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7. Market Access in Portugal

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7.1 Introduction

The Country: Portugal

An independent kingdom since 1143, Portugal is one of the oldest nations in Europe.

A former world power during the XV and XVI centuries, Portugal lost much of its wealth, power and status following the destruction of Lisbon in a 1755 earthquake, the occupation during the Napoleonic Wars, and the independence of Brazil in 1822 [1,2]. In 1910, a revolution deposed the monarchy, leading to the 1st Republic, which lasted until 1926 and was followed by the subsequent four decades of the repressive governments of the 2nd Republic, which lasted until 1974 [3].

Figure 1. Portugal

On the 25th of April of 1974, a left-wing military coup installed democratic reforms, which led to the independence of all African colonies. Since 1974, the country has had a democratic regimen – the 3rd Republic – and has seen remarkable human, social and economic development, embodied by the membership of the European Community in 1986, and the Euro Zone in 1999 [4].

Following the military coup, Portugal adopted a new Constitution in 1976, which established a democratic republic after 48 years of dictatorship. The main institutions are the President of the Republic, who is elected by direct universal suffrage for a period of four year, the Parliament, which has 230 members elected by universal suffrage for a period of four years, the government, and the courts. The President appoints the Prime Minister, based on election results and following consultations with all political parties with parliamentary seats, and the other members of the government, who are recommended by the Prime Minister [4].

The Parliament holds the legislative power, while the government develops and guides policy implementation [4].

Portugal is a unitary state, respecting the autonomous regimen of the Azores and Madeira regions, which have their own regional governments and Parliaments [4].

Portugal is located in the south-west of Europe (Figure 1) and it comprises the mainland, which has one land border with Spain to the north and east, and a long coastline with the Atlantic Ocean to the west and south; two archipelagos lying in the Atlantic Ocean, the Azores, with a total of nine islands, and Madeira, with two main islands – Madeira and Porto Santo. Two additional small islands, Desertas and Selvagens, are also part of Portugal [4].

The climate is temperate maritime, with hot summers and wet winters, affected by Atlantic, Continental and Mediterranean influences.

In Portugal, the first social security law was enacted in 1946. It provided healthcare for the employees and their families through social security and sickness funds, financed by compulsory contributions from both employees and employers [4].

After the revolution of 1974, a process of restructuring the health services began. It culminated in 1979 with the establishment of the National Health Service (*Serviço Nacional de Saúde* – SNS), a universal tax-financed system [4].

Currently, the Portuguese health system is characterized by three co-existing and overlapping systems: the universal SNS, the health subystems – which are special health insurance schemes for certain professions or sectors (e.g. civil servants – ADSE, employees at banks and insurance companies), and private health insurance [4].

Demography

According to recent estimates for 2017, Portugal has a total of 10.3 million inhabitants [5]. Since the last census in 2011, the resident population in Portugal has decreased by 1.9% [5].

In Portugal, the distribution of the population is highly unbalanced, and this unbalance has increased over the years, due to migration to the metropolitan areas of Lisbon

and Oporto and the coast, with the population of the interior decreasing. This trend has been accompanied by a gradual aging of the population, due to the increasing life expectancy and the steady decrease of birth rate [4].

According to Eurostat, in 2013, Portugal had the lowest fertility rate among the European Union (EU) Member States (1.2 total fertility rate, compared with an estimated rate of 1.5 in the EU). An increase in life expectancy and the decline in fertility rates are causing in Portugal a "double aging" effect, which will pose major challenges to the Portuguese health system in the coming years [4].

The Economic Crisis and the Bailout

The international financial crisis that started in 2008 had a major impact in Europe, and Portugal was no exception. Following several years of weak economic growth (an average gross domestic product – GDP – growth of 0.8% between 2001 and 2010), the Portuguese economy experienced recession in 2009, 2011 and 2012 [4].

The economic slowdown was coupled with a steady rise in unemployment and by a public debt crisis. The economic downturn and the turmoil that followed the Greek and Irish bailouts led to an increased difficulty in Portugal accessing the financial markets [4]. In this context, Portugal was unable to refinance its debt, which led the country to request financial assistance from the EU, the European Central Bank and the International Monetary Fund (also known as the "troika"). In May 2011, Portugal signed the Memorandum of Understanding in exchange for a total loan of 78 billion Euros [4].

The agreed Economic and Financial Adjustment Program included 34 measures aimed at increasing cost-containment, improving efficiency and increasing regulation in the health sector. Reforms implemented since 2011 by the Ministry of Health included the rebalancing of the pharmaceutical market through new rules for price setting, the reduction in the prices of pharmaceuticals and the increase in the use of generic drugs [4].

For this reason, since then Portugal has been subjected to several legal changes, that over the years pushed the prices down in both the retail and hospital sectors.

