



**FIGURE 2.** GDP per capita adjusted to the PPP, one of the factor that would influence the price formation according to a DP perspective (from The World Bank, 2014 (35)).

revenues in more price sensitive countries (31,34). Applying Ramsey principles, effectiveness does not enter in the price negotiation, and there is a formula that, for each case, gives the *Ramsey optimal pricing* (ROP), being this the one with highest possible social welfare, assuring a determined profit for the producer (36). Current differences in prices seem not to be fair neither optimal, and DP could be the most direct way to address this, and to promote greater access to medicines in all European markets (37). Yet so, this strategy does not include a cost-effectiveness assessment, which is a lowering point, since this aspect must and should be valued.

- c) *Value-based pricing*. This mechanism consists of a negotiated price on new health technologies, based on the value offered by this, as assessed through HTA, reflecting the current trends in health economics (38,39). As a response to the limitations of EPR, many MS are adding VBP elements in their pricing (and reimbursement) decisions, but this policy has only been fully implemented in Sweden (combined with free pricing) (4). The UK, since 2014, also integrated some VBP aspects in their Pharmaceutical Pricing Regulation Scheme (PPRS) in the form of flexible prices and patient access schemes (40). Pharmacoeconomic offer different analytical methods to assess the value or relative value as: 1) *cost-of-illness evaluation* (COI), 2) *cost-minimization analysis* (CMA), 3) *cost-benefit analysis* (CBA), 4) *cost-effectiveness analysis* (CEA), 5) *cost-utility analysis* (CUA), and 6) *quality of life evaluation* (QOL) (see **Table 2.**). In this context, the concept “cost” can be quite complex for those countries that use formal economic evaluation, being these classified into four categories: 1) *direct medical costs* (product and medical acts), 2) *indirect medical costs* (not related to the disease), 3) *direct non-medical costs* (*i.e.* transports, time for patient), and 4) *indirect non-medical costs* (*i.e.* loss in labour market productivity). The notion of value-based pricing is possibly the most logical since it ensures that the paid prices reflect the benefits we get and, as said before, EU countries are progressively adopting and developing sophisticated procedures (HTA) to assess the value. But measuring a therapy’s value is incredibly difficult, and it is easy to have distorted cost-effectiveness assessments, being this possibly the primary cause for the predominance of other methodologies as main strategies (39).

TABLE 2. Summary of Pharmacoeconomic Methods (adapted from DiPiro *et al.*, 2014 (41)).

Method	Description	Application	Cost Unit	Outcome
COI	Estimates the cost of a disease on a defined population	Baseline to compare prevention/treatment options	€€€	---
CMA	Finds the least expensive cost alternative	When benefits are the same	€€€	Assume to be equivalent
CBA	Measures benefit in monetary units and computes a net gain	Compares programs with different objectives	€€€	€€€
CEA	Compares alternatives with therapeutic effects measured in physical units; Computes a cost-effectiveness ratio	Compares drugs/programs that differ in clinical outcomes and use the same unit of benefit	€€€	Natural Units ( <i>i.e.</i> years of life gained)
CUA	Measures therapeutic consequences in utility units rather than physical units; computes a cost-utility ratio	Compares drugs/programs that are life extending with serious side effects or those producing reductions in morbidity	€€€	QALYs
QOL	Physical, social, and emotional aspects of patient's well-being that are relevant and important to the patient	Examines drug effects in areas not covered by laboratory or physiologic measurements	---	QOL score

- d) *Free pricing*. The best product launch mechanism is generally considered as the one that provides the fastest commercialization, and this mindset is seen in countries where manufacturers are free to set prices (42). This is the system used in Germany, combined with EPR and VBP, and according to this, MAH have the right to set prices, and after a certain period, during which these medicines are fully reimbursed and early benefit assessments are conducted, the prices are re-negotiated. This decision takes into account the results from the assessment and added therapeutic benefit compared to the alternatives (4). In order to facilitate the comprehension of this mechanism, **Figure 3.** summarizes the AMNOG law, in which the German pricing system is based on. Until 2011, prices in Germany were about 26% higher than the average across the EU. By 2015 it was already clear that the new law was successful in reducing the government's pharmaceutical bill (43). Besides Germany, Denmark and the UK also include a free pricing strategy features in their system. Although this is a reasonable mechanism to overcome the limited intellectual patents protection, to stimulate R&D, to accelerate market entry and to assess the added value of new and innovative pharmaceuticals, it can only be supported by a healthcare system with a robust budget allocation. For instance, in

a country like Portugal, with a tight and controlled pharmaceutical budget and a NHS type of healthcare, it would be difficult to have a policy based on free-pricing.

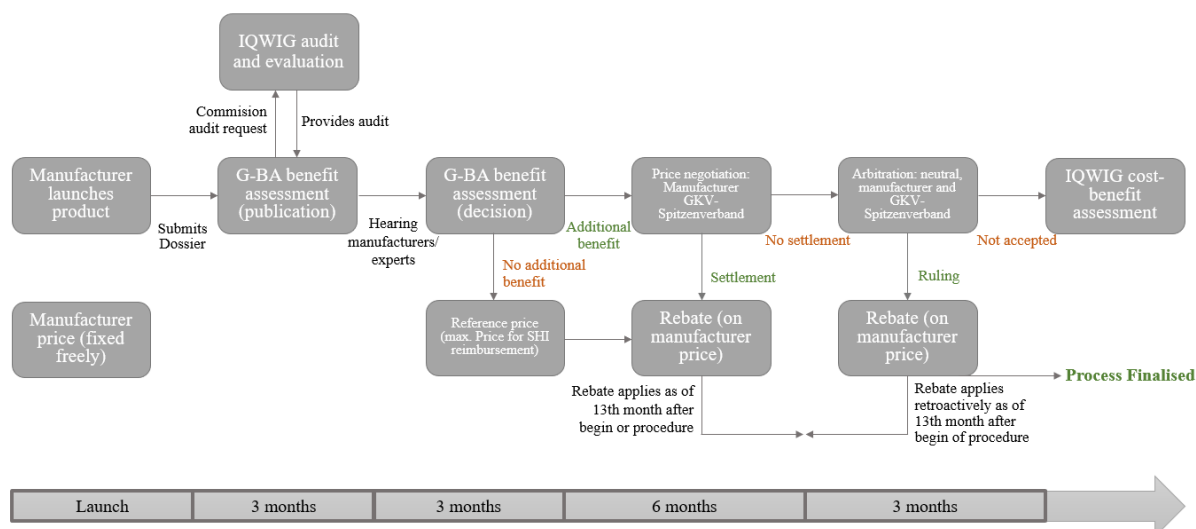


FIGURE 3. AMNOG process overview (adapted from MAP BioPharma, 2017 (44)).

e) *Pharmaceutical Price Regulation Scheme*. This pricing strategy results from a voluntary agreement between the UK government and the Association of the British Pharmaceutical Industry (ABPI), in which the MAH has the right to freely set their prices for branded medicines, under agreement with the Department of Health, up to a maximum profit (4). In exchange, companies must pay quarterly, a percentage correspondent to the growth of the medicines bill, which is limited by the DH (see **Table 3**). Any firm not in membership of the PPRS is subject to the statutory scheme which controls prices and not profits. Since 2014, PPRS, more specifically NICE, uses a value-based assessment to evaluate/approve the fairness in the price asked for the new pharmaceutical (45).

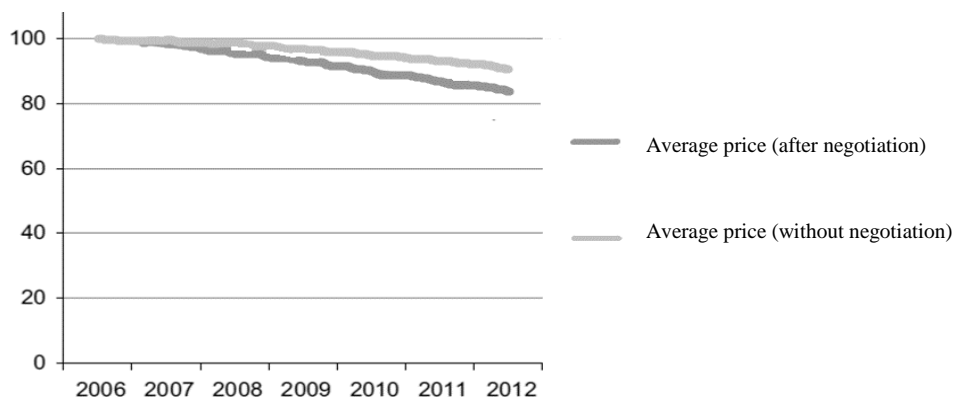
TABLE 3. Agreed values for PPRS 2014-2018 (adapted from ABPI, 2014 (45)).

	2014	2015	2016	2017	2018
<b>Allowed growth (YoY growth %)</b>	0%	0%	1,8%	1,8%	1,9%
<b>Agreed joint forecast (YoY growth %)</b>	3,87%	3,52%	3,85%	2,14%	3,09%
<b>Estimated payment percentage</b>	3,74%	7,13%	9,92%		
		(depending on the actual med bills growth)*			

\*The actual percentage growth will be reviewed versus the forecast, and the initial estimates of payment percentages for the future years will be adjusted to reflect the actual percentage growth, actual use of new products, any over or underpayment from the previous year, and a revised forecast percentage growth for the following years.



f) *Negotiations*. Negotiations end up being part of all the previously described methods, having a greater impacting in hospital settings (36), although some countries use it for a significant volume of medicines in ambulatory care. In this process, basically, the government negotiates the lowest price for an agreed quantity of a pharmaceutical, and/or for a certain duration., generally with relatively satisfactory results (see **Figure 4.**). However, the resulting discounts are becoming more complex, and this is starting to blur the transparency in many negotiations—companies are setting list prices knowing that they will be asked for discounts, and payers are not accepting the list price, because they prospect to have a discount. Discounts and rebates are commonly linked to risk-sharing and further managed-entry agreements, which will be analysed later.



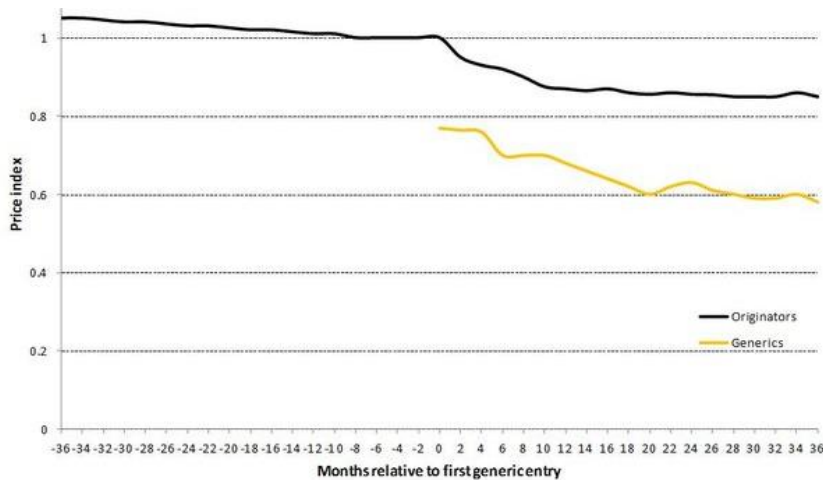
**FIGURE 4.** Average impact of price negotiation, compared to the most common pricing method - EPR (adapted from Panagiotis Petrou, 2016 (46)).

Countries with EPR or VBP strategies have the lowest prices on in-patent medicines (4).

### 2.1.2.2. Off-patent medicines and Generics

In the EU, 56% of the dispensed medicines are generics, and this correspond to 22% of the pharmaceutical expenditure. Besides the fact that these medicines have attractive prices, generally, the originator medicine (off-patent), motivated by the market competition caused by generics, also have its price reduced (47) (see **Figure 5.**). The shift from a product protected by a patent, marketed exclusively by a pharmaceutical company, to an unprotected drug,

potentially produced by an unlimited number of firms in the form of generics, leads to significantly different approach in the pricing strategies (48).



**FIGURE 5.** Development of originator and generics price indices for medicines with generics entry (from GaBI online, 2011 (49)).

- a) *Price capping*. Also known as price ceiling, this methodology is the most used one in Europe to regulate off-patent and generic medicines prices. The regulator can either set a *maximum price* that can be charged for each medicine, or determine that the price of generic medicines needs to be set at a determined *percentage below* the price of the originator (26). This second type of price cap regulation changes the expected market competition – each newly introduced generic has its price reduced to a certain value, and there is evidence that manufacturers do not reduce prices beyond what is imposed by regulation (50). Besides this, the originator can decrease its price to a value where is no longer sustainable to produce generics, creating a monopoly much more sensible to drug shortages (26).
- b) *External price referencing*. As described in the previous chapter, this mechanism is based on an *international benchmarking* of price. The rationale is: If a country/group of countries have similar characteristics, the price of a health technology should also be similar. This is much more common on in-patent drugs, although it can also be found on off-patent ones, to level prices and increase fairness (26).
- c) *Internal price referencing*. Although this mechanism is generally associated to reimbursement policies, it is also used to set prices of medicines after patent loss. It is similar to EPR, but the reference price refers to the ones seen inside the correspondent homogeneous therapeutic category (26,51). A form of IPR is the

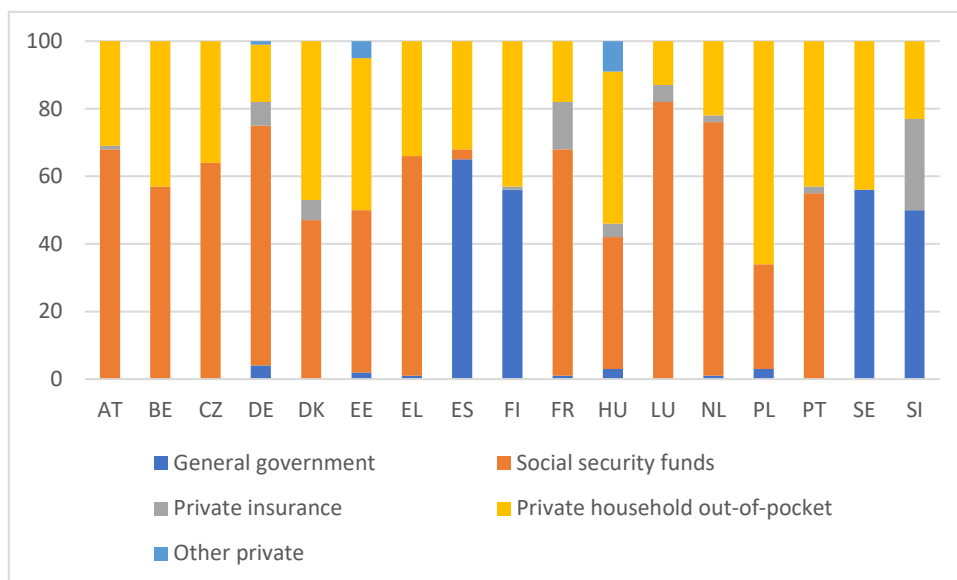
*generic price link*, that also adds that generics have to be priced at a defined percentage lower than the originator (14).

- d) *Free pricing*. In 2007 a study revealed that 17% of the European countries apply a free pricing strategy to generic and off-patent medicines (50). As described before, in this type of mechanism the company can freely set prices, and although in the previous case of in-patent pharmaceuticals, the resulting price was higher, when applied to off-patent and generic drugs, a study supports this mechanism as the one that guarantees the lowest prices (4,52).
- e) *Tendering*. As described before in section 2.1.2.1, this type of mechanism is more prominent in the hospital sector, although it is being applied in some countries in the ambulatory sector. This strategy has a significant impact on the health systems, and it is essential to regulate tendering activities with a *legal basis* – publication of the award criteria, the frequency of tenders, and the obligation of publishing the outcomes (53). The best bidder has the right to have its drug in the public drug plan, being this the only drug available in the homogeneous therapeutic category, and often, in an entire class of drugs, within a hospital, a determined group of hospitals, or even the whole country (50,54). This method helps the payer in controlling the pharmaceutical expenditure since negotiation can bring prices to lower levels. On the other hand, it creates market vulnerabilities to drug shortages, since the purchasing of equivalent medicines from other supplier becomes difficult (26).

### **2.1.3. Procedures in reimbursement decisions**

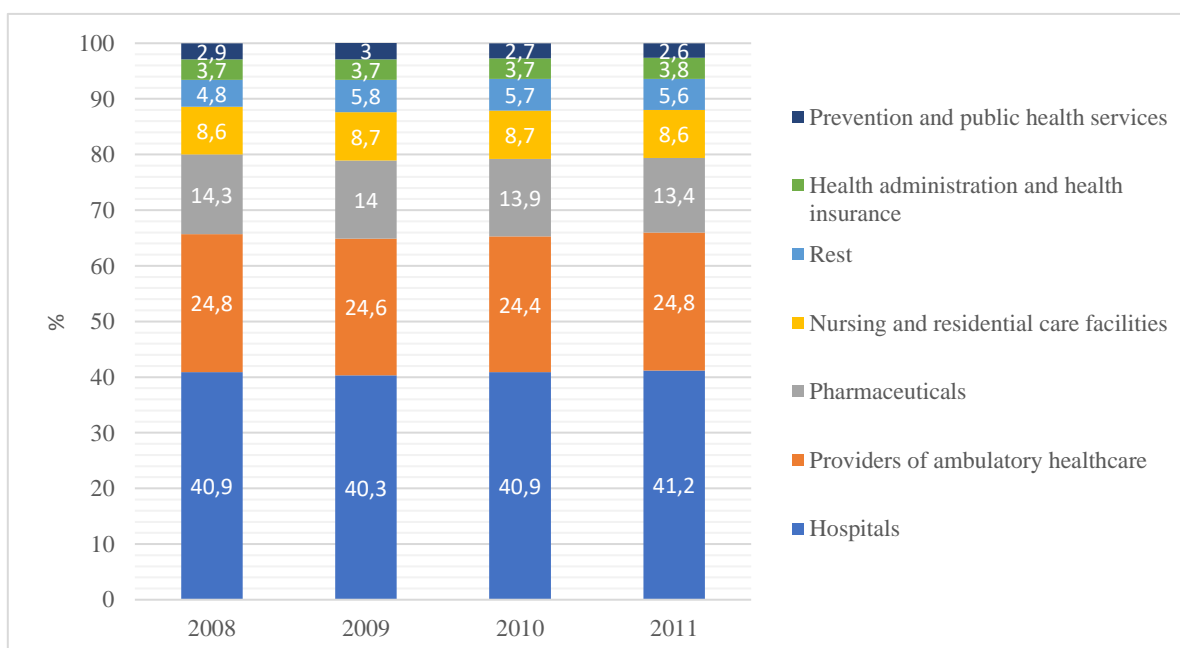
In terms of health, in the EU, the subject that creates a larger distance between Member States in their access to medicines, in particular between Western and Eastern countries, is the national financing decisions – *reimbursement* (55). As described before, these decisions are taken at a national level, and consist in the payment, by a third-party, of a certain amount of the total cost of a health technology. In the case of outpatient medicines, generally the patient has to contribute to the costs, being these called *out-of-pocket* payments (OOP), which will be analysed in section 2.2.2.2. On the other hand, medicines used during inpatient stays or the “restricted prescription” medicines, are funded entirely by basic health coverage (56).

