







## Regulatory intelligence of health technologies in Greece

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### Abstract

Greece has a public universal health system, the National Health System (ESY) – with mandatory insurance coverage (IKA) for all working people (either employees or self-employed). On top of that, people can voluntarily have private insurance. EOPYY (National Organisation for Healthcare Provision) is the only responsible party for purchasing health services funded by public resources based on the National Social Security Fund (EFKA) contributions and state budget. There is only a limited number of drugs being exclusively provided by the public health care system, for free (EOPYY pharmacies) like the high-cost medications. Other than these, patients can buy any drug they want. National Organization for Medicines (EOF) is the regulatory authority and also responsible for pharmacovigilance of medicines, medical products, of beauty and veterinary drugs. In 2011, the pricing and reimbursement processes were separated, with pricing taking place after marketing authorization; subsequently, analysis for reimbursement by the social health insurance is allowed with inclusion in a positive list. New pharmaceutical products follow an external reference pricing system, in which the maximum ex-factory price for medicines under patent is defined by the mean of the three lowest prices for the same drug in European Union (EU) countries, this same rule being applied to biological and biosimilar medicines. Generic drugs are priced either by the mean of the three lowest prices charged in the EU or by a 50% price reduction in relation to the period in which the medication was under patent; thus, the maximum prices of the generic drugs are set at 65% of the price of the respective reference product. In 2018, the Health Technology Assessment (HTA) was introduced in the country to evaluate medications and to issue recommendations to the Ministry of Health on the inclusion or removal of products from the Positive List. As the HTA process is still being reformed in Greece, it is believed that, in the coming years, the country will have the opportunity to improve the implementation, having the linking of the HTA results with the clinical guidelines as one of the major challenges.

**Keywords:** Greece; Incentive Reimbursements, Access to medicines, Health Services Accessibility.

## Inteligência regulatória de tecnologias de saúde na Grécia

### Resumo

A Grécia possui um sistema de saúde público e universal, o Serviço Nacional de Saúde (ESY), com cobertura de seguro obrigatório (IKA) para todos os trabalhadores (empregados ou autônomos). Além disso, os indivíduos podem ter, voluntariamente, seguro privado. A EOPYY (Organização nacional para provisão de serviços de saúde), a única responsável pela aquisição de serviços de saúde financiados por recursos públicos baseados nas contribuições do Fundo Nacional de Seguridade Social (EFKA) e do orçamento estadual. Há um número limitado de medicamentos fornecidos exclusivamente pelo sistema público de saúde, gratuitamente (farmácias EOPYY), como os medicamentos de alto custo. Além desses, a população pode comprar qualquer medicamento que deseje. *National Organization for Medicines (EOF)* é a autoridade regulatória e responsável também pela farmacovigilância de medicamentos, produtos médicos, de beleza e medicamentos veterinários. Em 2011, os processos de precificação e reembolso foram separados, sendo que a precificação ocorre após a autorização de comercialização, em seguida, é permitida a análise para reembolso pelo seguro social de saúde com a inclusão numa lista positiva. A precificação de novos produtos farmacêuticos segue um sistema de referenciamento externo de preços, onde o preço de fábrica máximo para medicamentos sob patente é definido pela média dos três menores preços para o mesmo medicamento nos países da União Européia (UE), sendo essa mesma regra aplicada para medicamentos biológicos e biossimilares. Medicamentos genéricos são precificados pela média dos três menores preços praticados na UE ou pela redução em 50% do preço em relação ao período em que o medicamento estava sob patente. Assim, os preços máximos dos medicamentos genéricos são fixados em 65% do preço do respectivo produto de referência. Em 2018, a Avaliação de Tecnologias em Saúde (ATS) foi introduzida no país para avaliar medicamentos e emitir recomendações ao Ministério da Saúde sobre a inclusão ou remoção de produtos da Lista Positiva. Como o processo de ATS ainda está sendo implementado, acredita-se que nos próximos anos, o país terá a oportunidade de aprimorar a implementação dessas técnicas, tendo como um dos grandes desafios a vinculação dos resultados das ATS com as orientações clínicas.