In the hospital market, values decreased for the first time in 2013, due to several cost-containment measures introduced throughout 2013, including severe restrictions in access to innovation and the first annual price review done on the hospital sector, using as reference the lowest price in the reference basket instead of the average used in the price of other medicines. This trend continued in 2014, although with a less accentuated slope. However, in 2015 and 2016 the marked started going up again, even in spite of severe limitations to the inclusion of new innovative drugs [6].

In the retail sector, values decreased between 2010 and 2013, the years of the intervention of the "troika" in Portugal, and since then have remained relatively flat, with a slight growth tendency in the last year. This was caused by pressure on the prices and mandatory price cuts, changes to distribution margins and also the strong promotion of generics by government authorities [6].

Total health expenditure in Portugal has risen steadily from 7.5% of GDP in 1995 to 10.4% of GDP in 2010, above the EU average of 9.8% in 2010. In 2011 the economic re-

cession and the austerity measures required by the Economic and Financial Adjustment Program reversed this trend, with the total health expenditure decreasing to 9.5% of GDP in 2014 [4].

In 2015 the total health expenditure as a quota of the GDP in Portugal was 8.9% of GDP, well below the EU average of 9.9% [7].

OECD data from 2014 show that, when compared with the EU27 average of 402 € PPP, Portugal has a low pharmaceutical expenditure, with only 297 € PPP per capita [7].

Also, Portugal has always had a large level of out-of-pocket co-payments, currently at a level of 28% of the overall health expenditure [7].

7.2 Healthcare System and Subsystems in Portugal

SNS: The Portuguese NHS

The Portuguese health system is characterized by three co-existing and overlapping systems: the SNS; the health subsystems (i.e. special public and private insurance schemes); and private health insurance.

The health care delivery system in Portugal consists of a network of public and private health care providers; each of them is connected to the Ministry of Health and to the patients in its own way.

All the people residing in Portugal have access to the health care provided by the SNS, which is financed mainly through general taxes.

Out-of-pocket payments have been increasing over time, not only in terms of co-payments, but also in terms of direct payments for private outpatient consultations, examinations and pharmaceuticals [4].

The level of cost-sharing is at its highest for the pharmaceutical products, since many medicines are not reimbursed or have high patient co-payments (up to 85% of their price).

Between one-fifth and one-quarter of the population has a second (or more) layer of health insurance coverage through health subsystems (for specific sectors or occupations) and private health insurance [4].

The central government, through the Ministry of Health, is responsible for developing health policy, and overseeing and evaluating its implementation. The policy-making process takes place within the government. It is frequent that government rulings go to institutional partners for consultation, but the final resolutions are always issued at Governmental level with seldom cases of intervention by the Parliament [4].

Other Subsystems

In Portugal there are several health subsystems in place, both State-owned and private.

Among all, ADSE (*Assistência na Doença aos Servidores Civis do Estado* or Assistance in Disease to Civil Public Servants) stands as the most prominent subsystem serving the

gross majority of public employees and their families. Overall, it covers more than 10% of the total Portuguese population, with more than 1 million insured. The financing of the system is done by a 3.5% tax on salaries of public employees, which gives them access to a system that allows both treatments at the SNS, but also at private sector entities that have agreements with ADSE.Other subsystems in place cover the military, the police, and Justice employees, among others.

In the private sector, the biggest and better known system is the SAMS (*Serviços de Assistência Médico Social* or Medic and Social Assistance Services), which covers bank employees and their families [8].

Private Systems

Several large private systems exist in Portugal, which provide coverage to a part of the population that has private insurance schemes and also to the subsystems that have agreements with these private providers.

This system is mainly used for small interventions, with the majority of the population still using the SNS when disease costs become catastrophic.

7.3 Pathways to Market Access

The Marketing Authorization

Marketing authorization (MA) for new medicines is granted in accordance with Decree-Law 176/2006, which establishes the legal framework regarding the marketing authorization and its changes, and the manufacture, import, export, marketing, labelling and information, advertising, pharmacovigilance and use of medicinal products for human use (including homeopathic medicinal products, radiopharmaceutical medicinal products and traditional herbal medicinal products) and their inspection [9].

MA can be granted through one of four possible procedures, namely, the national procedure, the mutual recognition procedure, the decentralized procedure, and finally, the centralized community procedure handled by EMA and the European Commission [9].

After MA approval, and regardless of the type of process used, the Marketing Authorization Holder (MAH) must request that Infarmed issues local country code numbers for each individual type of package that will be available [9].

Following the release of local country codes and their inclusion in the packages, the medicines can be introduced into the market, provided that they comply with the pricing rules set for the type of medicines in question (hospital, retail, prescription-free) [9].