The variations on reimbursement across the EU are mostly related with the decisions about including a medicine in the “reimbursable” group or not and about the percentage of the total price that is reimbursed in outpatient medicines (see **Figure 6.**). This influences the fluctuation



**FIGURE 6.** Spending on pharmaceuticals by financing agent 2012 (or nearest year) (adapted from Valérie Paris et al., 2016 (56)).

that is possible to see on the public share of spending on pharmaceuticals compared with other health expenditure segments (see **Figure 7.**). In this type of graphics as seen in **Figure 7.**, without further data, we cannot take many more conclusions, since *GDP per capita*, type of healthcare system, co-sharing strategies, among others, influence the interpretation. However,



**FIGURE 7.** Distribution of public health expenditure by areas in the EU from 2008 to 2011 (adapted from European Commission, 2013 (57)).

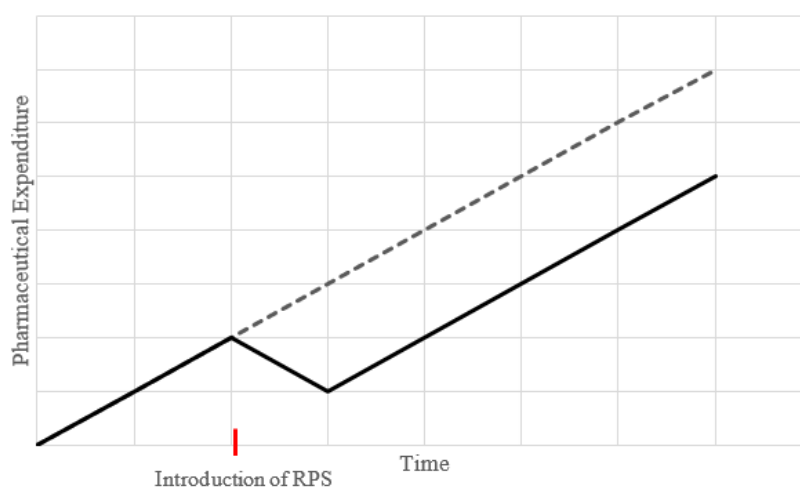
we can see that from 2008 to 2011 the public pharmaceutical expenditure in the EU Member States was around 14% of the total health expenditure, which probably reflects high values – for instance, in the year of 2013, after the most critical times of the global economic crisis, the public pharmaceutical expenditure of Germany was around 34 000 M € (1,2% of the GDP), while in the Netherlands it was near 4 600 M € (0,7% of the GDP), and in Portugal 1 400 M € (0,8% of the GDP) (58). Besides this, it is important to point out that on average, 75% of the health expenditure and 65% of the pharmaceutical expenditure of the Member States are covered by the public payers (59).

Since not all new pharmaceuticals can be reimbursed, countries developed procedures to help in the decisions:

- a) *Reference price system*. This system determines that the reimbursement is fixed by a certain reference value, which is applied to a group of interchangeable medicines – *reference group*, that can either be composed by active substance, pharmacological class, or therapeutic class. Before this, countries generally applied the principles of a *Pure reimbursement system*, where a certain percentage  $a$  was defined, and the patient had to pay  $(1 - a) \times p$  (being  $p$  the price of a given medicine). The difference between a higher or lower price was partially perceived by the patient, since the third-party payer was going to take a percentage of that difference. The reference system changes the paradigm in favour of the government – the reimbursement is applied to the reference value  $p^r$ , and the patient must pay  $p - a \times p^r$ , being this value superior to  $a \times p$  whenever  $p > p^r$ . In other words, the patient has to pay  $(1 - a)$  of the reference price plus the difference between the medicine price and the reference price (60). There are several methods to set reference prices, all these based on the price of a group of medicines (see **Table 4.**). This mechanism implies an attempt to save public money with unnecessary expensive drugs when there are cheaper alternatives, leaving to patient's consideration the decision between more or less pricy medicines (see **Figure 8.**)

**TABLE 4.** Methods for setting reference prices in European Countries 2011 (adapted from Dylst et al., 2012 (61)).

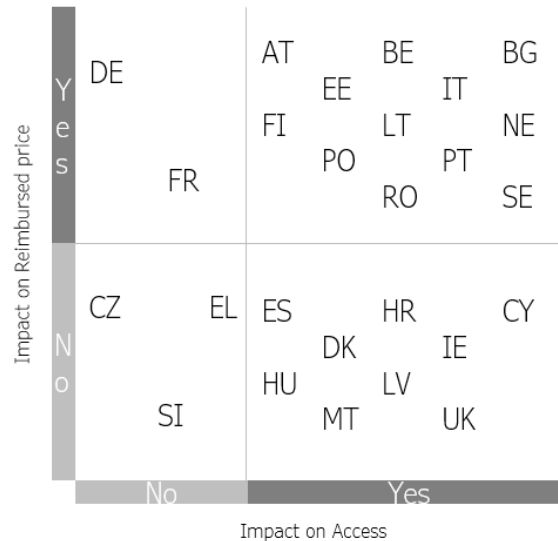
Reference price	Country
Based on the average price of medicines	Croatia, Hungary
Based on the average price of generic medicines	France
Based on the lowest priced medicines	Bulgaria, Czech Republic, Finland, Hungary, Italy, Latvia, Poland, Spain, Turkey
Based on the lowest priced generic medicines	Bulgaria, Denmark, France, Latvia
Based on the average of five lowest priced generic prices	Portugal
Based on the percentage of the originator price	Belgium
Based on the weighted average of all products in one group and calculated by regression analysis (econometric model)	Germany
Based on the weighted average price of medicines (1999 prices)	The Netherlands



**FIGURE 8.** Impact of reference pricing system on long-term pharmaceutical expenditure (from Dylst et al., 2012 (61)).

- b) *Positive and negative formularies.* The most common approach used by third-party payers is to define a list of pharmaceuticals which are covered by public funds in part or in full – Positive lists (62). Criteria as clinical trial data on efficacy, cost-effectiveness and safety are the primary criteria for the inclusion decision on this continually updated list. Negative formularies are exclusive, listing pharmaceuticals that are not covered, being common in the UK and in Germany. These are less common since they require constant updates to exclude inferior, less effective or less safe drugs, over-the-counter (OTC) medicines, among others (26,63).
- c) *Health technology assessments.* This methodology emerged during 1970s, being described by the WHO as a “systematic evaluation of properties, effects and/or impacts of health technology. It is a multidisciplinary process to evaluate the social,

*economic, organizational and ethical issues of a health intervention or health technology.*” (64). Economic evaluation (plus safety and efficacy) is a central focus of HTA, which has a great impact in access and reimbursement decisions, and in fact, in most EU Member States, HTA agencies influence these two aspects (see **Figure 9.**) (27). An effective HTA must consider criteria as: therapeutic benefit,



**FIGURE 9.** Scope and Impact of HTA by market (adapted from N. Balko, 2016 (65)).

patient benefit, cost-effectiveness, budget impact, pharmaceutical/innovative characteristics, availability of therapeutic alternatives, equity considerations, public health impact and R&D. These factors, applied to reimbursement decisions, help to reduce the waste of resources in health technologies that are not safe and/or effective, or have insufficient cost-benefits (66). This type of procedures can be, and in most of cases are, used concomitantly with the previous described methods – formularies and reference price system.

- d) *Contracts.* Negotiated reimbursement contracts between MAH and third-party payers are increasing, meaning this that most of the times list prices do not correspond to the real rebated value, mainly in the hospital setting (67). This strategy has some benefits as: 1) *lowers pharmaceutical expenditure*, 2) *reduces the risk* of overpaying for a pharmaceutical, 3) patients have *less out-of-pocket expenses*, and 4) companies can *accelerate the availability* of new treatments, and so on (68), but it can also bring some challenges. First, when the contract involves health outcomes, most of the times it is *difficult to agree* on what is a meaningful clinical benchmark, and besides this, generally the *time between* the payment and the health outcome has a delay that make inviable the rebate. Besides this, these

contracts may expose payers to “gaming” by manufacturers, because once the initial contract expires, the manufacturer can *stop offering rebate*, while the payer is already loyal to the product (67).

#### **2.1.4. Portugal framework**

In the group of EU Member States, Portugal has been on top when the analysed aspect is pharmaceutical expenditure as % of GDP *per capita*, being only exceeded by Greece (which is a particular case, since the pharmaceutical consumption *per capita* is extremely high). However, the low level of wealth has a profound impact on this indicator, and when we analyse pharmaceutical expenditure *per capita*, adjusted to purchasing power, Portugal comes on the bottom of the list. Nevertheless, all EU Member States have some commonalities – accelerated pharmaceutical expenditure growth (caused by a greater consumption and the introduction of new health technologies) and a willingness to control costs (60).

In Portugal, medicines prices are strongly regulated, which makes sense since it was one of the most affected countries by the global financial crisis and has a NHS type of health system – *Serviço Nacional de Saúde (SNS)*, where the government acts as the main payer.

##### **2.1.4.1. Portuguese health system**

The Portuguese health system can be divided into three co-existing and overlapping systems – 1) the universal *NHS*, 2) the *subsystems* for professional groups, and 3) the *private VHI*.

The NHS was established in 1979 as “*a universal, comprehensive and free-of-charge National Health System*”, but only in 1990, with the Basic Law on Health (Law No. 48/90, of 24 of August) the overall legal framework was established (see **Figure 10.**). From this year on, emergency visits, primary care, out-patient prescription drugs, medical devices, among others, are subject to a user charge, and in 2015, OOP payments accounted around 27,6% of total health expenditure. Regarding specifically pharmaceutical care, *prescription drugs* are subject to variable patient coinsurances based on effectiveness criteria, while *hospital drugs* and special regimen drugs (applied to patients with specific conditions) are covered entirely. In 2014,



62,5% of the pharmaceutical expenditure was public, whereas NHS users' co-payments were around 37,5% (69).

In addition to the coverage provided by the NHS, approximately 25% of the population are covered a health subsystem or VHI. *Subsystems* are often described as a historical remnant of the pre-existing welfare system, offering additional benefits to members of a specific profession and their families. *Private health* insurance was introduced in 1978, and allows people who are willing to pay for this service get a double coverage (or even triple, if there is a system from their job also present) (69).

Since around 2012, still at the peak of the financial crisis, Portugal has suffered a lot of changes, transiting from a static and outdated pharmaceutical pricing mechanism, to a dynamic and bold one, but the greatest change happened around 2014, with the idealization of an innovative system – SiNATS.

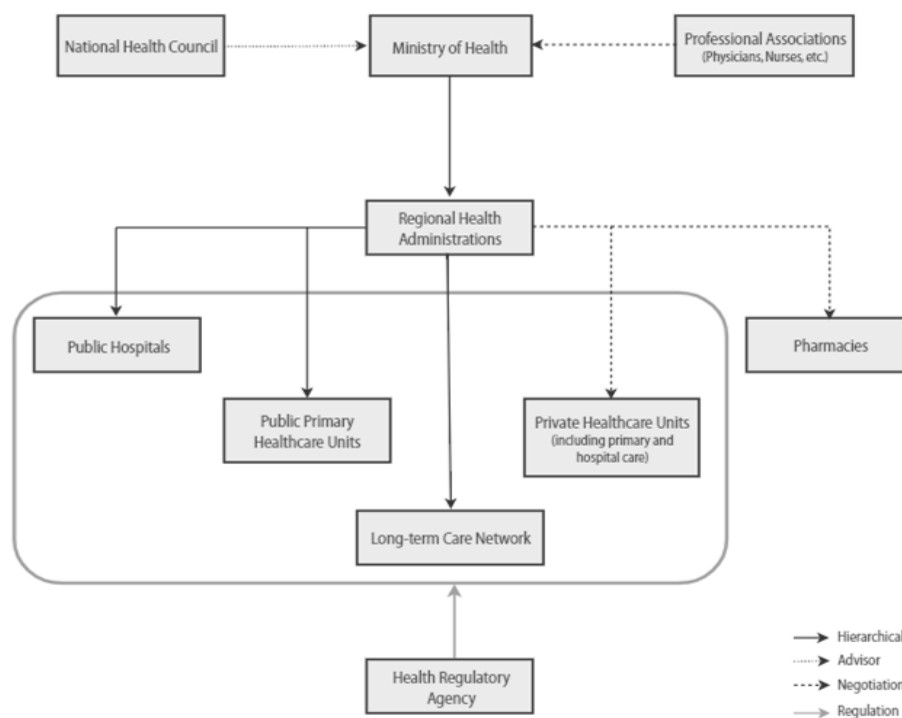


FIGURE 10. Overview chart of the health system (from Simões et al., 2017 (69))

#### 2.1.4.2. Legal-framework – pharmaceutical pricing

The National System for Health Technology Assessment (SiNATS), a body managed by INFARMED (the Portuguese national competent authority), was launched in 2015 (Decree-

Law No. 97/2015, of 1 of June) and covers all public and private institutions that produce, commercialize or use health technologies (69). Aiming at the extension of HTA, risk-sharing and ongoing evidence, and reassessment of current technologies (70), SiNATS brought some profound changes to the pharmaceuticals assessment (see **Table 5.**): 1) inclusion of *medical devices* in the assessments, 2) initiation of the *ex-ante* evaluation in a point where real world data is already collected (after the commercialization), 3) establishment of a *continuous monitoring system*, 4) approximation to the *European model* (joint evaluations and sharing of the conclusions), among others (71).

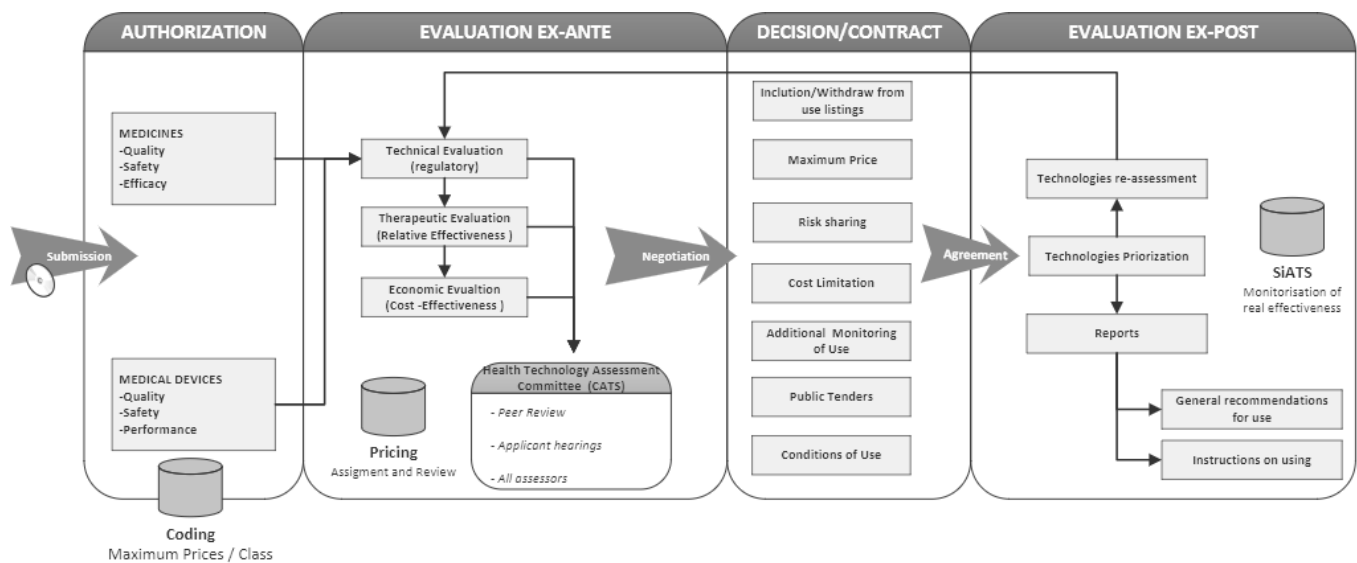
**TABLE 5.** Greatest changes from the old system to SiNATS (adapted from Martins et al., 2014 (71))

Old System	SiNATS
<b>Technology</b> -Medicines	<b>Technology</b> -Medicines + Medical devices + Others
<b>Assessment</b> -Relative Effectiveness -Cost-Effectiveness	<b>Ex-ante evaluation</b> -Relative Effectiveness -Cost-Effectiveness -Other dimensions
<b>Decisions</b> -Maximum price -Public financing/reimbursement/public hospital entry -Control and cost limitation	<b>Decisions</b> -Maximum price -Public financing/reimbursement/public hospital entry -Control and cost limitation -Risk sharing -Additional monitoring of use -Deliberation for public tenders -Utilization conditions and recommendations -Acquisition recommendations
	<b>Ex-post evaluation</b> -Reassessment of technologies on the market (use, acquisition, financing)
	<b>Participation in the European model</b> -EunetHTA, other HTA networks and participation in the creation of the HTAN in the EC

In parallel with the creation of the SiNATs, some other evaluation bodies were created, that intervene in distinct phases of the process (see **Figure 11.**):

- a) *Health Technologies Assessment Commission (CATS)* – This commission is formed by independent experts able to generate *scientific advices* and to help with scientific knowledge in any phase of the global process. It permits a much more robust, strict and *transparent* evaluation procedure, completely independent and merely scientific. It is important to note that the assessment must not have in consideration other dimensions as other existing alternatives, access, resource allocation, health priorities, available budget, among others (71).

- b) *Health Technologies Assessment Information System (SIATS)* – This system is one of the pillars of SiNATS, since it is responsible for the *monitorization of the performance* of the technologies, providing information (mainly cost-effectiveness) for assessments and posterior reassessments, to support public financing decisions. To carry out their functions, it must be strongly connected with the *EUnetHTA* (which will be explored in section 2.2.1), with *other HTA agencies*, with *hospitals*, *academic centres*, *MAH* and even with the *national patient registry* (71).



**FIGURE 11.** Health technologies route, from the submission for the authorization, to the continuous monitoring (from Martins et al., 2014 (71))

In addition, the Decree-Law No. 97/2015 also dedicates some space to other matters, as the formation of *ambulatory medicines prices* (composed by the *ex-factory price*, the *wholesaler margin*, the *pharmacy margin*, a *special tax* earmarked for INFARMED and a *value-added tax (VAT)* of 6%) and to the hospital medicines prices, composed by the *ex-factory price* plus *VAT* (72).

Right after the publication of the Decree-Law relative to the SiNATS, several ordinances were published, complementing and updating the entire pricing system. Regarding the *definition, change and review of medicine prices*, Ordinance No. 195-C/2015, of 30 of June, showed a significant importance, emphasizing above all the *maximum price system* (applied to prescription and non-prescription medicines which are reimbursed), and revealed the criteria for the *determination of PRPs* (73):

- a) The *ex-factory price* is determined using the ERP strategy, that is, the average ex-factory price of the selected reference countries, which are chosen yearly (74). If

none of these countries have the medicine, the external price is the ex-factory price in the country of origin.