**Keywords:** Grécia, reembolso, acesso à medicamentos, acessibilidade ao serviços de saúde.



## Greece and its health system

Located in southern Europe, Greece has nine geographic regions, totaling 131,957 km<sup>2</sup> and more than ten million inhabitants, of which 22.3% are older adults, according to a census carried out in 2020. Most of the population lives in urban areas and the country presents a demographic density of 81 inhabitants per km<sup>2</sup>. The country has a unique geographical specificity with more than a thousand islands and mainland remote areas which also affects the development of the health care network.<sup>1</sup>

In Greece, the Human Development Index(HDI) is 0.872, considered as very high by the United Nations, which leaves the country in the 32<sup>nd</sup> position of the HDI ranking.<sup>2</sup> Currently, the fertility rate in Greece is 1.3 children per woman of a reproductive age. In relation to life expectancy at birth, Greece is the 16<sup>th</sup> country with the highest life expectancy of the European Union (81.2 years old)<sup>1</sup>. Since 2009, the overall fertility rate in Greece (1.34 in 2012) dropped to 18% below the mean of the region. Combined with the increase in longevity, this decline transformed the population's structure.<sup>3</sup>

The Greek economic crisis exerted a negative effect on the population's health. Monitoring of the 2020 health goals showed improving trends for 10 of the 19 main indicators and worsening trends were observed in three indicators: prevalence of excess weight, unemployment rate, and Gini coefficient in income distribution<sup>3</sup>. The main causes of death in the country are related to cardiovascular diseases (ischemic heart disease and stroke) and to cancer, totaling more than 60% of all the causes.<sup>4-5</sup> The infant mortality rate in Greece is 3.7 per 1,000 live births, which is more than 20 times lower than that of countries with the highest infant mortality rates in the world. Likewise, in 2017 Greece presented the lowest maternal mortality rates in the world: less than 10 maternal deaths for every 100,000 life births<sup>1</sup>. The incidence of infectious diseases is generally low, excluding the HIV and AIDS rates, which increased rapidly in the last few years.<sup>3</sup>

Greece has a universal health system, considered mixed (public-private), as it combines a national health service (ESY - *Ethniko Systema Ygeias*) with insurance coverage, mandatory social (IKA) and voluntary private health insurance<sup>6</sup>. The national healthcare service is funded by general taxation, and social insurance, by contributions from employers and employees. In addition to that, nearly 15% of the Greek population has some private health insurance. According to a report issued in 2000 by the World Health Organization (WHO), the Greek health system was ranked as the 14<sup>th</sup> best performer out of 191 countries surveyed<sup>7</sup>. Until 2009, total health expenditure in Greece was among the highest in the European Union, corresponding to 9.5% of the country's GDP and mainly relying on public funding (nearly 68.5% of total health expenditure). After the beginning of the financial crisis in Greece, in 2010, health expenses corresponded to 10.6% of the GDP and, of this total, 24.8% corresponded to medications and pharmaceutical inputs<sup>8-9</sup>.

In 2008, the per capita expenses in pharmaceutical products were approximately 800 euros, the highest in the European Union, according to the OECD<sup>10</sup>. However, since 2008, Greece started to face a severe economic crisis, with several fiscal problems associated with high deficits and public debts. To contribute to the resolution of the crisis, the European Union, the International Monetary Fund, and the European Central Bank offered financial assistance to the country and, as part of the agreement, unofficially called Troika, Greece pledged to reduce

its public expenses, including those destined to health.<sup>10</sup> Between 2009 and 2015, health-related expenses dropped. The crisis also exerted an impact of public funding for health-related expenses, which was reduced from almost 70% to 59.1% during the same period. However, during this time in addition to the economic crisis in Greece, at the same time we saw the development of electronic health services (e.g., e-prescription) that resulted in serious containment of the relevant services. So, the hospitals also started issuing their financial reports based on international standards, which resulted in the development of the appropriate monitoring of hospital supplies and drugs, which was not possible previously.<sup>11-12</sup> In 2000s, Greece was among the European Union countries with the highest pharmaceutical expenditure. However, between 2009 and 2015 and due to the crisis, pharmaceutical expenses dropped from 2.6% to 2.1% of the GDP<sup>12</sup>. It is noted that, according to the goal established by the Troika agreement, pharmaceutical public expenditure should not exceed 1% of the GDP<sup>13</sup>. The Greek government's key expense containment measures included price reductions, reintroduction of a positive list that includes all reimbursable pharmaceutical products, changes in the pharmacies' and distributors' profit margins, and standardization of hospital-use medications<sup>10</sup>.