Obtaining Medicines

Pharmaceuticals requiring prescription can only be sold to the public in a pharmacy.

Prescriptions can be obtained by individuals either in the private sector or the public one, either from an SNS doctor in a primary care unit or from the outpatient department of a hospital.

Under special circumstances, individuals may also obtain medicines directly from hospital pharmacies, when the medicines in question are not supposed to be available in retail pharmacies.

Regarding non-prescription medicines (over-the-counter or OTC), two types of OTC medicines exist, those that can only be sold at a pharmacy without a medical prescription and those that can be sold in specialized stores.

Primary care centers provide and administer vaccines that are part of the National Immunization Program, and are supplied for free.

Price of medicines

In Portugal, there are currently several types of prices, as can be seen in Figure 2.

Pricing in Portugal is mainly ruled by the Decree-Law 97/2015 [10] and subsequent Decree-Orders implementing the several types of prices [11-14].

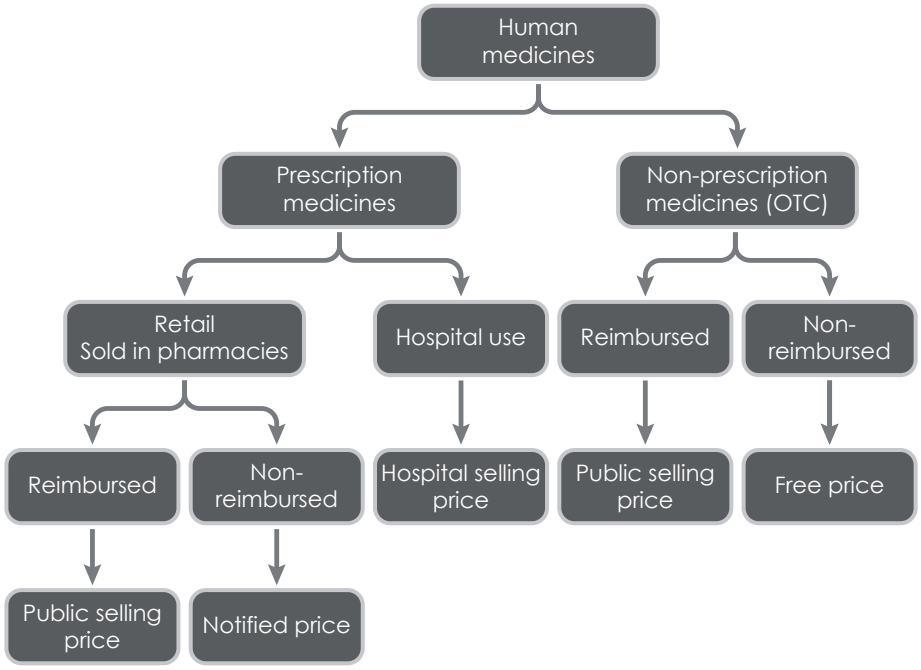

Figure 2. Types of drug prices in Portugal

Free prices

The prices of the OTCs, which require no prescription, are free, unless they are reimbursed (a rare situation), in which case they follow the same rules as a normally prescribed and reimbursed product.

Price and margins are defined by each individual pharmacy or store licensed by Infarmed to sell OTCs.

Hospital Selling Price – PVH

"Hospital use only" medicines have no official public selling price, since they cannot be sold to the public.

For these medicines, price is set as PVH (Hospital Selling Price or *Preço de Venda Hospitalar*), which is the value charged by the MAH (PVA) plus a 0.4% tax and 6% VAT.

For products that are not limited to the hospital environment but for which the MAH intends only to sell to hospitals, the price rules are basically the same as for "Hospital use only" medicines, although these products may or may not have an official public selling price (PVP). If they do have a public selling price, then they comply with the rules set out for the price setting of prescription products.

For purely private hospitals, these medicines can be purchased immediately after the approval of the national country codes, at the price set by the MAH.

For SNS hospitals, or hospitals that are in some way related to the SNS, this was also true until 2006, when the Government introduced new legislation requiring that all new hospital medicines or new indications for current ones should undergo HTA assessment by Infarmed [15].

Since then, hospitals are allowed to purchase new medicines only after they have been evaluated by Infarmed in a process known as *Avaliação Prévia* or Prior Assessment. Initial official timelines for such a procedure were 60 business days, but this has been increased to 180 calendar days under the current SiNATS legislation [10,11,15].

In this HTA process run by Infarmed, authorities negotiate with the MAH the conditions for the product to be made available at hospitals, namely its price (which can remain unpublished and thus confidential) and the number of patients to be treated (translated into the maximum expenditure incurred by the Government with such use). Additional conditions can also be agreed, such as risk-sharing, new data development, and price review conditions [10].