- b) The *maximum PRP for generic medicines* depends on the reference medicine price (the average maximum PRP of the originator medicine over the last 2 years), where the first generic price must be at least 50% lower than the reference price, or 25% if the ex-factory price is inferior to 10€. If the originator medicine was not authorized in Portugal, the ERP procedure is applied.
- c) The *maximum PRP for medicines subject to parallel importation* must be at least less 5% than the maximum PRP approved for the medicine.
- d) The *maximum ex-factory price for hospital medicines*, which was added in the Ordinance No. 290-A/2016, of 15 of November, for non-generic medicines must not be higher than the ex-factory price for the reference countries, and the generic medicines have to be at least 30% less than the reference medicine price (75).

Besides this, the cited ordinance also defines the mechanism for the *price authorization, alteration and revocation*, and the *maximum commercialization margins*. Another important section is about price reviews, being described the procedure for the *annual review for non-generic medicines* (based on the ERP procedure), *for generic medicines* (where the value is normalized to, at least, 50% of the PRP of the reference medicine, or 75% if the price is lower than 10€), the *exceptional review* (motivated by public interest or initiative of the MAH) and the *annual review for hospital medicines* (where the ex-factory price cannot be superior to the lowest ex-factory price of the reference countries neither to the previous revised and approved prices) (73).

Concerning the *notified prices system*, Ordinance No. 154/2016, of 27 of May, defines that the MAH has the freedom to set the price of the medicines subject to this mechanism (non-reimbursed prescription medicines). According to this system, the price is agreed between the MAH and the government, and it can only vary up to 10% each year, being the commercialization margins 20% for pharmacies and 8% for wholesalers (76).

### **2.1.4.3. Legal framework – reimbursement**

Regarding reimbursement decisions, the procedure is described in the Ordinance No. 195-A/2015, of 30 of June, from the request to the acceptance or rejection. The evaluation of the application is also explained and, as detailed before, the *pharmacotherapeutic assessment* is assured by the *CATS*, and the report generated in this assessment must be accepted by the *National Pharmacy and Therapeutic Commission* (CNFT), that decides if the medicine will be included in the *National Medicines Formulary* (FNM). Only after the approval by *CATS*, the pharmacoeconomic evaluations starts. The final decision should be taken in 30 days for generic medicines and 75 days for non-generic medicines. If the medicine is approved, it must be reassessed from time to time (77).

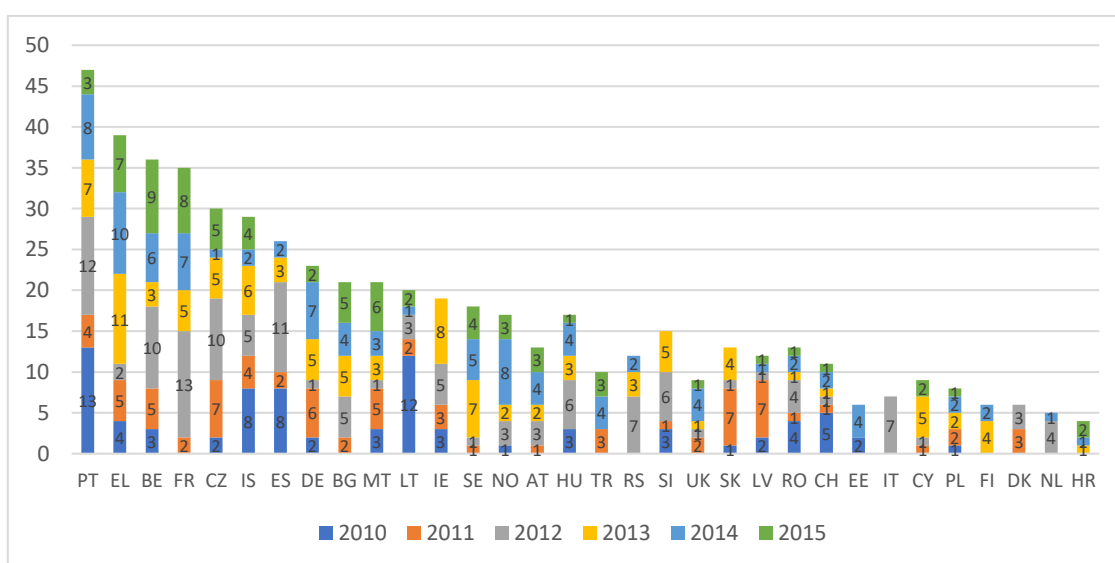
The previously described procedure is similar to the one used in *previous evaluation of hospital medicines* – firstly an evaluation by the *CATS*, then approval by the *CNFT*, and then the decision-making bodies have 75 days to give the final decision (77).

The reimbursement is distributed by *4 tiers*, where the *reference price system* is applied – A, corresponds to 90% of the reference price; B, corresponds to 69% of the reference price; C, corresponds to 37% of the reference price; D, corresponds to 15% of the reference price (78). In case of pensioners and specific diseases, an extra percentage is added. As showed before in Table 4, the reference price is based on the *average of five lowest priced generic prices* in the same homogeneous therapeutic category (medicines with the same qualitative and quantitative composition, dosage, administration route, pharmaceutical form or equivalent, that have at least one generic in the market) (79). In Portugal, a positive formulary system is also used to define which pharmaceuticals are reimbursed or not, being this list updated and published periodically by *INFARMED* (77).

## **2.2. Policy interventions to control pharmaceutical expenditure**

Although pharmaceutical policies can address several topics, the key goal is generally to serve the public health objective by assuring access to medicines while maintaining the financial sustainability of the health system. This means that, in spite of the differences related to pricing and reimbursement, it is possible to see a pattern across Europe regarding the reduction of the pharmaceutical expenditure (80).

In 2016, a study performed by Sabine Vogler et al. (80) found a total of 557 measures implemented between January 2010 and December 2015 in 32 European countries, with a higher number of measures applied between of 2012 and 2013. Overall, measures impacting medicine prices accounted for a total of 126 measures (23%), and the second most “crowded” area was generics, with a total of 101 measures (18%). Portugal was the country that during this period implemented most measures, which is not surprising giving the Portuguese economic situation at that time that led to many austerity policies (see **Figure 12.**).



**FIGURE 12.** Number of pharmaceutical policy measures per year in each of the 32 European countries during 2010-2015 (adapted from Vogler et al., 2016 (80)).

### 2.2.1. European initiatives and projects in the field of pharmaceutical pricing

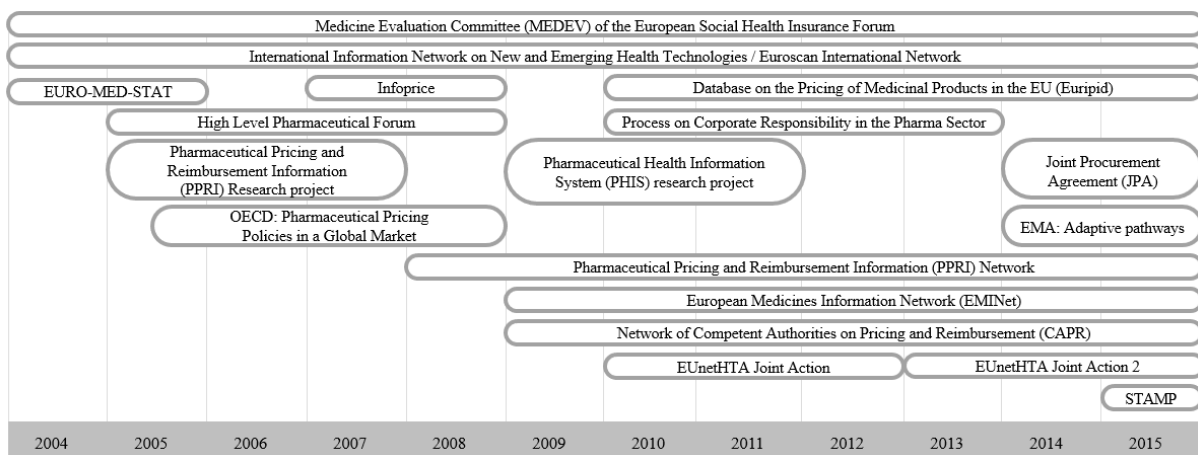
Since the beginning of the new millennium, the EU held some interventions in the area of the medicines, mostly in the shape of *recommendations* (see **Figure 13.**). Around 2002, the *G10 group* was established with the purpose of gathering MS and stakeholders to enhance competitiveness and innovation while addressing pricing issues. Later, in 2003, a Communication called *A stronger European-based pharmaceutical industry for the benefit of the patient – a call for action* was released to provide a forum to generate and share information about pricing and reimbursement.

In 2005, the *High Level Pharmaceutical Forum*, composed by the EC, all MS and other stakeholders, was created, with the aim of ensuring patient’s access within a sustainable healthcare budget. It had three main working groups on: *Information to Patients, Pricing and*

*Reimbursement*, and *Relative Effectiveness*. One of the final recommendations was that MS should control the prices of reimbursable medicines, but allow MAH to set freely the price of non-reimbursable medicines, which ended up having a great impact in pharmaceutical policies around the EU (4,20).

Still having the sharing assumptions in mind, the *network of Competent Authorities for Pharmaceutical Pricing and Reimbursement* (CAPR) was set, aiming to provide a sharing platform for competent authorities and generates reports about pricing and reimbursement matters. Later, in 2010 the European medicines price database called *Euripid* was established, working as a self-administered and self-funded project (4). Besides Euripid, there are other 3 known databases – *Ecphin*, *EudraNet* and *Infoprice*.

More recently, some greater projects started, mainly linked to the initiative started in 2005 with the name of *European Network on Health Technology Assessment* (EUnetHTA), having by now 78 organizations from 29 countries. This platform, that is commonly referred to as “*a preferred facilitator of high-quality HTA collaboration in Europe*”, is already responsible for three *Joint Actions* (JA) with the purpose of establishing a permanent network of HTA in Europe. *JA1* (2010-2012) focused attentions on relative effectiveness, uniting national HTA agencies and procedures (81). *JA2* (2012-2015) had the goal of establishing a general strategy, principles, and to test the capacity of producing common HTA methodologies (34). In 2016, *JA3* was launched aiming to finally achieve a sustainable model for the scientific and technical cooperation on HTA, with rapid decentralised HTAs (81).



**FIGURE 13.** Initiatives, projects and reports in the field of pharmaceutical pricing in the EU (adapted from European Commission, 2015 (4)).

Signed for the first time in 2014, the *Joint Procurement Agreement* (JPA) is another arrangement made by EU Member States, for *pandemic vaccines and medical countermeasures*. This agreement has a voluntary nature and is based on the concept of multi-country joint procurement of medicines, allowing a strengthened purchasing power and assuring an equitable access to medical countermeasures. It has significant advantages when compared to the regular purchasing methods, as: 1) *equitable representation* and criteria for allocation of scarce supplies, 2) *competitive tender* and bid process, preventing frauds and corruption, 3) *security of supply*, increasing the predictability for both sides, 4) *minimization* of the operational costs and administrative burden, 5) possibility of a regional or supranational *financing*, among others. The JPA was initially thought to reach beyond vaccines, and it can be seen as a *pilot project* for a greater cooperation mechanism with the purpose of improving the financial equity and access to medicines across the EU Member States (4,81,82).

### **2.2.2. National tools and measures**

From a general point of view, starting from a basic analysis, a typical market has two basic economic units – suppliers and demanders. In the specific case of pharmaceutical markets, it is more complex since the demand side has at least three decision-making components – the patient, the prescriber and the pharmacist (although it is not clear if pharmacists are part of the demand or supply side) (17). Besides this, at a national level, measures are quite specific, so it is important to know each health system, patients' behaviour, and national economies to fully understand the strategies and decisions to control the pharmaceutical expenditure. The following analysis, that describes some national tools to control pharmaceutical expenditure, will have this division into account, based on the approach made by Jaime Espín and Joan Rovira in a study from 2007 funded by the EU (17).

#### **2.2.2.1. Supply side practices**

The supply side refers to all the stakeholders that are responsible for the *provision of pharmaceuticals* – manufactures, wholesalers and pharmacies, and this is the most regulated side of the pharmaceutical markets, with measures involving the control of prices, of total expenditure, return on investment, and others.



a) *Control of prices*. These measures can be divided in three types of activities – *pre-launch* (anticipate potential requirements and impact, and prioritize therapeutic innovation), *peri-launch* (related to pricing and reimbursement decisions for in-patient medicines) and *post-launch* (centred on an evidence-based assessment, to address the appropriate and sustainable use of medicines) (84).

i. *Pre-launch activities*:

1. *Horizon scanning and Forecasting*. *Horizon Scanning* practices are used essentially to detect the emerging technologies before they are launched. One of the most frequent objectives of this mechanism is to decrease, or at least *predict, the economic consequences* of an upcoming technology (risks, benefits, necessary evidence...). *EUROSCAN network*, which appeared in the previous topic, is a project that aims to promote collaboration and exchange of information collected from horizon scanning activities (27,83). *Forecasting*, on the other hand, is based on the analysis of the pharmaceutical use and expenditure to improve the *resource allocation and the predictability of procurement*. This is a growing field, and the EU started an initiative, previously described – *JPA*, that consists in a joint procurement based on future forecasts (84).

2. *Cost-effectiveness analysis*. In the perspective of “pre-launch activities”, cost-effectiveness studies help the decision-makers in deciding about the “fair” value to pay for a determined health technology. These studies are also part of the post-launch activities, used both to support the assessment of the performance of a determined health technology according to the terms firstly agreed and for price reviews (27).

ii. *Peri-launch activities*:

1. *Price regulation*. Also referred to as product price control, administrative or statutory pricing, or price cap, this strategy consists in a *fixed or maximum price* applied to the product in an initial stage or in posterior price changes. Depending on the way this cap is calculated,

there are several other associated concepts: 1) *cost-plus pricing*, calculated according to the cost, plus a certain margin; 2) *external price referencing*, where the price is limited to the price applied for the same product in other countries; 3) *internal price referencing*, based on the cost of similar existing treatments (80,17).

2. *Negotiations*. As described in section 2.1.2.1, a price negotiation is based on an agreement made by the payer and the supplier, and is one of the most common methods to achieve lower prices. Generally, this results in a price reduction, made under specific conditions. However, it masks the real practiced price, generating inequity in access (80).
3. *Generic price linkage system*. This is a form of *IRP*, applied to generic medicines, that require these products to be priced at a defined percentage below the originator's price. In some countries the additional followers and even the original products after patent loss, have to lower their prices according to pre-defined rates (14,80). Countries that do not have a generic price link policy have to rely on competition to reduce generic prices (14) (see **Table 6.**).

**TABLE 6.** Generic price link policy in European countries in 2014 (adapted from Vogler et a., 2014 (14)).

Country	Generic price link	Country	Generic price link
AT	Yes	IE	Yes
BE	Yes	IT	Yes
BG	No	LT	Yes
CH	Yes	LU	Yes
CY	Yes	LV	Yes
CZ	Yes	MT	No
DE	Yes	NL	Yes
DK	No	PL	Yes
EE	Yes	PT	Yes
EL	Yes	RO	No
ES	Yes	SE	No
FI	Yes	SI	No
FR	Yes	SK	No
HU	Yes	UK	No

iii. *Post-launch activities.*

1. *Price reviews.* In the area of *price control*, the main activity performed in a *post-launch phase* is the evaluation of the price of certain pharmaceuticals in order to contain costs. Usually this is made by *comparison* with other countries, but with the constant growth of HTA, *pharmacoeconomic studies* made by evidence/patient registries collected during a determined period are also being used (specially to check the accomplishment of agreed provisions as in managed-entry agreements) (14,80).

2. *Price changes.* These are characterized by the increase or decrease of a price, generally at ex-factory level, and in fact price changes can be divided in *price cuts*, related to external economic pressure (84) and in *price freeze*, where the price of a pharmaceutical is fixed at a given level for a certain period (17).

b) *Control of total expenditure.* This type of procedures, contrary to the previous ones, aim to affect the pharmaceutical expenditure in generally, *not affecting list prices*. Sometimes these are *more effective*, since price control can lead to higher consumption, and by consequence, to greater expenditure (17).

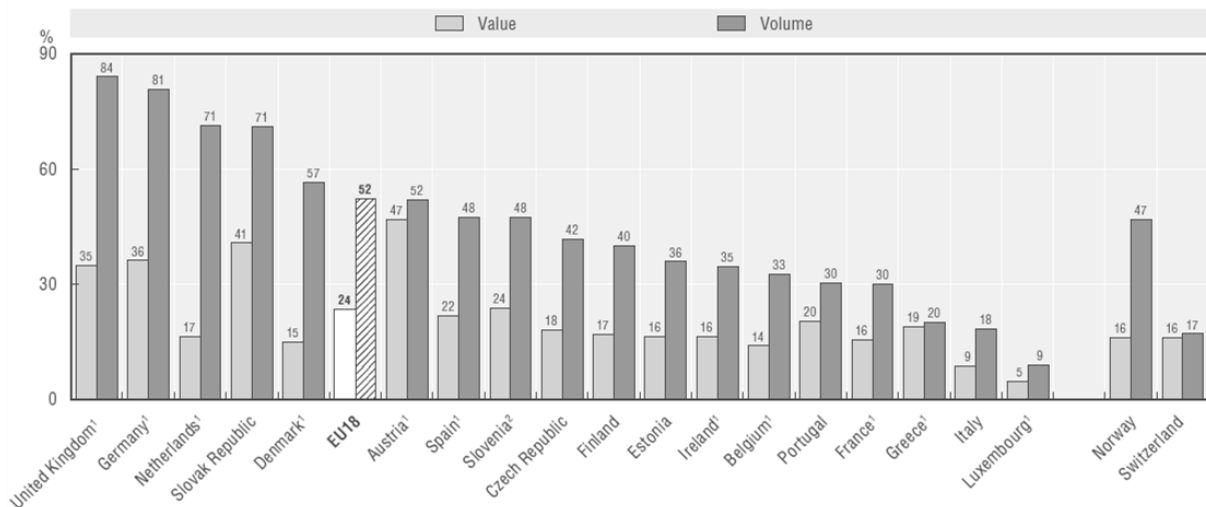
i. *Payback.* This mechanism comes from an agreement between the manufacturer and the payer, that requires manufacturers (individually or via their association) to *return part of their revenue* if the sales exceed an agreed maximum amount (17).

ii. *Clawback.* These policies aim to reduce pharmacy margins by classifying as *a revenue to the public payer*, the discounts on the dispensing fee of pharmacies (17). In Spain and in the UK a progressive percentage applied to the pharmacy's monthly turnover is applied. This mechanism rely on pharmacists and wholesalers to report the actual rebates received, which can be seen as a weakness (84).

iii. *Rebates.* This is a payment made by the supplier to the payer, after the purchase, where the manufacturer has to return a share of their overall

revenue (percentage of sales of reimbursed products, generally) (80). These do not require any previous agreement on a ceiling revenue/sales (17).