The National Organisation for Healthcare Provision (EOPYY) [*Εθνικός Οργανισμός Παροχής Υπηρεσιών Υγείας (Ε.Ο.Π.Υ.Υ.)*] was established in 2011, acting as the sole responsible for purchasing publicly funded health services for patients served by ESY. The private sector can complement the services offered by means of contracts with EOPYY. Specific legislation regulates the activities of third-party payers and service providers, the purchasing process, and the levels of prices and refunds within ESY<sup>4</sup>. In 2018, of the country's total health spending, with almost 60% of this spending on public spending and the rest on private spending.

## Pharmaceutical market

The pharmaceutical market in Greece is composed of pharmaceutical companies (manufacturers and importers), wholesalers (both devoted to storage and distribution) and pharmacies. Normally, high-cost medications are exclusively provided by the EOPYY pharmacies and hospitals. According to ECONOMOU *et al* (2017), in 2015, nearly 73.5% of the total sales(84.5% by volume) were made by wholesalers and private pharmacies and the remainder, 26.5%, were sold to EOPYY pharmacies (15.5% by volume) and to hospitals<sup>4</sup>.

Public spending on medications includes the social insurance funds to finance prescription drugs that are reimbursed by the Social Security Funds (SSF), while private spending includes co-payment rates and payment for non-reimbursed medications and products, in addition to those that users pay or choose to pay in full<sup>14</sup>. High expenses in pharmaceutical products are one of the main objectives for cost containment in the country. One of the strategies used has been to promote the use of generic drugs, as the country has a high rate of use of medications that are protected by patents, when compared to the European Union (EU) mean (9.3% vs 6.3% of the volume, respectively, in 2019). The market share of medications not protected by patents accounted for 67.9% in 2019, with 34.3% corresponding to generic drugs. At the same time, the EU mean was 61.5% of generic drugs. Such difference is partially justified by the prices of the medications, which are significantly lower in Greece than in other EU countries<sup>4,14</sup>.

## Pharmaceutical regulation

Considering that medicines and pharmaceutical products belong to a special category of products, not only the manufacture, but also the authorization for marketing and distribution, require the fulfillment of specific conditions<sup>15</sup>. In Greece, entry of new medicines and pharmaceutical products into the market can occur in four ways: through the centralized procedure carried out by the European Medicines Agency (EMA) and by mutual recognition and decentralized procedures with other EU members, in addition to the national procedure, carried out by the National Organization for Medicines (EOF - Εθνικός Οργανισμός Φαρμάκων)<sup>12,15</sup>.

In addition to marketing authorization, the EOF is also responsible for pharmacovigilance activities, evaluating adverse drug reactions and suggesting or complementing information about the products<sup>15</sup>. In 1986, pharmacovigilance activities were initiated in Greece, according to the standards established by the WHO and followed by all the EU members. Regarding the collection of data on adverse drug reactions, the notifications are sent by “Κίτρινη Κάρτα” (or yellow card, the tool used by EU countries to report adverse events), by health professionals or by means of the CIOMS (Council for International Organizations of Medical) forms to EOF<sup>15,16</sup>. The notifications are evaluated and entered into the EOF national pharmacovigilance database, in addition to being part of the European database (EudraVigilance) and of the WHO database (Vigibase WHO Uppsala Monitoring Center- UMC).

## Overview of pricing and reimbursement of medicines

In April 2021, a WHO sub-office was implemented in Athens, with a focus on care quality and patient safety: the WHO Centre of Excellence for Quality of Care and Patient Safety. Serving as a center of excellence, with the support of the Greek Government, the sub-office will work in the following main areas: providing support to the countries, including national strategies and frameworks; sharing best practices in health to scale up the successful interventions; innovations and knowledge in care quality and patient safety; and analysis of policies aimed at care quality and patient safety. The objective is to attain the highest levels of well-being, health and health protection in this European region of the WHO, in line with the Sustainable Development Goals<sup>7</sup>.