Public Selling Price – PVP

For prescription products, following marketing authorization and obtaining of the local country codes per pack, an international reference pricing system is applied to define the maximum market price for each presentation [10,12].

The international reference pricing system uses a basket of several EU countries, which can be changed every year by the Government (usually before November 15th).

For 2018, the basket is composed of France, Italy and Spain, but in recent years countries such as Slovenia and Slovakia have been used for reference [16].

For retail medicines, the ex-factory price, or PVA, cannot be higher than the average of the price in the reference countries. If the exact same medicine does not exist, a simi-

lar one is used (similar dosage and pharmaceutical dosage form). If the price is not available, the price of a similar product on the Portugal market or the price at point of origin may be used.

The public selling price of medicines in Portugal is the sum of several components:

$$PVP = (PVA + MgA + feeA + MgF + feeF + Inf\ Tax) \bullet 1.06$$

Where:
PVP = the Public Selling Price with VAT;
PVA = the MAH price to wholesalers, also known as ex-factory;
MgA = the margin gained by the wholesalers;
feeA = the fixed fee gained by wholesalers;
MgF = the margin gained by the pharmacists;
feeF = the fixed fee gained by pharmacies;
Inf Tax = the tax retained by the MAH and paid to Infarmed.

Values for each individual parameter depend on the PVA/PVP as can be seen in Table 1, with the sole exception of *Inf Tax* which is 0.4% of PVP without VAT (VAT equal to 6%) [12].

Application for price approval is performed online on the SIATS website [17]. Following application, price must be approved by Infarmed in no more than 15 business days, after which the price is considered tacitly approved [12].

This price is set as the maximum price that the medicine can have. However, the MAH may unilaterally decide to lower the price temporarily provided that it notifies Infarmed within adequate timeframes.

Once a year there is a price review, in which a price recalculation takes place, taking into consideration the current basket. After this review, prices can decrease but so far never increased.

PVA (€)	MgA (%)	feeA (€)	MgF (%)	feeF (€)
< 5.00	2.24	0.25	5.58	0.63
5.01-7.00	2.17	0.52	5.51	1.31
7.01-10.00	2.12	0.71	5.36	1.79
10.01-20.00	2.00	1.12	5.05	2.80
20.01-50.00	1.84	2.20	4.49	5.32
> 50.00	1.18	3.68	2.66	8.28

Table 1. Values for each individual parameter that compose the public selling price of medicines in Portugal
feeA = the fixed fee gained by wholesalers; feeF = the fixed fee gained by pharmacies;
MgA = the margin gained by the wholesalers; MgF = the margin gained by the pharmacists;
PVA = the MAH price to wholesalers, also known as ex-factory

Public Selling Price for generics

The maximum PVP of the generic medicine must be at least 50% lower than the maximum PVP of the reference medicinal product, of equal dosage, or if it does not exist, with the closest dosage and in the same pharmaceutical form [12].

If all PVA prices for all presentations of a specific medicine are below 10 €, then the maximum PVP for the generic must be, at least, 25% lower than the maximum PVP of the reference medicinal product with the closest dosage and in the same pharmaceutical form [12].

Public Selling Price for parallel import medicines

The maximum PVP of parallel-imported medicines should be, at least, 5% lower than the maximum PVP charged for identical or essentially similar medicinal products with a marketing authorization in Portugal [12]. If the concerned medicinal product has no approved price in Portugal, a PVP is calculated for that medicinal product and then the 5% reduction is applied [12].

Notified price

Since 2016 a new system has been implemented by the Government to allow greater flexibility in the pricing of prescription medicines that are neither reimbursed nor reimbursable [12-14].

For these products MAH can request price increases yearly, provided that these price increases follow the rules below:

- The increase of the PVP is not greater than 10%;
- The increase of the PVP is not greater than 2.50 €.

These increases have different margin rules than the normal price setting [12-14].

Infarmed may or may not accept the price increase request, however since no impact exists for the State budget, the tendency is to allow MAH to raise prices [12-14].

SiNATS: The National System for HTA

In 2015 the Portuguese government approved a new law revoking previous ones regarding the access to market of medicines and medical devices [10].

Decree-law 97/2015, June 1st, created the SiNATS (***Si****stema Nacional de* ***A****valiação de* ***T****ecnologias de* ***S****aúde* or National System for Health Technologies Assessment), a system which was introduced with the following stated objectives:

1. Maximizing health gains and citizens' quality of life;
2. Contributing to the sustainability of the National Health Service;
3. Guaranteeing the efficient use of health public resources;
4. Monitoring the use and effectiveness of technologies;
5. Reducing waste and inefficiencies;
6. Promoting and awarding relevant innovation development;
7. Promoting equal access to technologies.