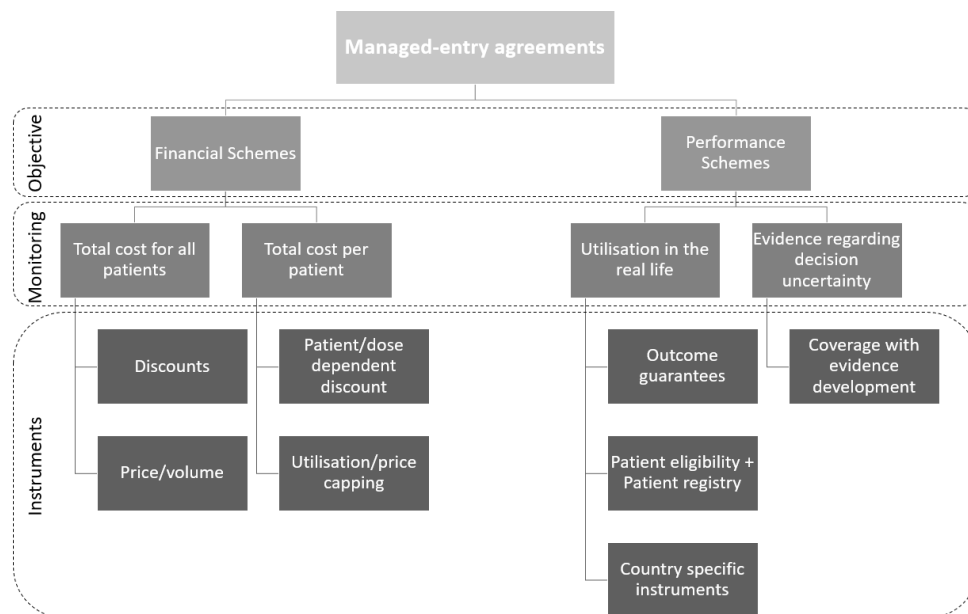
- iv. *Public tendering.* By definition, tendering is “any formal and competitive procurement procedure through which tenders/offers are requested, received and evaluated for the procurement of goods, works or services.” (85). As described in section 2.1.2.1, tendering is typically applied in the in-patient sector, and, indirectly, helps to control expenditure, without controlling directly the prices (53).
- v. *Share of generic market.* The encouragement of a greater use of low-cost generics (and biosimilars) accompanied most of the EU Member States during these recent years to managed budget impact (see **Figure 14**). An higher share of generics can be achieved by several parallel methods as *generic price link, INN prescribing and mandatory generic price reduction* (84).



**FIGURE 14.** Share of generics in the total pharmaceutical market, 2014 (adapted from OECD/EU, 2016 (86))

- vi. *Managed-entry agreements.* MEAs are formal arrangements between payers and manufacturers with the purpose of sharing the financial risk due to the uncertainty on actual real-life outcomes of mainly new, innovative, expensive technologies. These instruments are possibly the most complex group of procedures in the “Policy interventions to control pharmaceutical expenditure”, combining non-financial and/or financial elements to achieve four main goals – *limiting budget, improving cost-effectiveness, improving*

use, and increasing access (87). The nature of MEAs differ a lot between countries, yet a report published in 2013 by Alessandra Ferrario and Panos Kanavos (87) proposed a new, simple and flexible taxonomy for MEAs, in which this section will be based on (see **Figure 15.**). Agreements can often be divided into financial and health-outcome based agreements (which can fall into the financial group). Purely financial schemes include: 1) *Price-volume agreements (PVA)*, that limits treatment to the target population, defining a threshold (or several tiers) of expenditure/sales after which a rebate is triggered (87,88). 2) *Discounts*, that were described previously in this section. 3) *Capping schemes*, which involve the establishment of the duration of the treatment, dose or cycles of treatment, total expenditure, among others, after which, the manufacturer is penalized and has to provide a discount or



**FIGURE 15.** Proposed taxonomy for MEAs (adapted from A. Ferrario and P. Kanavos, 2013 (87))

pay if any of those aspects are exceeded (88,89). 4) *Patient/dose dependent discount*, which involve an initial discount on all doses, free initial doses for eligible patients, or free doses for a number of treatment cycles (87).

On the other hand, *performance-based* risk-sharing arrangements can be divided in two important categories – *performance linked reimbursement schemes*, that aim to link the performance at the individual patient level to payment or reimbursement, and schemes where the *coverage decision is*

*conditioned* upon the collection of data/evidence (89). Within the first group there are: 1) *Outcomes guarantees*, where the payer only pays for the responder patients, or has a discount/refund for non-responders (87). 2) *Process of care*, where the payment/access is limited to patients that satisfy certain criteria for a treatment, which is monitored through the registries (87,89). The second group, is based on *Coverage with evidence development* (CED) schemes, where the countries have a determined period to collect additional data (from specific patients, or from all patients using the drug) to update the final coverage decision, based on the cost-effectiveness results of the HTA (87,89). Besides the great opportunities and strengths of these strategies, MEAS can be a great threat for healthcare systems, especially if manufacturers start proposing higher entry prices in expectation of engaging in a MEA (87).

- c) *Others*. This category gathers all the measures that do not include a control of the drug price or of the expenditure, which are more specific of determined MS.
- i. *Tax benefits*. These are used to improve and incentivize the company's investment in R&D or in manufacturing capacity, being common in Belgium (17).
  - ii. *Value-added tax*. Since the early 1990s, VAT has become a strategy to raise government revenues, and there is even a trend for VAT to replace sales tax. In the EU, VAT on medicines ranges from 0 to 25%, and in general it is lower on medicines than on other products (33).

### **2.2.2.2. Demand side practices**

The demand side refers to the agents that are responsible for prescribing, dispensing and consuming medicines, and these practices aim to influence/change the behaviour of this group. The most obvious “demanders” are physicians, patients and even pharmacists, but we can also include the third-party payers (the one that reimburses) as the fourth agent (17,90):

- a) *Physicians*. These health professionals can be seen in most of the health systems as opinion leaders, meaning this that measures that aim to change physicians'

behaviour generally have a great positive impact. Their performance can be influenced by several effective mechanisms, that might be always reinforced by financial or non-financial incentives for good prescribing practice (17,90):

- i. *Educational*. In this type of initiatives, we can include: 1) *Clinical practice guidelines/ prescription guidelines*, that help doctors in choosing cost-effective pharmaceuticals, and in few countries enforce doctors to prescribe by the INN, and 2) *Academic or computerized support*, to improve rational prescribing (17,90).
  - ii. *Steering*. These methods include some monitoring actions from the third-party payer side, in order to analyse and to ensure the accomplishment of stipulated targets: 1) *monitorization of prescribing patterns*, to incentivize physicians to adhere to the guidelines made by regulatory agencies, which can be easily done by using electronic prescriptions (92); 2) *prescribing quota*, to limit the average cost of prescriptions by physician, incentivizing a more rational prescribing, or to define a target of the percentage of generics to be prescribed (17,91). 3) *maximum pharmaceutical budget*, which is a maximum pharmaceutical budget defined for a period, region, speciality and physician (91).
  - iii. *Incentives*. These methods can be seen as rewards or punishments, to be applied if they follow or ignore prescription guidelines, quotas and budgets (17).
- b) *Patients*. These are the most important agents of the entire system, since everything depends on them. If patients are not willing to pay, they will not. Even when the pharmaceutical is fully reimbursed, if patients do not want to take it, they will not. In general, therapeutic compliance is very low, and this is a major health problem, bringing attached economic consequences. There are several action being taken across the EU to improve citizens' health literacy and to make them conscient of the costs that some action bring to the healthcare system (93).
- i. *Educational*. The most common strategy to aware people about health problems is *information campaigns* and *public health educational campaigns*, and the same applies when the theme is the rational use of medicines (91).

- ii. *Steering*. In this category there is a method that is recently disseminating around the EU – *conditional reimbursement*. The goal of conditional reimbursement is to promote effective and efficient use of pharmaceuticals, by limiting reimbursement to specific criteria or rules – to specific categories of patients, by authorized physicians, or with prior authorization from the health insurance company. This mechanism aims to limit the expenditure in certain expensive pharmaceuticals, especially when there is a risk of inappropriate use (94).
  - iii. *Incentives*. Several methodologies are being put to practice to increase the price sensitivity of patients, reduce the unnecessary use of medicines, and to reduce expenditure of public payers, namely *cost-sharing* practices. This may be applied as a: 1) *deductible* or excess, which is an out-of-pocket payment, with a fixed value, that must be paid for a service in the form of a percentage or total cost before any payment of benefits can take place; 2) *co-payment* or user fee, that is also an out-of-pocket payment, with a fixed value, to be paid for a service or a health technology (*i.e.* prescription fee); 3) *co-insurance* or percentage co-payment, in which the patient pays a certain fixed proportion, where the health system pays the remaining proportion (17).
- c) *Pharmacists*. Community pharmacists are most accessible the health professionals, making them great agents to improve responsible use of medicines (95). This motivated some voluntary and mandatory measures that governments are taking:
  - i. *Educational*. Information campaigns directed to pharmacists can be quite effective, showing practical data and evidence on how a change in behaviour can bring great saving to the health system (91).
  - ii. *Steering*. The greatest and most obvious strategy used to control public expenditure on medicines where pharmacists have greater impact is *generic substitution*. Pharmacists have either the right or the obligation to substitute the brand medicine for a cheaper (generic) one. The cost-saving potential is high because generics have lower prices, so if the reimbursement tier remains the same, the absolute *reimbursed value decreases*. Besides this, generics increase competition, leading to *global lower prices* (91).



- iii. *Incentives*. There are many reported methods that aim to put pharmacists in harmony with the main health systems' goals, being the most used ones: 1) *control of margins*, where the gross profit of pharmacies is a fixed percentage of the pharmacy retail price, and generally the percentage is set to give regressive margins or there are fixed fees, so pharmacist do not dispense expensive over cheaper medicines (91); 2) *financial incentives* over the dispensing of generics, cheaper medicines or for providing professional services beyond dispensing medicines (96).
- d) *Reimbursement*. As described before, some methods aim to modify the impact that the reimbursement of some medicines has on pharmaceutical expenditure: 1) classification according to a *reference group*, to set a reference price which will be the value that corresponds to the reimbursement, being this revised every three months; 2) introduction of *negative* (non-reimbursed medicines) and *positive list* (reimbursed medicines); 3) reclassification from prescription to OTC medicine, which generally are not reimbursed; 4) change in *reimbursement lists and rates*, since the social value for which the government pays can change over the years (91).

### **2.2.3. Portugal strategies to control pharmaceutical expenditure**

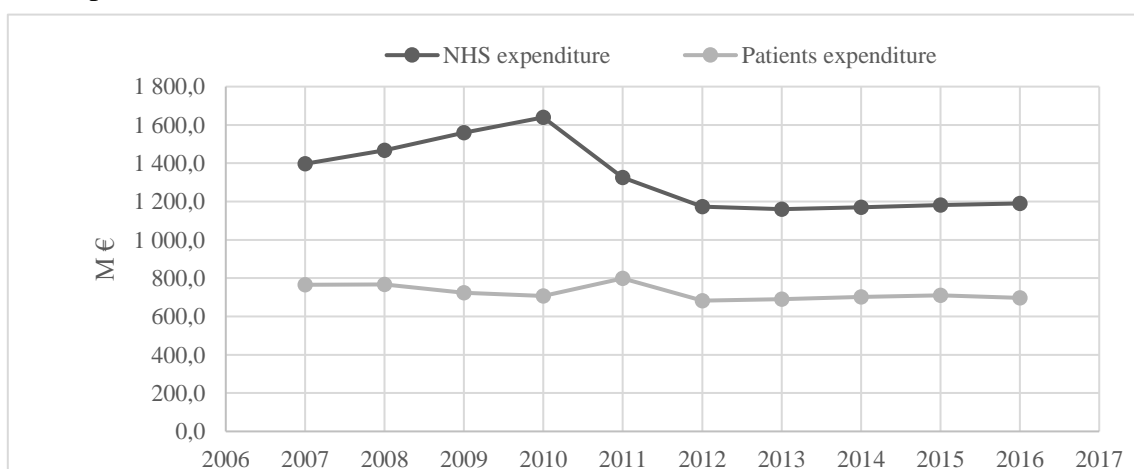
During the last years, Portugal stood out from the rest of the EU Member States in term of number of pharmaceutical regulatory actions. In part, this was motivated by urgent and imperative need to reduce the public expenditure, encouraged by the Financial Assistance Program (97). Portugal witnessed measures that decreased commercialization margins, enlarged the generics market share, that reduced (voluntarily and mandatorily) prices in general, increased the co-payments, changed prescription patterns, among others (98). Currently, the strategies in which Portuguese pharmaceutical policies are based on, are described in the National Medicine and Health Products Strategy 2016-2020 (99):

- a) “(...) *reassessment of the reimbursement of medicines (...) namely in groups as antidiabetics (DPP-4) and fixed association drugs for HIV. (...) to ensure a better control of public expenditure (...). Additionally, readjustment processes are in course to reduce or exclude from the reimbursement lists medicines that have a*

*higher price (>20%) than the therapeutic alternatives, or with effectiveness or efficacy is not proved.”*

- b) *“Systematic reassessment of medicines of which there is no comparative effectiveness demonstration, motivated by lack of effectiveness or excessive cost. Modifications on the Reference Pricing System, mainly in the reference price definition criteria (...). Review of the reimbursement system, (...) to assure a greater therapeutic rationality and a better equity in the financing (...).”*
- c) *“(…) implementation of a campaign (...) to guarantee the access to the most adequate treatment and maximum savings to patients and to the NHS. Review of generic medicines prices (...), modification of the formation principles of homogeneous groups and respective reference prices (...).”*
- d) *“At a hospital medicines management level, the publication of information regarding the use and expenditure with medicines will continue (...). Also, the use of biosimilars will be an instrument to a more rational use of resources. “*

Even the State’s Budget for 2017 dedicates some articles to necessity of controlling the public expenditure on medicines mainly by “(…) increasing the market share, in value, of generics to 40% (...)”, and by promoting the centralized acquisition of pharmaceuticals by national health structures, in articulation with the SPMS and ACSS, among others (100). During the last years, since the signature of the Memorandum of Understanding (MoU), the public expenditure has been around 1200 M € (see **Figure 16.**) that corresponds to 13% of the total health expenditure (101).



**FIGURE 16.** Evolution of the expenditure with medicines in continental Portugal from 2007 to 2016 (adapted from PORDATA, 2017 (101))

Between 2010 and 2015, before the publication of the cited National Medicine and Health Products Strategy, Portugal summed up 47 measures, which, as said before, corresponded to the highest value of action in the EU (80). The most recent and relevant ones were:

- a) *Creation of the SiNATS*. As described before, SiNATS was launched in 2015 with the aim of assessing health technologies and their utilization, and has one major goal – *control of expenditure in medicines*, by maximizing health gains, contributing to the sustainability of the NHS, guaranteeing an efficient use of resources, and by promoting the equitable access to health technologies (69, 72). Specifically, Decree-Law N.º 97/2015 dedicates several paragraphs to matters as: 1) *health technologies assessment*, and its importance for the financial sustainability; 2) relevant aspects to establish *reimbursement or previous evaluation contracts*, introducing new managed-entry agreements; 3) prediction of situations where a health technology is *excluded from reimbursement*, and the process by which a product can be reimbursed; and 4) description of the *previous evaluation of health technologies*, and the assumptions that this process implies or can imply (72). Most of these points will be explained in the following paragraphs.
- b) *Definition/review of reference countries*. Although in Portugal EPR is used as a pricing procedure, it can also be seen as a budgetary policy to reduce pharmaceutical expenditure, since it can be used to give *additional information* during price negotiations and to *control the price* of medicines (31). Since 2015, with the establishment of the SiNATS, it was decreed that the reference countries should be defined in an annual basis. For the year of 2017, Ordinance No. 290-B/2016, of 15 of November, defined that the reference countries are *Spain, France and Italy* (74).
- c) *Contribution over the pharmaceutical industry*. Law No. 82-B/2014, of 31 of December, introduced a contribution over the pharmaceutical industry, aiming to *control the volume and value of sales*. This law determines that for pharmaceuticals that are reimbursed, subject to restrict prescription, subject of exceptional use or exceptional authorization, medicinal gases, blood derivatives and orphan

medicines, the company has to pay a percentage of the value that results from total sales (102).

d) *In the ambulatory sector.* Summing up all the legal measures that were published during the last years, the majority focused on the ambulatory market, influencing directly the profits and strategies of the companies:

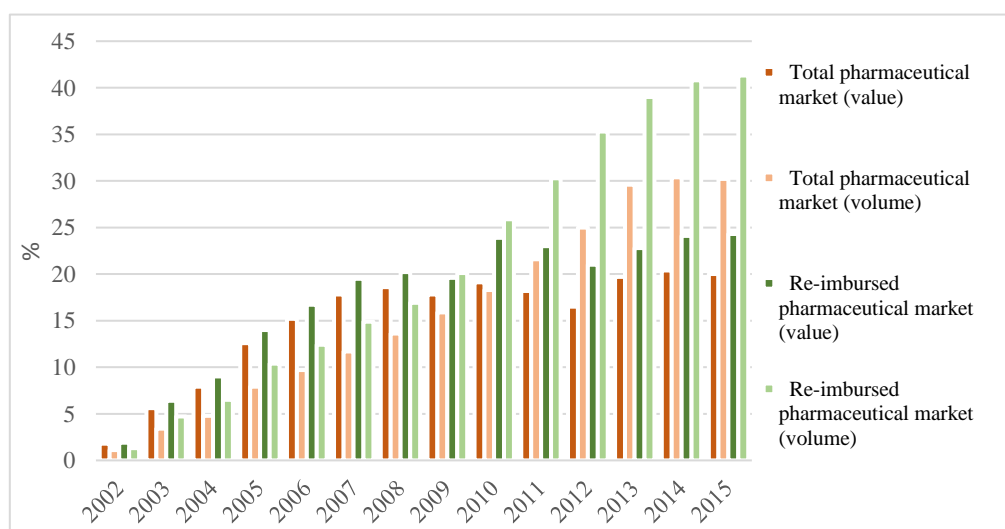
i. *Direct impact in the PRP or in the public expenditure.* Analysing all the measures affecting medicines prices, from the period of 2000 to July 2017, it is possible to conclude that – within the 53 collected legal laws, 77 measures were accounted, where 9 imposed *price reductions*, 19 brought new rules to the *pricing formation* methodology, 6 focused on the regulation of *commercialization margins*, and 38 made alterations to the *reimbursement* percentage or covered groups (see Annex 1.) (103). A study revealed that among these, the most effective strategy is to change the price formation rules, which decreases the total expenditure, the PRP, the total expenditure *per capita* and the package price (98).

ii. *Annual review of medicines prices.* Once a year, prices are reviewed, and this practice is associated with the EPR strategy, since prices are generally compared with the ones practiced in the reference countries. Decree-law No. 97/2015, of 1 of June (72) and particularly Ordinance No. 195-C/2015, of 30 of June (73), regulate the procedures for both *originator* and *generic medicines*. The main difference between these two is that generic medicines prices have to be reduced to 50% of the maximum price or to 75% if the ex-factory price is inferior to 10€. In both cases medicines with a maximum PRP inferior to 5€ (originator) or 3,25€ (generics) are exempt of this rule. This is a powerful methodology, since a regular price review is a key factor to have price-drops (4). From 2000 to 2017, 5 measures affecting the annual price review were found (103).

iii. *Exceptional review of medicines prices.* Whenever there is a public interest or the MAH has the initiative, there can an extraordinary price review, which is referred in Decree-law No. 97/2015, of 1 of June (72) and detailed in Ordinance No. 195-C/2015, of 30 of June (73). The decision depends on the

indispensability, the economic viability, and the alternatives cost, among others, being the *evaluation done by the CATS*.