For each medicine or pharmaceutical product that receives market authorization in Greece, regardless of the approval route, a periodic product safety monitoring report is required. In this report, a precise summary of data and documents must be inserted assessing the risk-benefit ratio of the product, concluding on any possible needs for further investigation or possible modification of information in the product marketing authorization<sup>16-17</sup>.

In 2011, the pricing and reimbursement processes were separated in Greece. Pricing occurs after market authorization, a stage that, in fact, encompasses from authorizing to selling the medication or product in the country. Thus, after pricing, analysis for reimbursement is enabled<sup>12</sup>.

As a measure to contain drug-related costs, in response to the financial crisis, a positive list, which had been abolished in 2006, was reintroduced in the country, including all medicinal products that are reimbursed by social health insurance. A list of non-reimbursable pharmaceutical products was also elaborated, which included products that had already been reimbursed<sup>18-19</sup>.

## Health Technology Assessment and reimbursement

There is an Evaluation and Reimbursement Committee for Medications for Human Use, which is responsible for the inclusion or exclusion of licensed medications from the positive list. To be reimbursed, new medications must be previously approved for reimbursement in other European countries that use Health Technology Assessment in their incorporation processes<sup>10,12,18</sup>. In Greece, some reimbursement and copayment rates are applied, defined according to some population or medication groups. Medicines for severe chronic conditions (such as cancer, Type 1 diabetes and hepatitis) or for vulnerable social groups enjoy 100% reimbursement in relation to the reference price. Medicines for some defined conditions (such as Parkinson's disease, Type 2 diabetes and epilepsy) or for pensioners enjoy a 90% reimbursement (and 10% copayment). The “standard” reimbursement rate is 75% of the reference price, with 25% copay. However, this applies to prescription drugs, for which, previously, in addition to the co-payment of the percentage defined by category, a fee of €1 is applied per prescription. However, this fee is not applicable anymore. Over-the-counter medications are not reimbursable<sup>19</sup>. The high-cost medications on the positive list are fully reimbursed (100%), without copayment, by public hospitals or EOPYY pharmacies<sup>18-20</sup>. Another cost-reduction measure was the mandatory prescription for a chemical substance (generic name) and the dispensing of the lowest-cost generic drug available. However, due to pressure from medical entities, prescription by brand name was allowed and, if the patients chose this product, they would have to pay the difference between this and the lowest-cost generic drug available<sup>10</sup>.

In addition to the positive list of medicines, the country has a package of benefits that includes imported pharmaceutical products for exceptional cases, special nutrition products and medical devices for personal use<sup>18</sup>.

In relation to transparency and accountability in the decision-making process, although there are institutions in Greece in charge of fighting against corruption and increasing transparency in the public administration, these efforts have historically had limited effectiveness. However, some reforms have been implemented since 2010, with the objective of fighting against lack of transparency in the health sector. Among the measures adopted, we can highlight the creation of the “Clarity Programme”, which promotes the transparency and openness of the Greek government and its policies (Diavgeia), through the online publication of the decisions taken by ministries, public institutions, regulatory authorities, and local governments. Another reform applied was the mandatory electronic prescription for physicians linked to the Greek health system, in addition to the creation of the Price Monitoring Tool, which it monitors the patients and their medications published by hospitals<sup>4,21</sup>.

Public participation, on the other hand, remains outside the pricing and reimbursement decision-making process in Greek politics. On the government website, the consultation tool is not a formal process for effective public participation, as opinions expressed in surveys are not considered for decision-making. In addition to that, the regional health councils, which require social participation, were never established and, therefore, do not function as an advisory body in the planning and implementation of health policies<sup>4</sup>.



After marketing authorization by the EOF, the agency itself starts the correspondent medicine pricing process. The pricing of new pharmaceutical products for human use in Greece follows an international reference pricing system, which is based on drug prices in other EU countries<sup>12</sup>. According to the Greek legislation, any price record published in official documents (for example: factory price, wholesale or retail price, price registered in hospitals or health insurance) can be used, if conversion of the price collected to the factory price is respected, according to the methodology established by the EOF<sup>13</sup>. The maximum factory price for medications for human use under patent is defined by the mean of the three lowest prices for the same drug in EU countries. The same rule is applied to biological and biosimilar medications. The medications that are exclusively produced in Greece are priced according to the estimated production cost plus a maximum fixed profit rate of 8.5%. Generic drugs are priced either by the mean of the three lowest prices in the EU or by a 50% reduction in cost in relation to the period when the medication was under patent<sup>13</sup>.