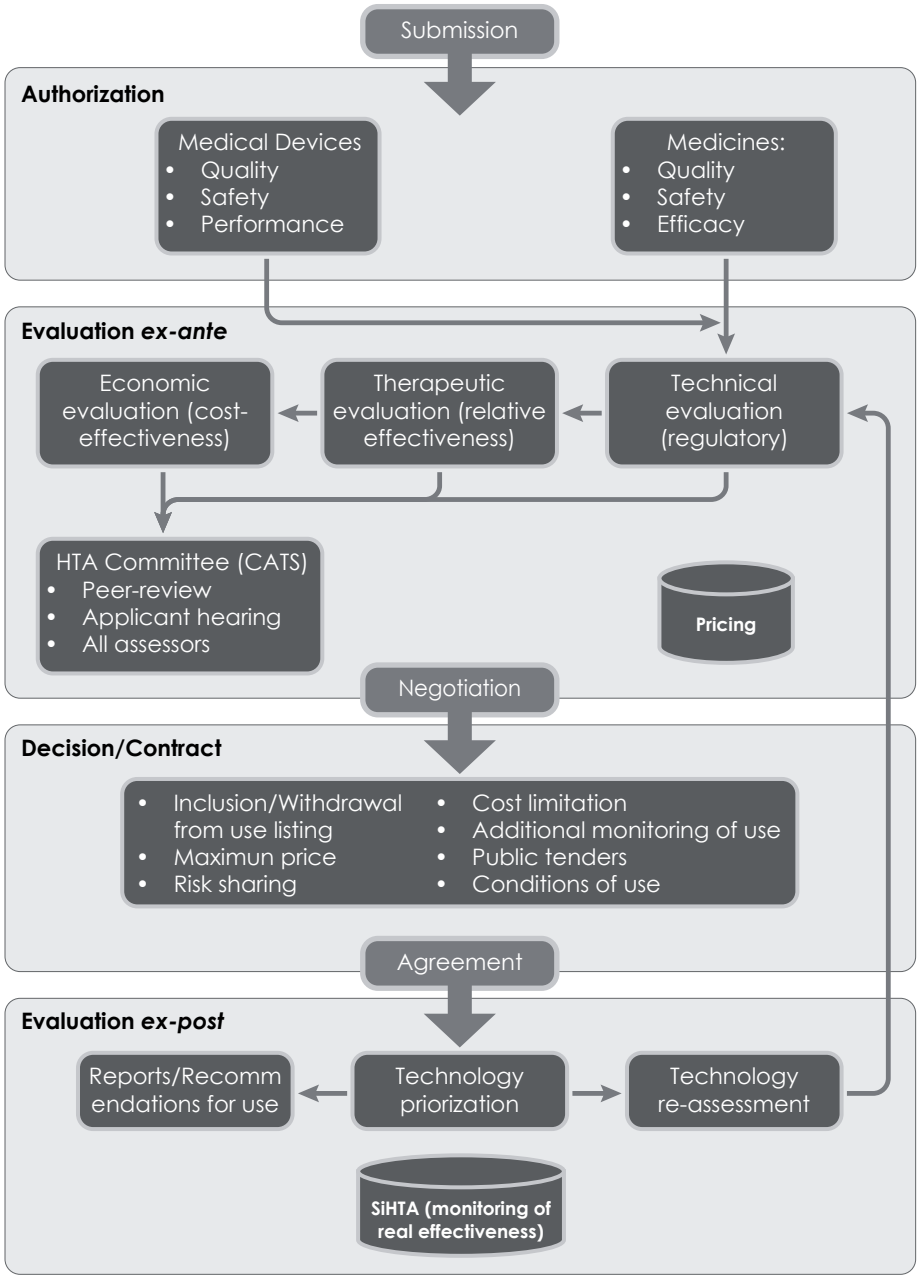

Figure 3. The National System for HTA (SiNATS). Modified from [18]

SiNATS covers all public and private institutions that produce, commercialize or use health technologies. Also, the assessment performed by SiNATS covers all health technologies.