- iv. *Increase of generic market share*. Even though the generic medicines market was born in the 90's in Portugal, only in 2000's there was the recognition of its importance. The market share kept quite regular in value and volume until 2010 (see **Figure 17**). From this year on, measures pressuring market competition arose, namely (60): *The change and review of prices, financial incentives to pharmacies*, other direct procedures as *campaigns*, and indirect measures as the *mandatory use of INN prescription*. The second group of methodologies had its start in 2015, with the Ordinance No. 18-A/2015, of 2 of February (104), which described the payment of a *remuneration per each dispensed unit*, if the market share increased according to a table, or the payment of a value correspondent to the *savings* generated by the pharmacy. Later, in 2016, Ordinance No. 262/2016, of 7 of October (105) defined a specific *remuneration for medicines with a value equal or less than the fourth lowest price*, which was thought to be a more effective way to reward pharmacies for dispensing the cheapest medicines. Regarding the *change and review of generic medicines prices*, it was the main factor for the decrease of prices and increase of sales. As stated before the “first generic price must be at least 50% lower than the reference price, or 25% if the ex-factory price is inferior to 10€”, and besides this, some mandatory price reductions have been



**FIGURE 17.** Evolution of the generic market in Portugal from 2000 to 2015 (adapted from OECD, 2017 (106))

implemented (73). Although it is known that the penetration of generic medicines is more successful in countries that permit free pricing, price regulation generates lower prices, increasing competitiveness between suppliers (107). In July of 2017, the market share of generics was 47,8% (108).

- v. *Modification of patients' behaviour*. Even though there are plenty measures allowing a direct reduction of the pharmaceutical expenditure, recently, decision-makers are giving more importance to patients. The *Responsible Use of Medicines*, is the name of one of the most well-known *informational campaigns*, promoted by the Portuguese Order of Pharmacists. This campaign aimed to spread advices about the *correct use of medicines* – adherence to therapy, use in the right time, optimization of antibiotics use, reduction of medication errors, promotion of generics use and management of polymedication, while giving emphasis to the potential savings that some behaviour changes can bring (109). Another effective measure is the introduction or changes in *co-payments*, which are proved to influence demand, decreasing the moral risk inherent to a free of cost service (110). The changes verified in the co-payment rates, relate directly with the reimbursement percentage change which are one of the most common measure as seen before (87).
- vi. *Managed-entry agreements*. In Portugal MEAs are provided by law since 2010, to address uncertainties as budget impact, relative effectiveness and/or cost-effectiveness and eligible patient population, during the introduction of new drugs (111). Decree-law No. 48-A/2010, of 13 of May introduced two types of MEAs (112) – 1) PVA or *price-volume agreements*, which aims to limit budget impact and to restrict drug use. If the agreed budget is exceeded, the company must reimburse the difference to the NHS. If the health technology proves to provide added therapeutic value and/or cost-effectivity, a new budget limit is set (87). 2) CED or *coverage with evidence development*, that involves a temporary coverage, that can turn into a permanent or be extended if relative effectiveness and cost-effectiveness information regarding the health technology are collected after a period (87). The SiNATS (Decree-law No. 97/2015) introduced another risk-sharing

agreement, namely an *outcome guarantees agreement*, in which the NHS is protected from wasting resources, since the company must reimburse the payer or give rebates if the medicine fails to achieve the expected results (87). From 2005 to 2015 Portugal had 148 MEAs and 41% impacted over the out-patient sector, which is growing since 2014 (115).

- e) *In the hospital sector.* If in one hand we have the ambulatory sector, where every step is well described, and the prices are progressively decreasing, on the other we have the hospital settings, where there is little transparency, and where the expenditure is rising – the period between January and June of 2017 had a growth of 1,9% in comparison with same period of last year (see **Table 7.**) (113). This can be justified by the innovative health technologies that are being introduced, namely immunomodulators, antivirals and oncologic medicines (98).

**TABLE 7.** Evolution of the NHS expenditure with health technologies in hospital settings (adapted from INFARMED, 2017 (113)).

	<b>NHS expenditure</b>	<b>Homologous Variation (%)</b>
<b>Jan-Jun 2012</b>	519,5 M€	- 1,2%
<b>Jan-Jun 2013</b>	511,2 M€	- 0,5%
<b>Jan-Jun 2014</b>	485,1 M€	- 3,9%
<b>Jan-Jun 2015</b>	586,8 M€	+ 21,2 %
<b>Jan-Jun 2016</b>	594,7 M€	+ 1,3 %
<b>Jan-Jun 2017</b>	605,7 M€	+ 1,9 %

- i. *Previous evaluation.* Any new health technology before being introduced in the Hospital Medicines Formulary must be evaluated by a process called – Previous evaluation. This procedure helps to decide about the availability of medicines, and is based on *technical and scientific* criteria and on the *economic* advantage over other existing options (114). This strategy was introduced in 2006 (115), and the latest version corresponds to Decree-law No. 97/2015. In this legal rule it is stated that a maximum acquisition price must be defined, being this at least 10% inferior than the alternative, and that generic medicines must be at least 30% cheaper than the reference medicine (72).

- ii. *Annual review of medicines prices.* As described for ambulatory settings, prices are reviewed annually, being this provided by Decree-law No. 97/2015, of 1 of June and particularly Ordinance No. 195-C/2015, of 30 of June. The ex-factory price cannot exceed the price of any of the reference countries prices, and it cannot overreach the price approved during the previous review (73).
- iii. *Exceptional review of medicines prices.* This measure proceeds as described for the ambulatory sector.
- iv. *Tendering.* As stated before, when we refer to hospital medicines prices, we are talking about the *official hospital price*, which can be found in international price comparisons. *Actual prices* can be quite different, and they even variate between hospitals (mainly because of discounts and rebates), because in Portugal there is still no centralised acquisition procedure, and each hospital/group of hospitals make individual arrangements. This justifies the fact that there is no possibility to impose price cuts or to modify price formation rules. Although there is no detailed information about the agreements made by hospitals and the laboratories, it is known that tendering procedures are common (62). Generally, the company that *offers the best conditions* (price per unit, need to re-pack, need to pay postages, speed of delivery, among others) win the right to supply the hospital/group of hospitals.
- v. *Increase of generic market share.* Following the rationale behind tendering procedures, public hospitals are committed to an expenditure control, and the best offer has the possibility to supply an hospital for a certain period. Although sometimes originator medicines laboratories can offer the best deal, it is important to stimulate the generic medicines market, since this *increases competition, and leads to lower prices*, which by consequence leads to better agreements (50). As said before, generic medicines prices have to be at least 30% lower than the reference medicine price and once again, this price regulation leads to lower prices (75).



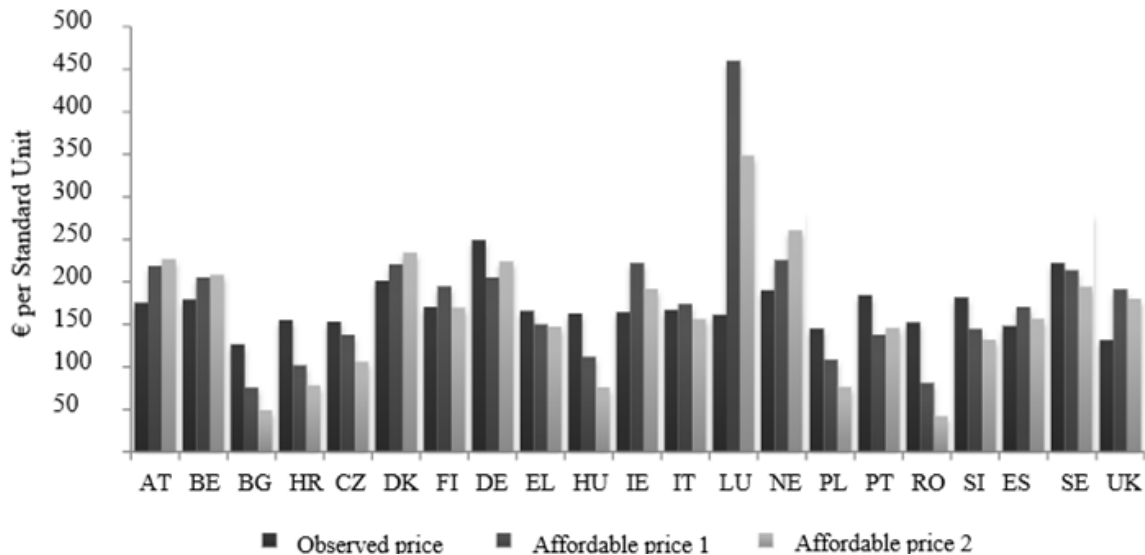
- vi. *Elaboration of the National Medicines Formulary (FNM)*. The National Medicines Formulary is a *compendium* of all the medicines considered to be necessary and adequate for the diagnose, treatment or prophylaxis, which can include medicines that do not have a market authorization in Portugal, non-reimbursable, or that do not need to pass through a previous evaluation. The Dispatch No. 2061-C/2013, of 1 of February, makes mandatory the use of this document, reinforcing also the responsibility of the *National Pharmacy and Therapeutic Commission (CNFT)* over the formulary (116).
- vii. *Managed-entry agreements*. Regarding inpatient medicines, MEAs were introduced in 2006 with the Decree-law No. 195/2006, which means that even before the global crisis could be predictable, hospitals were already negotiating this type of agreements with companies. Since 2006, the contracts signed between the hospital and the pharmaceutical firm could include *PVAs* and *CEDs*, and after 2015, *outcome guarantees* type of agreements were included in this group (72,115).

### 2.3. The future of access to medicines

In theory, prices should reflect the ability and willingness of countries' consumers to pay for a drug – if Member State X has an average income *per capita* twice as big as the European average, then in principle, MS X residents should pay twice as much for that drug in relation to the average European price. In the real world, other forces come into play, prices become multifactorial, and the observed values differ largely from the affordable costs (117). **Figure 18.** compares the *Observed average prices* of an arthritis drug in 2010, with two affordability indexes – *Affordable price 1* (related to the *per capita* income levels relative to the EU average), and *Affordable price 2*, (related to the total health expenditure in an EU Member State relative to the EU average), and the trend is – observed price convergence, so that Member States with higher income *per capita* and higher health expenditures have similar observed prices relative to the ones with lower affordability indexes.

Access to medicines was once considered an issue confined to low- and middle-income countries, however, the access to medicines debate in European countries is a present phenomenon, and despite the budgets range, all countries are struggling with the actual

unsustainable price structures. In fact, the pricing systems are the main reason for the unequitable access to the new and innovative health technologies, that in some cases are essential – orphan and oncologic medicines, among others (14,118). This issue is not entirely new but remains to be solved – IMS Health has predicted that global spending on



**FIGURE 18.** Observed average prices (€) versus Affordable prices for an arthritis drug in 2010 in the EU (adapted from Europe Economics, 2013 (117)).

pharmaceuticals will increase by 30% from 2015 to 2020, and although part of this percentage will depend on the “pharmemerging markets” (India, China, Brazil...), developed countries will also contribute for this growth (119,120).

As described before, the emergence of *expensive drugs*, with narrow and specific indications, the increase of the *biologic medicine* market associated with the difficulties that *biosimilars* are facing, *demographic factors* as aging bounded with chronic diseases, the necessity to *reduce pharmaceutical expenditure* and its balancing with the need to *reward innovation*, requires more, better and novel proposals, because it is becoming clear that the ones that are currently being used are not enough for the present and future challenges of the pharmaceutical market (98).

Presently, national authorities are establishing *departments to assess medicines prices*, to assure that health technologies are cost-effective, to *control lists of reimbursed medicines*, to promote *generic substitution*, among others, but these strategies are apparently insufficient to generate equitable access throughout the EU, as we observed in **Figure 18**. This is justified mostly by the *lack of transparency* among Member States, motivated by distorted tenders and rebates, where the MS is generally in a disfavoured position in terms of information, that results

in middle income countries paying the same (or more) than the richest ones (121). New methodologies to reduce public pharmaceutical expenditure are being proposed and predicted, for instance: 1) the use of *outcome based pricing* is rising, and it is expected feature the future contracts, especially for high priced medicines (122); 2) a shift from *public to private spending*, which is expected to reduce the total spending per patient through a decrease in consumption (119); 3) the end of the use of EPR methodology as we know (with listed prices), and substitution of this by the use of *real discounted prices*, which is already seen in Germany (14,123); 4) the *remuneration of pharmacists and pharmacies* for the provision of services, and not for margins associated with certain medicines or brands (3); 5) the creation of *new funding models* (14); 6) the improvement of legal rules, to ensure *well-structured agreements*, with the inclusion of early- and late-phase health economic and outcomes research, as Portugal did with the creation of the SiNATS (70), among others.

It is also important to highlight the fact that the EU is also gathering efforts to study the impact that some measures are having in the access to medicines. Recently it was started an evidence-based analysis on the *influence of patent monopolies and the affordability and accessibility crises* that Europe is facing, and also some investigations are being made in the pricing area, specifically on pricing practices (118).

An urge to reform the pharmaceutical system is being claimed all over the world, and the next chapter will explore a possibility that has already been considered by many authors, but never concisely planned.

### 3. Proposal

Several organizations are emphasizing the necessity to recognize the importance of effective policies, to assure equity in access of affordable, safe and effective medicines. In the European Union, EMA developed a document – *EU Medicines Agencies Network Strategy to 2020 – Working together to improve health*, that works as a complete guideline for the strategy for the Member States, for the period of 2015 to 2020, and, again, considers as a main goal the “*timely access to new beneficial and safe medicine for patients*” (124). So, it is crucial to improve pharmaceutical policies, and to shift the frame from several, individual and small viewpoints, fighting over the same matters, to a global, European and embracing model, with a single objective – to grant access to medicine to patients all over the EU.

One defined objective of this research work was to present a model that could optimize the effectiveness of the current pharmaceutical policies. After organizing details about the *rationale* of each pricing, reimbursement and expenditure control strategies, analysing the weaknesses and strengths of the methods used around the EU Member States, and collecting information about new trends, it was evident that one aspect was standing out – the current pricing and reimbursement methodologies, although in some cases involve the sharing of information, do not imply cooperation. However, from the EU point of view, the tendency is to promote participation, sharing and coordination between MS.

Following these premises, this section will explore one model passible to be applied in a community as the European Union.

#### 3.1. Centralized negotiation and acquisition model for the European Union

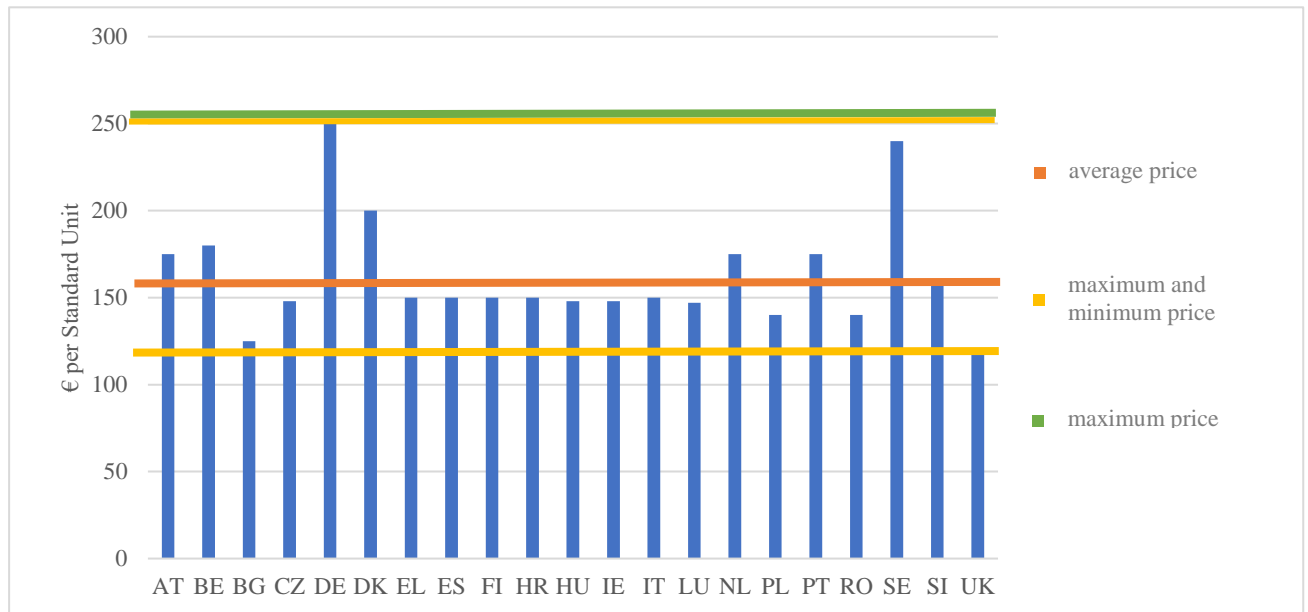
This model explores the potentialities of the European Union as a stakeholder with a common goal and interest – the equity on access to medicines by its citizens. The scaffold of this model would be the negotiation of an acquisition price for health technologies, which would be *distributed differentially* and *equitably* by the Member States, according to its most relevant characteristics.

It is important to highlight that a mechanism like this is only possible because of the existence of the single *centralised market authorization procedures* (CP), where the EMA's Committee for Medicinal products for Human Use (CHMP) carries out a scientific assessment, that if positive, allows the access to the market of the entire EU. This process, which is mandatory for some diseases/types of medicines, and optional for other innovative health technologies, implies that a certain drug has to have the same *dosage, package size, pharmaceutical form, labelling*, among others (32,125), permitting an harmonisation at this fundamental level, which opens the path for an harmonization at more distant levels, as pricing decisions.

### 3.1.1. Distribution of prices

It has been proven that if a market is *monopsonistic*, prices tend to be set near marginal cost (which is not the objective of this model), and that a pricing methodology based on the economic theory of *Ramsey pricing* (differential pricing) is the most efficient mean of covering joint costs (*i.e.* R&D) when payers have different price sensitivities, although it fails in the aspect of attributing value according to the gains in effectiveness (125).

So, to generate a robust pricing mechanism, it is important to focus efforts in two aspects – to generate the *lowest possible price while rewarding innovation*. This is possible by conjugating aspects both from *differential pricing*, that considers factors as price elasticity and GDP *per capita*, and *value-based pricing*, which rationale assumes the valorisation of the health technology for its improvements. Herein, the agreed acquisition price should be based in the *therapeutic innovation, health improvements and social value*. This price could correspond to an average, a maximum, or maximum and minimum price, and using real data from 2010 (ignoring factors that can compromise pricing equity), for a specific medicine, if the agreed average price was around 162€, or the maximum 250€, or the difference between the maximum and the minimum 130€ (maximum 250€ and minimum 120€), **Figure 19**. could represent a potential price distribution.



**FIGURE 19.** Observed average prices (€) for an arthritis drug in 2010, with emphasis of the minimum, average and maximum prices (adapted from Europe Economics, 2013 (117)).