Since 2012, the EOF has been responsible for the pricing process of pharmaceutical products, with price lists being submitted to the Ministry of Health, which publishes them by ministerial decision in a price bulletin<sup>22</sup>. For the pricing of a new medicine in Greece, prior pricing in at least three other EU countries is required, with this requirement being reduced to two countries in the case of orphan medications. However, for the medications that are exclusively produced in Greece, the maximum price is established based on production cost estimates, with a maximum net profit rate set at 8.5%<sup>22</sup>. Although health technology assessment studies are conducted in Greece, their results do not influence the pricing process. For the first generic of products without a valid patent, the maximum price is defined by the mean of the three lowest prices marketed in the EU member countries or by calculating 50% of the value of the same product during the period of valid patent, whichever is lower always prevailing. However, the value of this generic drug should not be lower than the lowest price in the EU countries. In Greece, the maximum prices of the generic drugs are established in 65% of the respective reference product<sup>22</sup>.

Price increases for existing medicines are not allowed, except for correcting an error; and the prices for all the medicines marketed in Greece (with the exception of negative lists and over-the-counter prescriptions) are reviewed twice a year. Currently, VAT (Value-added tax) rate are set at 6% for most pharmaceutical products and for other products sold in the pharmacy (such as vitamins) have different percentage of VAT (6%, 13%, and 24%)<sup>18</sup>. There is also the application of dynamic price reductions for off-patent and generic drugs, and for generics whose retail price is above €12 there is application of a dynamic price reduction, in which prices are reduced by 1% for every €250,000 in sales, with a maximum 15% reduction<sup>22</sup>.

In the hospital environment, some measures were taken as a way to reduce the costs of purchasing medical-pharmaceutical products, improve negotiation over payment time, carry out regular periodic purchases, transfer redundant materials between hospitals and reduce losses due to expiration dates; among them, the elaboration of structural agreements, that is, agreements between one or more contracting authorities and one or more suppliers in order to establish the terms of the contracts, especially when related to prices and quantities for a certain period. Another innovation was the implementation of a dynamic purchasing system, using electronic purchasing techniques, to help increase competition and streamline public purchases. In this

system, all suppliers are invited to submit their offers and technical specifications electronically using a specific coding system. Finally, a common procurement vocabulary was developed, establishing the reference nomenclature applicable to the public contracts, ensuring equivalence with other existing nomenclatures<sup>23</sup>.

There is also a 2011 ministerial decision that regulates the compassionate use of medicines without marketing authorization in specific situations<sup>24</sup>. Compassionate use refers to the temporary authorization to use certain medication, for a patient or group of patients with a serious chronic disease or risk of death, for which there is no authorized medication that is satisfactory. The request for compassionate use must come from a claimant (industry, sponsor of the clinical trial of the medication), who submits a proposal for a program for the temporary use of the drug. The dossier is evaluated by the EOF and, if there is solid scientific evidence of benefit and safety, as well as evidence that there is no suitable therapeutic alternative authorized in Greece, its use may be authorized for a fixed period of up to one year. Once temporary use is authorized, the claimant must ensure administration of the drug free of charge to the patients and without any cost to the State or health funds, unless special reimbursement rules have been implemented<sup>24</sup>.

Health Technology Assessment (HTA) emerged as a measure imposed on EU countries, through a transparency directive (TD 89/105/EEC), to ensure transparency in the pricing and reimbursement process of pharmaceutical products for use across EU member countries. However, until 2017, Greece had not been properly organized to ground its political decisions based on scientific evidence. Compilation of the positive reimbursement list and calculation of the reference price were done based on the *Anatomical Therapeutic Chemical Classification System* (ATC) list, by pharmaceutical group, grouping similar medicines (of the same ATC level) in the same reference group. The reimbursement applicant could present, as background material, decisions from other European HTA bodies, such as the National Institute for Health and Care Excellence and the Scottish Medicines Consortium. Likewise, presentation of economic evidence was not a prerequisite for decision-making either, but studies could be presented as a complement<sup>18</sup>. Consequently, the positive list was not able to fully promote the efficiency of the Greek health system, as it was based more on cash flows than on need, budget impact, or effectiveness.