When seen against the previous system, SiNATS has expanded Infarmed's reach in the following way (**bold denotes new areas**):

1. Health Technology Assessment National System
2. Technology:
   - Medicines + **Medical Devices**

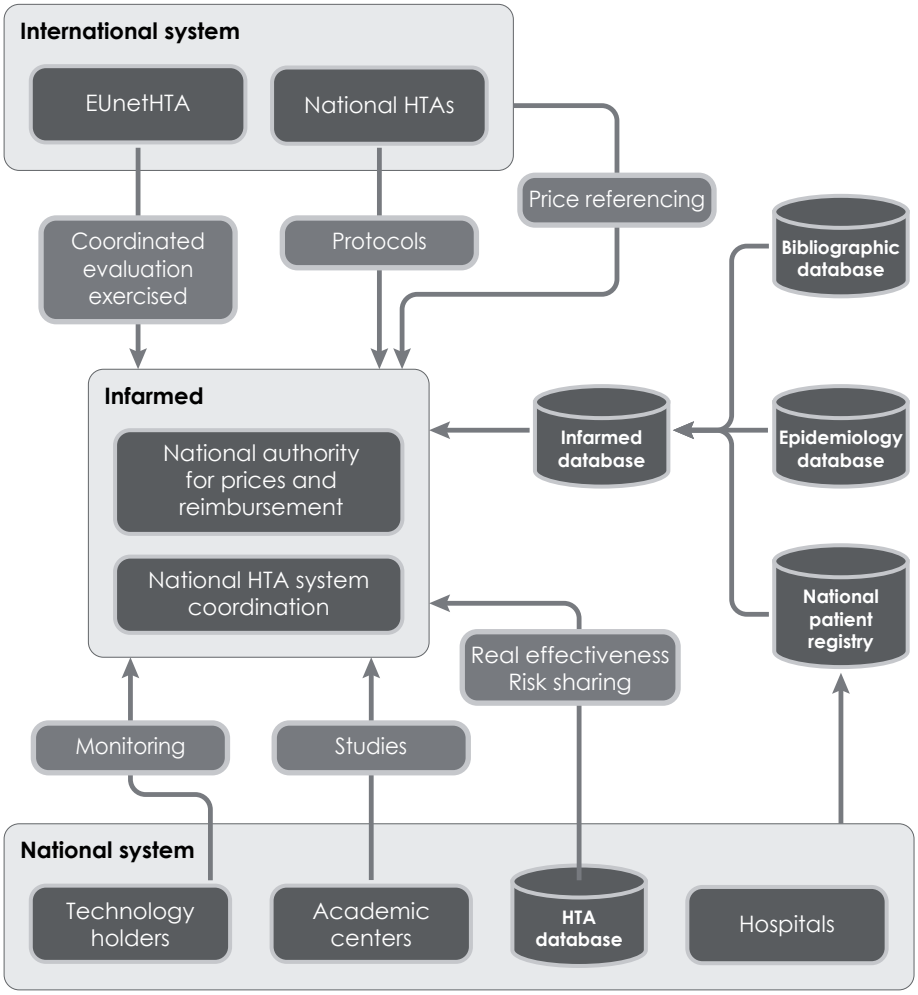

Figure 4. The integration of SiNATS in the EU system. Modified from [18]

3. Assessment:
   - Relative efficacy (Added value)
   - Cost-effectiveness (Economic value)
4. Decisions:
   - Price
   - Financing/Reimbursement
   - Control and cost containment
   - Risk Sharing
   - Additional use monitoring
5. **Reassessment of technologies on the market (*ex-post* evaluation)**
6. **Participation in the European model**

View of the intended structure of SiNATS and its integration in the EU system under EUnetHTA can be seen in Figure 3 and Figure 4 [18].

According to the Government SiNATS is expected to be able to subject health technologies to both assessment and reassessment with contracting with the MAH being its main way of regulation. The system which was created is supposed to be in line with the best European practices, and was considered to be an important step towards the improvement of the operations of the National Health Service [10].

When fully implemented, SiNATS will allow the technical, therapeutic and economic assessment of the technologies supported by an information system which collects and provides information to all entities interested in it. For these purposes, SiNATS will be supported by technical bodies such as the Health Technology Assessment Commission (CATS), which validate the information and assess the application of the health technologies.

One of the important aspects of the new system is the clear indication that the marketing approval and use of a health technology is a necessary, but not a sufficient condition for its financing by the SNS. As a matter of fact, the decision to authorize the use, within the SNS, of a certain health technology depends not only on the quality, safety and efficacy, which are behind the marketing authorization decision, but also on efficiency and effectiveness. These assessments allow to show that public resources are properly allocated and produce significant health gains [10].

Although fully approved in 2015, the SiNATS system had however several setbacks in its implementation, especially for what concerns the information system that should be used for the *ex-post* reassessment of health technologies, and also the full operationalization of the CATS, which has been so far slow in providing timely assessment of new medicines.

Reimbursement and Funding

Access to market funded by the SNS can mainly occur in two ways, either by reimbursement or by prior assessment.

Although frequently undistinguished by the majority of the public, both systems have substantial legal differences.

Reimbursement is mandatory by law, which means that all patients covered by the reimbursement (whole population, or special subgroups in the case of special reimbursements) have access to the reimbursement conditions within the entire SNS. This translates into an obligation for SNS hospitals to provide the medicines included in the reimbursement lists.