Regarding the “distributing factors”, to ensure equity for the purchasers, several aspects could be combined to achieve an optimal ratio of prices between Member States:

- a) *GDP per capita* or *GNI per capita*. Generally, GDP is the most used indicator, being a measure for a country’s overall economic output (represents the strength of a country). GNI is the total value produced by its citizens (constitutes the strength of the citizens) (126), reflecting more accurately the capacity to cover expenditures, and in some cases is preferentially used. Logically, a MS with a lower GDP/GNI *per capita* should pay relatively less for the same health technology. Despite this concept choice, it is interesting to point out that the World Bank defines a *intervention as cost-effective* if it buys a year of health life for less than the national average GDP *per capita* (121).
- b) *Number of patients* or *eligible patients*. The number of patients affected by a determined disease, or the number of patients that meet certain clinical requirements, related to the disease severity, influence the extent of the expenditure with a health technology. So, if a MS has a higher number of patients or eligible patients, the agreed price should be lower, because the overall expenditure will be higher.

- c) *Purchasing Power Parity*. PPP is a macroeconomic concept that reflects the quantity of a certain currency needed to buy a specified unit of a good. Although the EU has a single currency—Euro, some MS still have a national currency, making this concept relevant for an economic analysis that aims to fairly distribute prices. Besides this, PPP is closely related to the price levels of each country – a higher PPP is related to a higher cost of living, which is associated with higher product prices. So, a MS with a low PPP should practice lower pharmaceutical prices than a MS with a higher PPP. This notion is also related with *elasticity*, which reflects the sensitivity of, in this case, the demand side towards price flows on the supply side. Assuming that a country with a low PPP tends to have an elastic demand nature, a higher price can lead to a lower consumption than the expected, meaning this that some people might suffer from not having the treatment accessible (36,127).
- d) *Lowest or average cost of available treatments*. Even when a new health technology is an innovation and treats a disease for which there was no previous treatment available, or its relative effectiveness is considerably better, it is important to consider the price of the alternatives when according a price. If Member State X pays 100€ for the regular treatment while Member State Y pays 1000€, having both the same purchasing power, when distributing prices, the cost should be lower in the MS that pays a higher price for the alternative.
- e) *Average out-of-pocket share*. This factor can only be applied in the ambulatory market, where the public payer does not always pay the entire agreed price. In these situations, it is important to know the percentage that corresponds to out-of-pocket payments, because if most of the cost is absorbed by patients, the price sensitivity is much higher, and there is an increased risk of low therapeutic compliance. However, this logic has to be analysis in a case-by-case basis because countries with a lower reimbursement rate have also lower economic power and have to share the cost with patients.

### 3.1.2. Description of the process

Although this model requires a detailed process to sustain its main objectives, in **Figure 20.** simplified scheme, in which a further complex proposal could be based on.

Following the market authorization, which is assumed to be a centralised procedure, not only because of the harmonisation of the pharmaceutical characteristics, but also because this is the most efficient procedure, would come the negotiation procedure. This would be divided in two initial phases – *Economic assessment by a specific Committee* and the *Elaboration of a report by each National Competent Authority (NCA)*:

- a) *Economic assessment by a specific Committee.* In this phase of the process, there should be a negotiation between a Committee and the MAH to conclude about the *fairest price* to pay for the health technology, which could be either the average, maximum, or maximum and minimum price that the MSs would have to pay. This Committee could be the *CHMP* or a similar committee could be formed, composed also by one member nominated by each of the 28 EU Member States and by up to five experts in a particular scientific area, having the legitimacy to be responsible for assessing the cost-effectiveness of the pharmaceutical. It would also be responsible for proposing methodologies as *managed-entry and/or risk-sharing agreements*, if the conditions to fully evaluate the pharmaceutical and to have a final decision were not collected.
- b) *Elaboration of a report by each NCA.* The report should have a standardized configuration, to harmonize the information (which was described in the previous section) to be used in further *price distribution*, and should be filled within a time limit. This report should also contain a justification from the NCA in case of rejection of the national market entry of the health technology, which should be carefully analysed to evaluate and eventually re-assess the effectiveness and efficacy of the pharmaceutical. To fill the report, an additional aspect would be required – *updated patients' registries*, with a rigid surveillance of diseases and associated statistic, so that factors as “Number of patients/ eligible patient” can reflect real values. The need for these registries could be seen as an opportunity to improve pharmacovigilance systems, since most of the current diseases do not have a compulsory communication and reporting. Additionally, MS should define the



*individual supply necessity* – prediction of the required quantity for a defined period, which would improve the supply chain.

After having all the required information, the Committee would have to analyse the reports, and using economic formulas, based on the collected information, on the impact of each factor and on the agreed price, the price distribution phase would occur.

Following the phase of distribution of prices, it would be interesting to add a step of planning of the official contract, which could include a *prediction of the amount of product* that the EU would globally need for a certain period. This would prepare the company for the necessity, increasing the *predictability of revenues* and *decreasing the chance of shortage*. In case of shortage – when the demand is higher than the capacity of the manufacturer, the pharmaceutical should be *proportionally divided* between Member States.

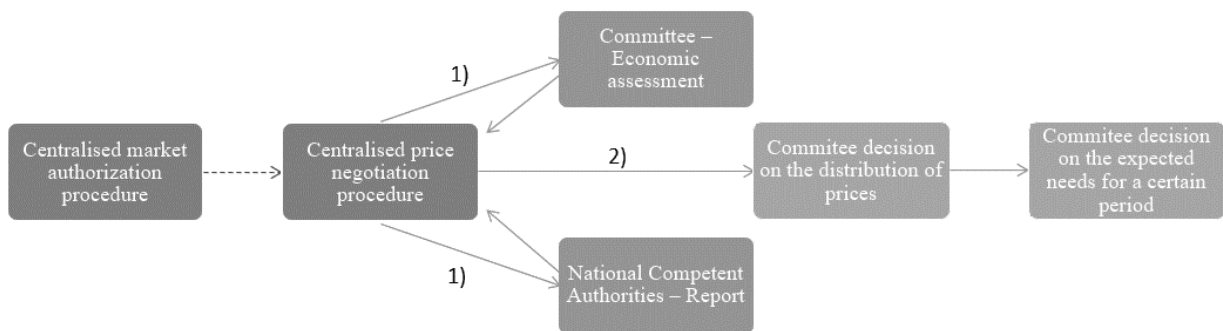


FIGURE 20. Proposed process for the model of price negotiation and distribution.

### 3.2. Literature review

Although there is still no such model as the one described in this work, there are several mechanisms that include or describe a joint negotiation and purchase of pharmaceuticals. Outside Europe there are several schemes as the *Global TB Drug Facility (GDF)*, the *Gulf Cooperation Council Group Purchasing Program (GCC/GPP)*, the *Pan American Health Organization vaccine revolving fund (PAHO RF)* and the *OECS/PPS*. These pooled procurement strategies help reducing the unit price, and the savings are generally used to purchase larger amounts. These mechanisms are operating successfully, some of them for more than two decades, with annual growths both in value and volume (128).

Inside the EU, as briefly explained in section 2.2.1, one example of a successful model is the *Joint Procurement Agreement*. Introduced in 2013, this agreement between the European

Commission, the ECDC, Member States, the EMA and the WHO unified efforts to improve the coverage of vaccine-preventable diseases, but also other threats of biological, chemical, environmental or unknown origin, by a joint procurement on medical countermeasures (129). This model of joint procurement has a *voluntary nature*, so a MS can choose not to participate, and even when the decision is positive, there is *no financial commitment*. The JPA predicts three types of contract – 1) *Direct contract*, which is a public supply contract that contain all details as time of delivery and quantity to be delivered; 2) *Framework contract*, which is used when the exact time and quantity of product cannot be defined in advance; and 3) *Specific contract*, that is basically a framework contract between an individual contracting party and an economic operator. In every case, the estimated *value of the contract is fixed before* the launch of the procedure (82).

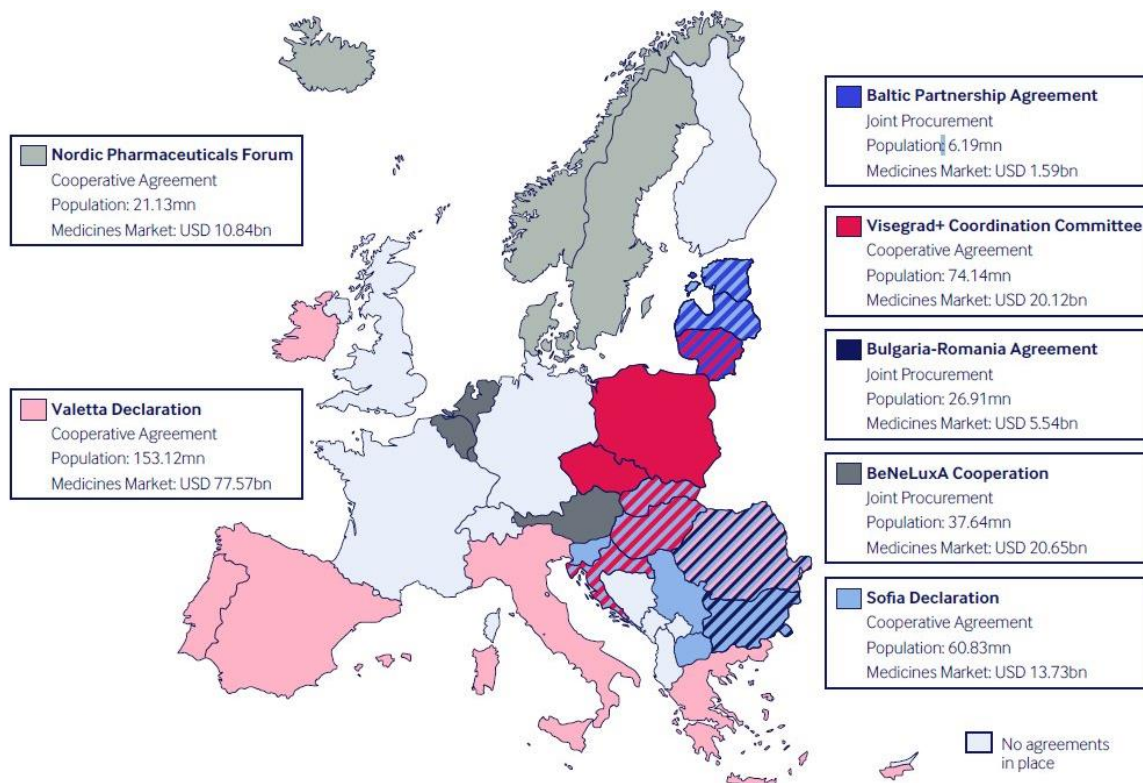
Recently, *intergovernmental collaborations* across the EU, which were felt to be inconceivable just a few years ago, are becoming frequent. Possibly motivated by the “Sovaldi phenomenon”, most governments in Europe are gradually growing aware that they stand a better chance of guaranteeing the sustainability of their health systems if they negotiate and/or purchase jointly (118). The most well-known examples are:

- a) *Baltic Partnership Agreement*. Composed by Latvia, Lithuania and Estonia, this collaboration had its beginning in 2012, with the aim of covering pharmaceuticals in general, in a *centralised joint purchasing* (tenders, negotiation, payment and distribution) (130).
- b) *BeNeLuxA*. This initiative was born in 2015, when the Belgian and Dutch Ministers of Health signed a declaration, which would later suffer the addition of Luxembourg and Austria. It includes four areas of collaboration – *joint horizon scanning*, *joint HTA*, *exchange of strategic information*, and *joint price negotiations*. By now there is already information about some failed agreements because of the excessive price and/or the lack of cost-effectiveness of certain medicines (131).
- c) *Romanian and Bulgarian Initiative*. On 2016, Romania and Bulgaria presented an agreement at the Work Meeting of the Health Ministers from Central and Eastern Europe, aiming to ensure the patients’ access to medicines. The Memorandum foresaw joint agreements with the producers in *purchasing*, to get *lower prices*, and *cross-border exchange* of medicines in short supply, granting *quick access* to the

newest and most efficient medicines, and *budget savings* to both countries. During this meeting the governments of Croatia, Estonia, Latvia, Macedonia, Serbia, Slovenia and Hungary signed a statement of intent, to collaborate in terms of price negotiation, being this called the *Central Eastern European and South Eastern European Countries Initiative* (130,132).

- d) *La Valletta Declaration*. Signed in 2017, this declaration brings together eight Southern Mediterranean EU Member States – Portugal, Spain, Italy, Greece, Malta, Ireland, Romania and Cyprus. The goal was to establish a Technical Committee responsible for “*sharing information, identifying best practices, horizon scanning of innovative medicines and therapies, exploring possible mechanisms for price negotiations and joint procurement*” (133). Months later after this agreement, the *Portuguese and Spanish* Ministers of Health signed a bilateral declaration adding the aim to start centralised purchases of medicines, focusing on the funding and price setting (134).

Besides the cited ones, there are more collaborations happening around Europe, having as a main goal the sharing of information, price negotiation and joint purchasing – *Sofia Declaration, Nordic Pharmaceuticals Forum*, among others (see **Figure 21.**) (130).



**FIGURE 21.** European Cross-Border Collaboration in Pharmaceuticals (adapted from BMI Research, 2017 (135))

These partnerships have the potential to be game-changers and can be seen as pilot projects for something larger like a European model as the one described before. By now, the conclusions we can take from these joint procurements are that there is a *growing interest* for these initiatives, and that countries with *similar economies tend to negotiate together*, which is expected in agreements with this regional nature, and that the major European economies prefer to maintain their autonomy.

### 3.3. Advantages

As it has been referred several times during this chapter, the main goal/advantage of a European joint negotiation and purchasing procedure is the *improvement of access* to medicines, which is slowly starting to worry some of the greatest global economies. However, if we fully analyse the hypothetic scenario of having a European centralised acquisition of health technologies, many other benefits would rise:

- a) *Lower acquisition prices*. This is a basic premise of the proposal, but it can be seen through several perspectives: 1) This model generates a *greater demand*, because there is a *greater access*, granting *higher profits*. This can be easily explained because during the years in which the pharmaceutical is still protected by a patent, or the years in which the pharmaceutical is unique as treatment or diagnosis for a certain condition, there will be an increased volume of sales, an even if the price is lower, the profits will be higher. 2) In case of having more than one option in the market for a certain condition, with the same relative effectiveness, the *competition between manufacturers* will be higher, because if one shows to have a better cost-effectiveness, this will be the preferred one to figure a centralised negotiation and acquisition agreement. 3) Being this a centralised procedure, it would bring some *savings to the company* in terms of marketing (less investment before and after the agreement) and in bureaucratic procedures (one single harmonised document would reduce exponentially the costs implied in operational procedures). 4) The fact that there would be just one agreed, *fully transparent price* that would be distributed between the MS, could generate globally lower prices, especially if we have in mind the fact that discounts and rebates generally lead to worst deals to some countries (mainly low/medium income and/or small) (36). This type of process, more open

- and direct than the currently used ones, would also increase public accountability, reducing the chance of having improper behaviours as collusions between procurement bodies and companies. 5) An additional feature of this model could be the creation of a fund, to be used in high priced cost-effective essential pharmaceuticals, in order to have a *prompt payment*, which could reduce the price.
- b) *Greater equity*. Another fundamental assumption is the improvement of the access to innovative health technologies, by increasing the equity mainly on the negotiation and purchasing phases. However, in this context, equity can have various, but related, dimensions: 1) Being this model based on *differential and value-based pricing strategies*, equity would be achieved at all three levels of this negotiation – the *patient* (which will have timely access), the *third-party payer* (government or insurance, which will get adjusted and fairer prices for the health technologies; although this might be more obvious for low and medium income countries, the lack of transparency can be also harmful to high income countries), and the *pharmaceutical company* (which can expect a profit capable to cover and promote further investments). In addition, to fully achieve equity in the patient and third-party payer sides, it is crucial to define and *control country taxes, tariffs and distribution margins*, so low acquisition prices do not represent great expenses for patient (whenever OOP payments are involved). 2) Once the access is assured, another interesting aspect would be the creation of *consensual European guidelines*. Although this is a significant step, it would be a natural event, since the main factors to base these guidelines on, would be the *relative effectiveness or cost-effectiveness* and not budget containment.
- c) *Higher quality of service*. The proposed model could improve the quality of the process in two distinct aspects: 1) *Better quality products*, with less risk of counterfeit or substandard pharmaceuticals, since this could compromise the contract, and the company could risk losing some benefits or contract exclusivity. 2) The fact that the contract might include the needed quantities, for a time period, will increase the *planning capacity* of the company, thus enabling more *predictable revenues* for the firm, and *lower waiting times* and *less shortages* for the MS.
- d) *Improvement of the EU role in healthcare settings*. As it will be explained later, the EU does not have the power to define common market pricing mechanisms,

however, despite the restricted Treaty-based mandate for health, the EU has a relevant role to play, and during the last years has expanded its action beyond the expected. Interestingly, a study from 2013 indicated that the EU task to promote sharing was successful and “influential”, however the task of establishing monitoring and evaluation structures, was a failure from the viewpoint of public health experts (136). It is quite consensual that the EU should have a greater involvement in public health, which means that an initiative aiming to improve the assessment, the access, and the equity of MS towards innovative health technologies would be encouraged. Another important detail, is that such model would not require a policy convergence. Each MS would still control their healthcare system in an independent way, and the NCA would continue to have a significant role on this process.

### **3.4. Potential problems**

Among the described benefits that a centralised negotiation and acquisition procedure could imply, some constraints could also arise, and it is important to reflect about them, to find solutions and alternatives, to improve the proposed model:

- a) *Monopoly of the cheapest option.* If we think about a new, innovative treatment, or prophylaxis/diagnosis method, for a condition that do not have any other alternative, the market will be a monopoly. Generally, this monopoly does not last long, and few time after the first marketing years, while the health technology is still under patent protection, an alternative enters the market. If this alternative does not show a significant clinical improvement, but involves less costs, it will be classified as more cost-effective, and the market will focus in this new pharmaceutical. The first one would lose the supply contract for the EU Member States, and the second one would feature the new contract. In this case, there is a risk of the first one to abandon production and marketing, and thus, this would potentially open the door for another monopoly, eliminating a convenient competition, that could help in decreasing prices. This could be controlled by *limiting market share* to a maximum percentage, being this value correlated to the number of alternatives in the market and to the cost of these alternatives.

b) *Incapacity to assure lower prices.* The inability of the proposed mechanism to generate lower prices than the ones that MSs can arrange individually is a possibility. Even though a monopsonistic market is known for its capability to drive down prices to a marginal cost, the fact that this model is sustained on the idea of equity, might defy the theory behind this premise. A low- or even middle-income country will achieve a lower price in a joint procurement as the one described, because we can assume that its individual negotiation power is paired with the purchasing power, which is low. On the other hand, a high-income country will have its negotiation power shared with lower-income countries. We can translate this to – *the benefits and limitations of every Member State will be shared with each other.* However, pharmaceutical companies do not tend to entirely follow this logic. Generally, prices are neither in accordance with the capacity of each MS to pay, nor with their individual negotiation power, and in fact, there is no rule in pricing decisions from the companies' side, since during this last years, prices are converging among the Member States (117). This means that low-income countries are definitely paying more than they can afford, and consequently consuming less than they need, middle-income countries are probably paying more than they should, putting at risk their financial stability, and that high-income countries are possibly also paying more than what is considered cost-effective. A centralised negotiation procedure would increase the negotiation power of the MSs to the same level of the company, and the demand side decision would be more informed. Besides this, an increased access would intensificate the demand, which would generate the same or more profits even with lower prices. But if we ignore these aspects inherent to the process, and focus on solutions, there are several possibilities: 1) Increase the competition, which could be achieved by using measures to promote and attract the *market entry of generics* (free-pricing of generics during a certain period, making INN prescribing mandatory, promoting generic substitution, among others (137)). However, these mechanisms are only effective after the end of the patent, so another solution could be: 2) the creation of strategies to reward innovation in *alternative to patent protection*. A lot of experts are dedicating efforts to find other options to substitute the patent paradigm, and by now interesting ideas are rising – prizes funds (reward innovator/researchers for new knowledge, in exchange of the monopoly over its use (138)) and patent buy-

outs (which concept is similar to prize funds, but involves the purchase of patent rights over time, meaning this that the prize depends on the market outcomes (139)). Although this type of schemes is frequently associated with philanthropy, the EU, through funds, could also start using these mechanisms to reward innovation while decreasing the access cost, and to accelerate the market entry of other alternatives.