In 2018, a HTA law was introduced in the country, establishing an HTA and reimbursement committee for medicinal products for human use. This "*HTA Committee*", which is part of the EOF, has as its main task been to evaluate medications that have obtained market authorization and to issue recommendations to the Ministry of Health on the inclusion or removal of products from the Positive List. When the medication receives a positive recommendation, it is referred to a price negotiation committee, established by EOPYY, which is responsible, as payer, for negotiating the prices or discounts of the drugs to be supplied and/or reimbursed, and for informing the budget impact to the *HTA Committee*. The *HTA Committee*, in turn, evaluates the negotiation committee's recommendation and makes a final recommendation to the Health Minister, who makes the final decision. New substances, new drug associations, new indications for medications already reimbursed, therapeutic analogues, or even re-evaluation of new drugs included in the Positive List during the last three years can be evaluated<sup>23,25</sup>. A dossier must be submitted requesting the evaluation<sup>12</sup>.



The technology assessment criteria were defined by this new legislation, which includes clinical benefit, comparison with other medications already reimbursed, data reliability, cost-effectiveness and budget impact<sup>12,26</sup>. The assessment of clinical benefit focuses on three aspects: data quality, using the *Grading of Recommendations, Assessment, Development and Evaluations* (GRADE) criterion; added therapeutic value; beyond the level of innovation, using a five-category system known as “*Ahlqvist-Rastad system*”. Economic evaluation is required when requesting evaluation of the medications, adopting the perspective of the health system. Kanavos et al. (2019)<sup>26</sup>, however, pointed out the difficulty of conducting cost-effectiveness studies in the country, mainly regarding the definition of the parameters to be adopted, since there were no methodological guidelines in the country about these economic evaluations, but also due to the scarcity of records of epidemiological and cost data<sup>26</sup>. The final recommendation must include the therapeutic indication for which the medication will be reimbursed, in addition to prescription protocols<sup>12</sup>.

In 2018, authors from Greece, together with authors from other countries of the European Network for Health Technology Assessment (*EUnetHTA*), participated in the elaboration of a report of preliminary recommendations for a Horizon Scanning System (HSS) with the aim of establishing, from 2020 onwards, a single flow of identification, selection and prioritization of technology topics in the technological horizon to support activities within the *EUnetHTA* recommendations. However, like HTA, HSS is still very recent in Greece<sup>25,27</sup>.

Despite being the first legislation, after years without significant changes in the medication policy in Greece, some authors point out that there are still important aspects to be reviewed and improved<sup>26,28</sup>. Regarding transparency, for example, some problems are observed, such as non-publication of the ATS result (positive or negative). There is also no public report of the assessment performed, only a summary of the main findings of the HTA Committee and only for the positive recommendations, so the reasons for negative results are not clarified.

## Results and effects of pricing and reimbursement

Since the medicines pricing and reimbursement decisions are centralized in the Greek Ministry of Health, they still fall short in some aspect regarding transparency, equality and long-term sustainability<sup>12</sup>.

As the health technology assessment process is still being reformed in Greece, it is believed that, in the coming years, the country will have the opportunity to improve the implementation of these techniques in the reimbursement decision-making, thus improving efficiency of the access to treatments in a setting characterized by limited resources<sup>18</sup>. One of the major current challenges in Greece is linking the results of health technology assessments with the clinical guidelines, which can be partially solved with the development and dissemination of national clinical protocols and monitoring and evaluation of their impact<sup>25-26</sup>.

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All the authors collaborated in the development of the research and writing of the manuscript. MMB, CDZ, and IFZ worked in the conceptualization; data curation; investigation; methodology; writing – original draft; writing – review and editing. JAT, RMN, PK and FAA worked in the conceptualization; methodology; supervision; validation; writing – review and editing.

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## Conflict of interest statement

The authors declare no conflicts of interest in relation to this article.

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