Prior assessment, on the other hand, is not mandatory by law, as it is only a condition that must be implemented before hospitals can freely buy these products. Therefore, hospitals may choose if they want to provide these medicines to their patients, having no legal obligation to do so. Under most circumstances, hospitals do provide medicines free of charge to patients when these are medicines that are technically restricted to the hospital setting.

Reimbursement

Following the approval of its price, or at the time of price application, MAH can apply for the inclusion of its medicine on the reimbursement list.

Overall, there are four normal levels of reimbursement by the State, 90%, 69%, 37% and 15%, with the patients having to support the remaining cost.

Under the normal reimbursement law, the level of reimbursement is determined by the type of product/seriousness of disease, with more serious diseases having a higher reimbursement by the State. For example, antidiabetic drugs are reimbursed at 90%, where antihypertensive drugs are reimbursed at 69%.

Life-saving drugs, such as insulins, are fully reimbursed by the State, with no patient co-payment [19].

Overall the process of reimbursement can be defined in the following steps:

1. MAH submits application to Infarmed;
2. Infarmed validates information and sends information to CATS;
3. CATS defines group of experts for the evaluation of the medicine and proposes an evaluation protocol that is sent to Infarmed;
4. Infarmed sends the proposed protocol to the MAH;
5. The MAH discusses and approves the proposed protocol. The MAH may submit additional information at this time;
6. CATS performs the clinical assessment of the medicine and issues a report on the existence or absence of added therapeutic value vs a specific comparator technology/medicine;
7. Infarmed sends the report on added therapeutic value to the MAH who may challenge it;
8. Following clarification of the added therapeutic value in question, CATS performs an economic assessment of the medicine;
9. After the end of the economic assessment of the medicine, CATS issues a final proposal regarding the inclusion/non-inclusion of the medicine from the reimbursed list;
10. Final proposal from CATS is communicated to Infarmed and then subsequently to the MAH;

11. Infarmed negotiates with the MAH the final contracting conditions for the reimbursement of the medicine;
12. Infarmed and the MAH reach an agreement and a final reimbursement proposal is sent to the member of the government responsible for its approval;
13. The member of the government approves the reimbursement and sends the documentation back to Infarmed, which notifies the MAH;
14. The MAH notifies Infarmed of the date when it will begin the commercialization under reimbursement;
15. The product reaches the market.

The overall timeframe for the above mentioned process for new indications or medicines is 180 days, with new dosages and new presentations of already approved products being reviewed in 75 days and generics and biosimilars being reviewed in 30 days. However, it should be noted that Infarmed in the past very rarely has been able to comply with these timeframes, with current average reimbursements tending to take more than one year, sometimes closer to two.

Special reimbursement

The current law also allows for the reimbursement of specific drugs for specific diseases or specific patient groups, taking into account, namely, the beneficiaries' income, the prevalence of the diseases and the public health targets.

Through a Ministerial order, the member of the Government responsible for the health sector may establish reimbursements specific to:

- Certain pathologies or special groups of beneficiaries;
- Certain therapeutic indications;
- Integrated management systems of diseases.

The approval process is similar to the one observed for the normal reimbursement of medicines with the sole difference that the reimbursement needs to be officially published.

These special reimbursements either reimburse drugs that are not reimbursed for the public in general or change the reimbursement level, usually to a lower patient co-payment level.

Examples of such circumstances are:

- Immunomodulators;
- Cystic fibrosis treatment;
- Chronic kidney failure treatment;
- Treatment for transplant rejection;
- Amyotrophic lateral sclerosis;
- Growth and anti-diuretic hormones;
- Specific drugs for hemodialysis;
- Hemophilia treatments;
- Antivirals for hepatitis C;
- Antiretrovirals for HIV.

Prior assessment

Prior assessment is in many ways similar to the reimbursement procedure. The steps taken are the same, with a few exceptions at the end of the process, which are specific for the hospital sector.

Steps in market access through prior assessment:

1. MAH submits application to Infarmed;
2. Infarmed validates information and sends information to CATS;
3. CATS defines group of experts for the evaluation of the medicine and proposes an evaluation protocol that is sent to Infarmed;
4. Infarmed sends the proposed protocol to the MAH;
5. The MAH discusses and approves proposed protocol. The MAH may submit additional information at this time;
6. CATS performs the clinical assessment of the medicine and issues a report on the existence or absence of added therapeutic value vs a specific comparator technology/medicine;
7. Infarmed sends the report on added therapeutic value to the MAH, who may challenge it;
8. Following clarification of the added therapeutic value in question, CATS performs an economic assessment of the medicine;
9. After the end of the economic assessment of the medicine, CATS issues a final proposal regarding the positive or negative assessment of the medicine for use within hospitals of the SNS;
10. Final proposal from CATS is communicated to Infarmed and then subsequently to the MAH;
11. Infarmed negotiates with the MAH the final contracting conditions for the assessment to the hospital SNS market;
12. Infarmed and the MAH reach an agreement and a final positive assessment proposal is sent to the member of the government responsible for its approval;
13. The member of the government approves the positive assessment and sends the documentation back to Infarmed, which notifies the MAH;
14. Infarmed notified hospitals within the SNS of the positive prior assessment and the conditions agreed for the acquisition of the medicine;
15. Infarmed published online the assessment report for the prior assessment;
16. The MAH notifies Infarmed of the date when it will begin the commercialization;
17. The MAH negotiates with each single hospital the inclusion of the medicine in the hospital formulary;
18. The product reaches the market.