3) An additional form to ensure the capacity of the mechanism to generate lower prices, is a better *control of parallel trade*. This has been a matter of concern for most pharmaceutical companies because of the money losses this process brings, and for some Member States because of the drug shortages that countries with lower prices suffer. Several mechanisms are arising as – dual pricing (two-tier prices for the distribution chain depending on the final destination), free pricing (applies to wholesalers that export pharmaceuticals, where if a product is sold within the domestic market, the price difference between the free price and the regulated price is reimbursed by the company), supply quota restrictions (wholesalers are provided only enough products to cover domestic sales) and direct distribution systems (140). Most of these mechanisms are considered illicit. A EU-wide coordinated negotiation scheme would be a great indirect way to control parallel trade – each MS would have a defined amount of pharmaceuticals, which would be described on a contract, and the wholesalers would have the function to distribute the products, without changing the agreed quantity.

- c) *Disagreement on cost-effective health technologies*. This can be seen as an opportunity that could lead to a more embracing and rigorous discussion about the of therapeutic guidelines around the EU. Eventually there could be the creation of consensual guidelines, meaning this that a patient, all around the EU, would receive exactly the same treatment, prophylaxis or diagnosis method. Although this is still a hypothetical and distant theory, this would increase the chance to have reliable evaluations and to promote a consensual decision on the cost-effectiveness of health technologies.
- d) *Pharmaceutical companies might claim that the prices are insufficient to promote R&D*. The greatest and more recurrent reason for the high prices of pharmaceuticals, or at least the initial excessive prices, is the high risks and costs of research and development, which generally cannot be accessed (141). A study



published in 2015 put side to side the expenditure of some companies with Research & Development and Marketing & Sales, and nine out of ten firms showed to spend more on marketing than they do on R&D, being that in some cases the research costs are half the value involved in marketing strategies (142). This shows that the *biggest burden of pharmaceutical companies is marketing*, which is the main tool to assure that sales are maximised until the end of the patent protection period. In a model like the proposed one, marketing would have a less significant role, at least after an agreement is reached, because the assessment, the superiority of the pharmaceutical against a placebo or the standard choice, and the relative cost-effectiveness would be the main factors to determine the success of the new and innovative health technology. In addition, the EU could start incentivising companies to develop certain pharmaceuticals, which is already happening with orphan drugs (143), with strategies as: 1) *Fee reductions* (variations, annual fees, among others) in protocol assistance (scientific advice), in the application for market authorization, in inspections and post-authorization activities, and 2) *Central funds for research*, in the form of grants both for companies and the Academia.

- e) *Legal constraints*. A superficial analysis of the EU law is enough to conclude that some changes would have to be made in order to make a EU coordinated negotiation and purchasing scheme possible. The pharmaceutical market is a cross-sectional field of competence, making very hard to interpret what is considered legal or not. Two of the most relevant Principles are: the *Principle of Subsidiarity* (involves the sharing of powers between several levels of authority, ruling out EU intervention when the issue can be dealt by MS) and the *Principle of Proportionality* (limits the exercise of powers by the EU and its institutions within the sufficient to achieve the objectives of the Treaties) (144). This means that any mandatory scheme like the one proposed in the work would not be possible, because it would imply a transgression of the EU competences. In accordance with the TFEU, each MS is responsible for regulating pricing and reimbursement of medicines, while the EU can only encourage cooperation, provide guidance to promote an affordable and equitable access to medicines, transparency on pricing and reimbursement decisions, among others. Based on this, a scheme of this nature would imply either a change on the Principles, to open an exception for medicinal products, or a

voluntary agreement between Member States (just like the one seen in the Joint Procurement Action, previously described), where each one could integrate or not the centralised negotiation and purchase. Although this second option would prevent the maximisation of the advantages this model could bring (because some MS might prefer to deal with companies by themselves), it would still be a great step on the cooperation of MS on these matters. In addition, according to the principle of *free movement of goods*, it is prohibited to restrict importations or exportations, so it might be early to assume that a scheme where the wholesalers would not have the power to decide what to do with their products is possible.

## 4. Conclusions

European countries have been struggling to grant access to medicines, while conjugating the needs to control pharmaceutical expenditure and to reward companies for innovation. This was more notorious over these past few years, with the emergence of new, innovative, high-cost medicines, which was aggravated by the financial crisis.

The EU, in parallel with the Member States necessities, created and increased the number of entities, platforms, databases, and even promoted joint procurements, to accomplish what is within its competence, and what is predicted in the Fundamental Treaty. These actions revealed some weaknesses, some strengths, but mainly great opportunities, and from a starting point where the EU tried to promote sharing platforms and the creation of networks, the MS progressed to a stage where, on their free will, are joining efforts, and creating regional groups to share information about health technology assessments, to negotiate prices, and even to jointly purchase pharmaceuticals.

Following these premises, this study investigated the strategies implemented by MS to support pricing and reimbursement decisions, the measures taken to promote the balance between the necessity of containing costs, rewarding real innovation, and granting access to medicines. After analysing this information, a global conclusion was taken – these measures are insufficient. Although the effort from the demand side is enormous, and the policies are improving, the asymmetry of the information between the payer and the supplier impedes a fair, or at least transparent, assessment and agreement on the health technology value.

So, the current individual measures are not only ineffective, but also irremediably unsuccessful, because an equitable access, with equitable costs, requires a levelling between governments and companies, that is, by now, impossible, mostly because of the cited strategies. It is possible to imagine this as a cycle, on one hand, the preferred strategies imply a lack of transparency, which is well taken by most governments, because it supposedly grants lower prices, but on the other, this same lack of transparency leads to a decrease in the demand's negotiation power, and culminates in worst deals, which are feared by either high- and low-income countries.

As referred before, Member States are getting united to stop this vicious cycle, and are voluntarily developing networks and joint procurements, which are helping in having more accurate cost-effectiveness assessments, clarifying the negotiations, and equilibrating prices with very good results. And this seems to be the future way forward.

This rationale led to a model of a centralised EU-wide negotiation and purchasing of pharmaceuticals. This model was drafted in a very simple process, being based in some already consolidated procedures, involving well known entities, and having as a global goal the equitable access to medicines. The little intervention of the EU in health matters is commonly criticized, but at the same time is in accordance with the Principles of Subsidiarity and Proportionality. These Principles are possibly the greatest obstacles this model would face, so this scheme would defy the EU framework at a theoretical and practical level. At the same time, it would generate a need for an end of the EU “inactivity”, condemn several times by experts, while helping in addressing what might be the biggest challenge of the European healthcare systems.

This work is not finished, and there is a lot more to research and include in this proposal. In the future, it would be interesting to analyse how each factor could influence an eventual formula, and even develop this formula. Aspects related to the main procedure, such as the creation of a European fund for medicines, the improvement of reporting of certain diseases, or even the harmonization of European guidelines, must be explored and developed. Besides this, it would be interesting to analyse thoroughly the current joint procurements, to fully understand their weaknesses, strengths, threats and opportunities, and to improve the proposed centralised procedure.

## 5. Bibliography

1. Estorninho MJ, Macieirinha T. *Direito da Saúde - Lições*. Lisboa: Universidade Católica Editora; 2014. 244 p.
2. Governo de Portugal. Lei n.º 48/90, de 24 de Agosto, N.º 195, 1.ª série (1990).
3. Pita Barros P. *Um Novo Contracto Social para a Farmácia*, Assembleia da República (2015).
4. European Commission. *Study on enhanced cross-country coordination in the area of pharmaceutical product pricing*. Brussels: Directorate-General for Health and Food Safety; 2015.
5. Field M, Boat T. *Development of New Therapeutic Drugs and Biologics for Rare Diseases. Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington DC: National Academies Press; 2010.
6. Blackstone EA, Joseph PF. *The Economics of Biosimilars*. *Am Health Drug Benefits*. 2013;6(8):469-78.
7. Ayers A. *Personalized Medicine - Future Impact, Pharma Industry perspective*. *Journal of Biomolecular Techniques*. 2010;21(3):S5.
8. Pita Barros P. *Envelhecimento: Mitos e realidades das despesas de saúde e segurança social. O Envelhecimento Populacional: Portugal em Perspectiva Comparada*; Lisbon: Fundação Calouste Gulbenkian; 2010.
9. Fundação Calouste Gulbenkian. *Health in Portugal: a challenge for the future*. In: Portugal HC, editor. *Future for Health - The Gulbenkian Platform*; Lisboa. 2016. p. 44.
10. Mladovsky P, Srivastava D, Cylus J, Karanikolos M, Evetovits T, Thomson S, et al. *Health policy responses to the financial crisis in Europe*. *European Observatory on Health Systems and Policies*; 2012.
11. Thomson S, Figueras J, Evetovits T, Jowett M, Mladovsky P, Maresso A, et al. *Economic crisis, health systems and health in Europe: Impact and implications for policy*. *European Observatory on Health Systems and Policies*; 2014.
12. Kahana E, Kahana B. *Baby boomers' expectations of health and medicine*. *Virtual Mentor*. 2014;16(5):380-4.
13. Sacristán JA. *Patient-centered medicine and patient-oriented research: improving health outcomes for individual patients*. *BMC Med Inform Decis Mak*. 2013;13:6.
14. Vogler S, M. *Pharmaceutical Pricing in Europe*. In: Babar Z-U-D, editor. *Pharmaceutical Prices in the 21st Century*. New Zealand: Springer; 2014. p. 343-70.
15. Helmert U, Cacace M, Grimmeisen S, Wendt C, Rothgang H. [The changing role of the state in health care systems in OECD countries--research questions, research design and first results]. *Gesundheitswesen*. 2005;67(2):89-95.

16. Wendt C, Frisina L, Rothgang H. Healthcare System Types: A Conceptual Framework for Comparison. *Social Policy & Administration*. 2009;43(1):70-90.
17. Espín J, Rovira J. Analysis of differences and commonalities in pricing and reimbursement systems in Europe. Granada: D-G Enterprise and Industry; 2007.
18. Hogan Lovells International LLP. Pricing and reimbursement schemes in major european countries. 2014.
19. Wind A, Rajan A, van Harten WH. Quality assessments for cancer centers in the European Union. *BMC Health Serv Res*. 2016;16:1-474.
20. European Commission. High Level Pharmaceutical Forum 2005-2008. Brussels: Directorate-General Health & Consumers and Enterprise and Industry; 2008.
21. Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems, 89/105/EEC. Sect. 40 (1989).
22. EURO-MED-STAT. Recommendations for national registers of medicinal products with validated ATC codes and DDD values. European Commission DG SANCO; 2004.
23. Paoli F. Commission Communication on effective, accessible and resilient health systems. Brussels: SANCO; 2014. Document No.: unit D2.
24. Tsolova S. The Treaty of Lisbon and public health in the EU. *Eur J Public Health*. 2010;20(4):475.
25. Treaty of Lisbon Amending the Treaty on European Union and the Treaty Establishing the European Community, 2007/C 306/01 (2007).
26. De Weerd E, Simoens S, Hombroeckx L, Casteels M, Huys I. Causes of drug shortages in the legal pharmaceutical framework. *Regul Toxicol Pharmacol*. 2015;71(2):251-8.
27. Hartz S, John J. Public health policy decisions on medical innovations: what role can early economic evaluation play? *Health Policy*. 2009;89(2):184-92.
28. Kopp C. What is a truly innovative drug? New definition from the International Society of Drug Bulletins. *Can Fam Physician*. 2002;48:1413-5, 24-6.
29. WHO Collaborating Center for Pharmaceutical Pricing and Reimbursement Policies. Preferred Terms. WHOCC Glossary. Vienna.
30. Leopold C, Vogler S, Mantel-Teeuwisse AK, de Joncheere K, Leufkens HG, Laing R. Differences in external price referencing in Europe: a descriptive overview. *Health Policy*. 2012;104(1):50-60.
31. Toumi M, Rémuzat C, Vataire A-L, Urbinati D. External reference pricing of medicinal products: simulation-based considerations for cross-country coordination. European Commission; 2014.
32. Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs--evidence from twenty-five major markets in the 1990s. *Health Econ*. 2005;14(3):269-92.

33. World Health Organization. WHO Guideline on Country Pharmaceutical Pricing Policies. Geneva. 2013.
34. Pani L, Montilla S, Németh G, Russo P, Viceconte G, Vogler S. Balancing access to medicines and sustainability in Europe: An analysis from the network of competent authorities on pricing and reimbursement (CAPR). *Pharmacol Res.* 2016;111:247-50.
35. The World Bank. World Development Indicators. The World Bank Group. 2017 [Accessed on 27/03/2017]. Available from: <https://data.worldbank.org/data-catalog/world-development-indicators>
36. Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D and patents. *Int J Health Care Finance Econ.* 2003;3(3):183-205.
37. Towse A, Pistollato M, Mestre-Ferrandiz J, Khan Z, Kaura S, Garrison L. European Union Pharmaceutical Markets: A Case for Differential Pricing? *International Journal of the Economics of Business.* 2015;22(2):263-75.
38. Husereau D, Cameron CG. Value-based Pricing of Pharmaceuticals in Canada: Opportunities to expand the role of health technology assessment? Ontario: Canadian Health Services Research Foundation; 2011.
39. Paris V, Belloni A. Value in Pharmaceutical Pricing. Paris: OECD; 2013. Document No.: 63.
40. Paris V. Pharmaceutical Pricing in European Countries. LinkedIn SlideShare; 2015 [accessed on 18/08/2017]. Available from: <https://www.slideshare.net/cabetan/pharmaceutical-pricing-in-european-countries-valerie-paris-220115/4>
41. DiPiro J, Talbert R, Yee G, Matzke G, Wells B, Posey LM. *Pharmacoeconomics: Principles, Methods, and Applications. Pharmacotherapy: A Pathophysiologic Approach.* 8 ed: McGraw-Hill Education; 2011.
42. Rankin PJ, Bell GK, Wilsdon T. Global Pricing Strategies for Pharmaceutical Product Launches. In: Incorporated CRA, editor. *The Pharmaceutical Pricing Compendium.* London: URCH Publishing; 2003.
43. Sieler S, Rudolph T, Brinkmann-Sass C, Sear R. AMNOG Revisited - How has Germany health reform impacted pharma pricing and market access and what can the industry learn from the experience? Germany: McKinsey & Company; 2015.
44. MAP BioPharma. Market Access Steps - AMNOG process overview [Accessed on 18/07/2017]. Available from: <https://mapbiopharma.com/demo/market-access-in-germany/2016>
45. Association of the British Pharmaceutical Industry. Understanding the 2014 Pharmaceutical Price Regulation Scheme. London: ABPI; 2014.
46. Petrou P. Long term effect of tendering on prices of branded pharmaceutical products. *Health Policy and Technology.* 2016;5:40-6.

47. Medicines for Europe. Values of Generic Medicines. Brussels: IGES institution; 2016 [accessed on 21/08/2017]. Available from: <http://www.medicinesforeurope.com/publications/>.
48. Colombo GL, Agabiti-Rosei E, Margonato A, Mencacci C, Montecucco CM, Trevisan R. Off-patent generic medicines vs. off-patent brand medicines for six reference drugs: a retrospective claims data study from five local healthcare units in the Lombardy Region of Italy. *PLoS One*. 2013;8(12):e82990.
49. GaBI Online - Generics and Biosimilars Initiative. EU investigation tackles pay-for-delay. Belgium: Generics and Biosimilars Initiative (GaBI); 2011
50. Dylst P, Simoens S. Generic Medicine Pricing Policies in Europe: Current Status and Impact. *Pharmaceuticals (Basel)*. 2010;3(3):471-81.
51. Ruggeri K, Nolte E. Pharmaceutical Pricing: The Use of External Reference Pricing. *Rand Health Q*. 2013;3(2):6.
52. Davies S, Lyons B. Mergers and Merger Remedies in the EU: Assessing the consequences for competition. Cornwall: Edward Elgar Publishing; 2007. 288 p.
53. Kanavos P, Seeley L, Vondoros S. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium. London: LSE Health; 2014.
54. Better Pharmacare Coalition. What is tendering?. BPC; 2017 [Accessed on 20/08/2017]. Available from: <http://www.betterpharmacare.com/issues-cost-tendering.cfm2017>
55. Vogler S, Paris V, Ferrario A, Wirtz VJ, de Joncheere K, Schneider P, et al. How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. *Appl Health Econ Health Policy*. 2017;15(3):307-21.
56. Paris V, Hewlett E, Aaraaen A, Alexa J, Simon L. Health care coverage in OECD countries in 2012. Paris: OECD Publishing; 2016.
57. European Commission. Public expenditure on health: its growing importance, drivers and policy reforms to curb growth. Brussels: European Union; 2013.
58. OECD. Health at a glance 2015: OECD 2015. Paris: OECD Publishing; 2015.
59. Vogler S, Habl C, Bogut M, Voncina L. Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. *Croat Med J*. 2011;52(2):183-97.
60. Pita Barros P. *Economia da Saúde - Conceitos e Comportamentos*. 3 ed. Lisboa: Almedina; 2016.
61. Dylst P, Vulto AG, Simoens S. Reference pricing systems in Europe: characteristics and consequences. *Generics and Biosimilars Initiative Journal*. 2012;1(3-4):127-31.
62. OECD. *Pharmaceutical Pricing Policies in a Global Market*. OECD Health Policy Studies; 2008.
63. Harding G, Taylor KMG. *Pharmacy Practice*. 2 ed. Florida: CRC Press; 2015.



64. World Health Organization. Health Technology Assessment Geneva: WHO; 2017 [Available from: [http://www.who.int/medical\\_devices/assessment/en/](http://www.who.int/medical_devices/assessment/en/)]
65. Balko N. Convergence of assessment in Europe - reality or aspiration? AccessPoint. 2016;5(10):45-9.
66. Sorenson C, Drummond M, Kanavos P. Ensuring value for money in health care - The role of health technology assessment in the European Union. Denmark: The European Observatory on Health Systems and Policies; 2008.
67. Morgan S, Daw J, Thomson P. International best practices for negotiating 'reimbursement contracts' with price rebates from pharmaceutical companies. Health Aff (Millwood). 2013;32(4):771-7.
68. Junkins RJ. Outcomes-based contracts. Indianapolis: Butler University; 2017.
69. Simões JdA, Augusto GF, Fronteira I, Hernández-Quevedo C. Portugal - Health system review. United Kingdom: Instituto de Medicina Tropical da UNL; 2017. Document No.: 2.
70. Campbell C, Clark R. Portugal: A glimpse into Europe's future in an era of austerity and HTA reform? : Xcenda AmerisourceBergen; 2017.
71. Martins J, Rodrigues J, Antunes M, Ferrador F, Ramos I, Ramos R, et al. Sistema Nacional de Avaliação de Tecnologias de Saúde para Portugal (SiNATS) – Criar o futuro. Lisboa: INFARMED, I.P.; 2014.
72. Governo de Portugal. Decreto-Lei n.º 97/2015, de 1 de junho. N.º 105. 1.ª série (2015).
73. Governo de Portugal. Portaria n.º 195-C/2015, de 30 de junho. N.º 125. 1.ª série (2015).
74. Governo de Portugal. Portaria n.º 290-B/2016, de 15 de novembro. N.º 219. 1.ª série (2016).
75. Governo de Portugal. Portaria n.º 290-A/2016, de 15 de novembro. N.º 219. 1.ª série (2016).
76. Governo de Portugal. Portaria n.º 154/2016, de 27 de maio. N.º 102. 1.ª série (2016).
77. Governo de Portugal. Portaria n.º 195-A/2015, de 30 de junho. N.º 125. 1.ª série (2015).
78. Governo de Portugal. Portaria n.º 195-D/2015, de 30 de junho. N.º 125. 1.ª série (2015).
79. Governo de Portugal. Portaria n.º. 195-B/2015, de 30 de junho. N.º. 125. 1.ª série (2015).
80. Vogler S, Zimmermann N, de Joncheere K. Policy interventions related to medicines: Survey of measures taken in European countries during 2010-2015. Health Policy. 2016;120(12):1363-77.
81. EUnetHTA. About - European Network on HTA. The Netherlands: EUnetHTA; 2016 [accessed on 03/09/2017]. Available from: <http://www.eunetha.eu/about-us/history>
82. European Commission. Explanatory Note on the Joint Procurement Mechanism. Luxembourg: European Union; 2015.

83. Azzopardi-Muscat N, Schroder-Bäck P, Brand H. The European Union Joint Procurement Agreement for cross-border health threats: what is the potential for this new mechanism.
84. WHO Europe. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Denmark: WHO Europe; 2015.
85. Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsecs A. Discounts and rebates granted to public payers for medicines in European countries. *South Med Rev.* 2012;5(1):38-46.
86. OECD/EU. Health at a Glance: Europe 2016 - State of Health in the EU Cycle. Paris: OECD Publishing; 2016.
87. Ferrario A, Kanavos P. Managed entry agreements for pharmaceuticals: the European experience. Brussels: The London School of Economics and Political Science; 2013.
88. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med.* 2015;124:39-47.
89. Morel T, Arickx F, Befrits G, Siviero P, van der Meijden C, Xoxi E, et al. Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. *Orphanet J Rare Dis.* 2013;8:198.
90. Godman B, Shrank W, Andersen M, Berg C, Bishop I, Burkhardt T, et al. Policies to enhance prescribing efficiency in Europe: findings and future implications. *Front Pharmacol.* 2010;1:141.
91. Carone G, Schwierz C, Xavier A. Cost-containment policies in public pharmaceutical spending in the EU. Brussels: European Commission; 2012.
92. Jain S, Upadhyaya P, Goyal J, Kumar A, Jain P, Seth V, et al. A systematic review of prescription pattern monitoring studies and their effectiveness in promoting rational use of medicines. *Perspect Clin Res.* 2015;6(2):86-90.
93. Larsen J, Stovring H, Kragstrup J, Hansen DG. Can differences in medical drug compliance between European countries be explained by social factors: analyses based on data from the European Social Survey, round 2. *BMC Public Health.* 2009;9:145.
94. Niezen M, de Bont A, Stolk E, Eyck A, Niessen L, Stoevelaar H. Conditional reimbursement within the Dutch drug policy. *Health Policy.* 2007;84(1):39-50.
95. Noronha N. Trabalho dos farmacêuticos poupa 880 milhões de euros aos portugueses Lisbon: Lifestyle - Sapo; 2015 [accessed on: 09/09/2017]. Available from: <https://lifestyle.sapo.pt/saude/noticias-saude/artigos/trabalho-dos-farmacêuticos-poupou-880-milhoes-de-euros-aos-portugueses>.
96. Bernsten C, Andersson K, Gariépy Y, Simoens S. A comparative analysis of remuneration models for pharmaceutical professional services. *Health Policy.* 2010;95(1):1-9.
97. Pereira MC, Vilares H. Uma análise do mercado do medicamento em Portugal. Banco de Portugal; 2014.

98. Pinto AS. Análise da evolução do mercado do medicamento em Portugal. Porto: Universidade do Porto; 2014.
99. Governo de Portugal. Resolução do Conselho de Ministros n.º 56/2016, de 13 de outubro. N.º 197. 1.ª série (2016).
100. Governo de Portugal. Lei n.º 42/2016, de 28 de dezembro, Artigos 137º-145º, 273º. N.º 248. 1.ª série (2016).
101. INFARMED/MS. Serviço Nacional de Saúde (SNS) - Encargos com medicamentos Lisbon: PORDATA; 2017 [Accessed on 06/05/2016]. Available from: <https://www.pordata.pt/DB/Portugal/Ambiente+de+Consulta/Gr%C3%A1fico>
102. Governo de Portugal. Lei n.º 82-B/2014, de 31 de dezembro, Artigo 168º. N.º 252. 1.ª série (2014).
103. INFARMED. Legislação publicada Lisboa: INFARMED, I.P.; 2017 [accessed on 18/09/2017]. Available from: <http://www.infarmed.pt/web/infarmed/legislacao/legislacao-publicada>
104. Governo de Portugal. Portaria n.º 18-A/2015, de 2 de fevereiro. N.º 22. 1.ª série (2015).
105. Governo de Portugal. Portaria n.º 262/2016, de 7 de outubro. N.º 193. 1.ª série (2016).
106. OECD. Statistics. Paris: OECD Publishing; 2017 [accessed on 24/08/2017]. Available from: <http://stats.oecd.org/#>
107. Simoens S. A review of generic medicine pricing in Europe. Generics and Biosimilars Initiative Journal. 2012;1(1):8-12.
108. Ministério da Saúde. Genéricos batem recorde. Lisbon: Serviço Nacional de Saúde; 2017 [accessed on: 18/09/2017]. Available from: <https://www.sns.gov.pt/noticias/2017/09/04/genericos-batem-recorde/>
109. Ordem dos Farmacêuticos. Uso Responsável do Medicamento. Lisboa; 2014 [accessed on 19/09/2017]. Available from: <http://www.usoresponsaveldomedicamento.com/#section-enquadramento>
110. Paulo A. SNS: Caracterização e Desafios. Lisboa: GPEARI - MFAP 2010. Document No.: 09/2010.
111. Gonçalves L, Caldeira S, Teixeira M. Managed Entry Agreements: Portuguese Experience. ISPOR 19th Annual European Congress (2016); Vienna: INFARMED; 2016.
112. Governo de Portugal. Decreto-Lei n.º 48-A/2010, de 13 de maio, N.º 93. 1.ª série (2010).
113. INFARMED. Meio Hospitalar - Monitorização do Consumo de Medicamentos. Lisbon: SNS; Junho 2017.
114. Félix J, Vandewalle B, Silva MJ, Rabiais S, de Almeida JM. Financiamento público dos medicamentos em Portugal (2007-2011). Avaliação da acessibilidade e dos critérios da tomada de decisão sobre os medicamentos com novas substâncias activas ou novas indicações terapêuticas: EXIGO consultores; 2011. p. 1-86.

115. Governo de Portugal. Decreto-lei N.º 195/2006, de 3 de Outubro. N.º 191. 1.ª série (2006).
116. Governo de Portugal. Despacho n.º 2061-C/2013, de 1 de fevereiro. N.º 24. 1.ª série (2013).
117. Europe Economics. External Reference Pricing. London: Europe Economics; 2013.
118. Natsis Y. New game, new rules: Pathways for better and affordable medicines in Europe. European Public Health Alliance. 2017.
119. Belloni A, Morgan D, Paris V. Pharmaceutical Expenditure and Policies.
120. Fisher D, Wicks P, Babar ZU. Medicine and the future of health: reflecting on the past to forge ahead. BMC Med. 2016;14(1):169.
121. Henry D, Lang D, Hill S. Approach to the Valuation and Pricing of Future Medicines. WHO CC for Training in Pharmacology and Rational Drug Use; 2004.
122. Deloitte. Healthcare and Life Sciences Predictions 2020: A bold future? London: Deloitte Touche Tohmatsu Limited; 2014.
123. Seiter A. A Practical Approach to Pharmaceutical Policy. Washington: The World Bank; 2010. Document No.: 55203.
124. European Medicines Agency. EU Medicines Agencies Network Strategy to 2020 - Working together to improve health. London: Heads of Medicines Agencies; 2015.
125. Danzon PM. The Economics of Parallel Trade. Pharmacoeconomics. 1998;13(3):293-304.
126. The World Bank. World Development Indicators. The World Bank Group. 2017 [Accessed on 27/03/2017]. Available from: <https://data.worldbank.org/data-catalog/world-development-indicators>.
127. Investopedia. Terms [Internet]. IAC; 2016 [accessed on 04/11/2017]. Available from: <http://www.investopedia.com/dictionary/>.
128. Huff-Rousselle M. The logical underpinnings and benefits of pooled pharmaceutical procurement: a pragmatic role for our public institutions? Soc Sci Med. 2012;75(9):1572-80.
129. European Parliament, The Council of the European Union. Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC. 293. Strasbourg: Official Journal of the European Union; 2013. p. 1-15.
130. Espín J, Rovira J, Calleja A, Azzopari-Muscat N, Richardson E, Palm W, et al. How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe? London: European Observatory on Health Systems and Policies; 2016. Document No.: 21.
131. Natsis Y. Beneluxa: First results of multi-country cooperation on medicine price negotiations. Brussels: European Public Health Alliance; 2017.

132. Nineoclock. Romania and Bulgaria, agreement on the patients' access to medicines. Romania: NineO'Clock; 2016.
133. Michalopoulos S. Southern EU states present unified front in drug talks. EURACTIV. 2017 [accessed on 10/06/2017]. Available from: <https://www.euractiv.com/section/health-consumers/news/southern-eu-states-present-unified-front-in-drug-talks/>
134. Agência Lusa. Portugal e Espanha assinam declaração para negociar compra de medicamentos. Observador. 2017 [accessed on 24/08/2017]. Available from: <http://observador.pt/2017/07/09/portugal-e-espanha-assinam-declaracao-para-negociar-compra-de-medicamentos/>.
135. Business Monitor International. Cross-Border Collaborations In Europe Pose Upside and Downside Risks For Drugmakers London: BMI Research; 2017 [accessed on 03/11/2016]. Available from: [https://www.bmiresearch.com/articles/cross-border-collaborations-in-europe-pose-upside-and-downside-risks-for-drugmakers?utm\\_content=buffer0dc62&utm\\_medium=social&utm\\_source=twitter.com&utm\\_campaign=buffer](https://www.bmiresearch.com/articles/cross-border-collaborations-in-europe-pose-upside-and-downside-risks-for-drugmakers?utm_content=buffer0dc62&utm_medium=social&utm_source=twitter.com&utm_campaign=buffer).
136. Rosenkötter N, Clemens T, Sørensen K, Brand H. Twentieth anniversary of the European Union health mandate: taking stock of perceived achievements, failures and missed opportunities - a qualitative study. BMC Public Health. 2013;13:1074.
137. Vogler S. How large are the differences between originator and generic prices? Analysis of five molecules in 16 European countries. Farmeconomia Health economics and therapeutic pathways. 2012;13(3):29-41.
138. ET Bureau. Prize funds: These alternatives to patents might be the way forward to cheaper healthcare The Economic Times; 2012 [accessed on 25/02/2017]. Available from: <http://economictimes.indiatimes.com/opinion/et-editorial/prize-funds-these-alternatives-to-patents-might-be-the-way-forward-to-cheaper-healthcare/articleshow/13581248.cms?intenttarget=no>.
139. Galasso A, Mitchell M, Virag G. Market outcomes and dynamic patent buyouts. International Journal of Industrial Organization. 2016;48:207-43.
140. Liberatore F. Restrictions on Parallel Trade of Pharmaceutical Products and EU Competition Law. In: Cortese B, editor. EU competition law: between public and private enforcement. Alphen aan den Rijn: Kluwer Law International; 2014. p. 347-57.
141. Light DW, Warburton R. Demythologizing the high costs of pharmaceutical research. BioSocieties. 2011;6(1):34-50.
142. Swanson A. Big pharmaceutical companies are spending far more on marketing than research Washington: The Washington Post; 2015 [accessed on 07/10/2017]. Available from: [https://www.washingtonpost.com/news/wonk/wp/2015/02/11/big-pharmaceutical-companies-are-spending-far-more-on-marketing-than-research/?utm\\_term=.f67146e50318](https://www.washingtonpost.com/news/wonk/wp/2015/02/11/big-pharmaceutical-companies-are-spending-far-more-on-marketing-than-research/?utm_term=.f67146e50318)
143. Sash RR. Regulatory framework for the treatment of orphan diseases. In: Mehta a, Beck M, Sunder-Plassmann G, editors. Fabry Disease - Prespective from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006.

144. Raffaelli R. How the European Union works Brussels: European Parliament; 2017  
[accessed on 08/10/2017]. Available from:  
[http://www.europarl.europa.eu/atyourservice/en/displayFtu.html?ftuId=FTU\\_1.2.2.html](http://www.europarl.europa.eu/atyourservice/en/displayFtu.html?ftuId=FTU_1.2.2.html)

## 6. Annexes

**ANNEX 1.** Portuguese measures related to reimbursement changes, price formation rules alteration, decrease of commercialization margins, modifications on the annual review of prices, and applied price cuts from 2000 to 2017 (adapted from INFARMED, 2017 (103))

Legal Rule	Number of measures per Nature of measure
Decree-law No. 205/2000, of 1 of September	1 – Reimbursement (all)
Ordinance No. 713/2000, of 5 of September	2 – Price formation (non-prescription) 1 – Commercialization margins
Ordinance No. 577/2001, of 7 of July	2 – Price formation (generic) 1 – Commercialization margins
Ordinance No. 1279/2001, of 14 of November	1 – Price cut (all)
Decree-law No. 270/2002, of 2 of December	2 – Reimbursement (all)
Ordinance No. 1492-A/2002, of 5 of December	1 – Price cut (all)
Ordinance No. 914/2003, of 1 of September	1 – Price formation (generic)
Decree-law No. 234/2003, of 27 of September	1 – Reimbursement (all)
Ordinance No. 172/2004, of 23 of February	1 – Reimbursement (all)
Decree-law No. 81/2004, of 10 of April	1 – Reimbursement (all)
Deliberation No. 669/2004, of 26 of March	1 – Reimbursement (all)
Ordinance No. 561/2004, of 24 of May	1 – Reimbursement (all)
Decree-law No. 53/2005, of 13 of December	1 – Reimbursement (all)
Dispatch No. 358/2005, of 15 of March	1 – Reimbursement (all)
Ordinance No. 618-A/2005, of 27 of July	1 – Price cut (all) 1 – Commercialization margins
Decree-law No. 129/2005, of 11 of August	3 – Reimbursement (all)
Protocol No. 7/2006, of 10 of February	1 – Price formation (all)
Dispatch No. 15978/2006, of 26 of June	1 – Reimbursement (all)
Decree-law No. 127/2006, of 4 of July	1 – Reimbursement (all)
Dispatch No. 21787/2006, of 29 of September	1 – Reimbursement (all)
Law No. 53-A/2006, of 29 of December	1 – Price cut (reimbursed) 1 – Reimbursement (all)
Ordinance No. 30-B/2007, of 5 of January	1 – Price cut (all)
Dispatch No. 4130/2007, of 31 of January	1 – Reimbursement (all)
Decree-law No. 65/2007, of 14 of March	2 – Price formation (all) 2 – Price cut (generic) 1 – Commercialization margins
Dispatch No. 6434/2007, of 19 of March	1 – Reimbursement (all)
Ordinance No. 1016-A/2008, of 8 of September	1 – Price cut (generic)
Decree-law No. 129/2009, of 29 of May	1 – Reimbursement (generic)
Decree-law No. 48-A/2010, of 13 of May	1 – Reimbursement (generic) 1 – Price formation (reimbursed)
Ordinance No. 312-A/2010, of 11 of June	1 – Price formation (all)
Ordinance No. 924-A/2010, of 17 of September	1 – Reimbursement (all)
Decree-law No. 103-A/2010, of 1 of October	3 – Reimbursement (all)
Ordinance No. 1041-A/2010, of 7 of October	1 – Price cut (reimbursed)

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Dispatch No. 18694/2010, of 16 of December	1 – Reimbursement (compounded)
Ordinance No. 3/2012, of 2 of January	1 – Price formation (all)
Decree-law No. 152/2012, of 12 of July	1 – Price formation (prescription and reimbursed)
Decree-law No. 34/2013, of 27 of February	1 – Price formation (prescription and reimbursed)
Ordinance No. 335-A/2013, of 15 of November	1 – Price formation (all) 1 – Annual review
Ordinance No. 367/2013, of 23 of December	1 – Price formation (all) 1 – Annual review
Decree-law No. 19/2014, of 5 of February	1 – Price formation (prescription and reimbursed) 1 – Reimbursement (all)
Ordinance No. 158/2014, of 13 of February	1 – Reimbursement (hepatitis C)
Dispatch No. 9767/2014, of 29 of July	1 – Reimbursement (Crohn disease)
Ordinance No. 222/2014, of 4 of November	1 – Reimbursement (glucose strips)
Ordinance No. 114-A/2015, of 18 of February	1 – Reimbursement (hepatitis C)
Ordinance No. 216-A/2015, of 14 of April	1 – Reimbursement (hepatitis C)
Ordinance No. 195-C/2015, of 30 of June	1 – Price formation (all) 1 – Annual review 1 – Commercialization margins
Ordinance No. 195-D/2015, of 30 of June	1 – Reimbursement (all)
Rectification Statement No. 37-A/2015, of 28 of August	1 – Reimbursement (all) 1 – Annual review
Ordinance No. 35/2016, of 1 of March	1 – Reimbursement (glucose strips)
Ordinance No. 146-B/2016, of 12 of May	1 – Reimbursement (hepatitis C)
Ordinance No. 284/2016, of 4 of November	1 – Reimbursement (medical devices)
Ordinance No. 290-A/2016, of 15 of November	1 – Price formation (all) 1 – Annual review (prescription and reimbursed) 1- Commercialization margins
Dispatch No. 2019/2017, of 9 of March	1 – Price formation (medical devices)
Ordinance No. 141/2017, of 18 of April	1 – Reimbursement (arthritis)