As for the reimbursement, the overall timeframe for the above-mentioned process is supposed to be equal to the reimbursement one, 180 days for new products or indications, 75 days for new dosages or formulations and 30 days for generics and biosimilars. However, just like in the reimbursement situation, Infarmed very rarely is able to comply with these times. On average, prior assessments tend to take more than one year, sometimes closer to two.

Guidelines

The assessment of a health technology by CATS is ruled by specific guidelines, which define the procedures for both the clinical and the economic assessment of the new technology [20,21].

Guidelines for clinical assessment of healthcare technologies

In November 2016 the CATS issued some guidelines on their main procedures while evaluating the clinical added therapeutic value of any new technology [20].

The guidelines, which are comprehensive, adopt a methodology similar to GRADE.

Among other important elements, these guidelines define the rules used for defining the comparator against which the new medicine (or health technology) will be compared.

According to this, the comparator must:

1. Be commonly used in clinical practice;
2. Have data that validates its efficacy and safety for the said indication;
3. If more than one comparator exists that complies with the above, then the cheapest one must be selected;
4. Be chosen in a dosage regimen that is in accordance with its Summary of Product Characteristics (SPC);
5. Be funded by the SNS.

Economic guidelines for the assessment of medicines

Portugal does not have a tradition of health technology assessment, except for pharmaceutical products, in which it was a pioneer in the last years of the former century.

Although access to pharmaceuticals was facilitated through the existence of several insurance schemes, the real access to most of the population came about after the implementation of the Constitution in 1976 and the creation of the SNS in 1979.

Since then many laws over the years have governed the co-payment of drugs by the Government for patients in the SNS.

In 1992 a new law implemented the rules for reimbursement of medicines in Portugal, having been modified in 1998 to implement two important changes, the possibility of differential reimbursement for different patient populations and the possibility for the Government to request a health technology assessment during the reimbursement request assessment [22,23].

Also, in 2000, the possibility of specific contracting and the periodic re-assessment of reimbursed medicines was incorporated into the law [24].

Regarding HTA, Portugal was among the first countries in Europe to have Guidelines for implementing the assessment of HTA, having approved them in 1999. These guidelines – although considerably outdated – are currently still in force without a change, after more than 18 years [21].

Since the beginning of the millennium, the HTA in Portugal has slowly progressed, becoming mandatory in all situations in which a premium price is sought by the marketing authorization holder.

The currently existing guidelines present some challenges when viewed together with the ones used for the clinical assessment, since both were written at very different points in time and have considerable differences, for example, in the type of comparator that should be selected for an evaluation.

It is expected that with the implementation of SiNATS and CATS, new updated guidelines will have to be published in the foreseeable future.

Contracting

As already mentioned, contracting has been established under SiNATS as the preferred way to rule the relationship between MAH and Infarmed/Government in all that relates to the access to market of medicines.

The contracts used for both reimbursement and prior assessment conditions may rule a large number of parameters, including (non-exhaustive):

1. The presentations, strengths or pharmaceutical forms to be funded;
2. The maximum price deemed to be suitable for the concerned medicine;
3. The maximum amount of expenses to be borne by the State in the SNS based on a specific number of patients and the respective guarantee mechanisms;
4. The consequences of exceeding the previously agreed amounts;
5. The inclusion of targets to be met after the implementation of the health technology for the purposes of reassessing the latter;
6. The statement of all actions required for the creation and management of information which enables the assessment of the compliance with the targets set out for the medicine;
7. The monitoring mechanisms;
8. A clear and precise definition of the responsibilities of the different intervening parties;
9. The entities entitled to use the medicine in question;
10. Setting out restrictions to the use of the medicine;
11. The mechanisms of risk sharing regarding the use of the medicine.

An important issue to bear in mind when contracting with the Government is the fact that, according to the law, the MAH takes on the risk inherent not only to the possible non-compliance with the targets set out in the contract, but also the possible risk inherent to not getting sufficient information regarding the implementation of that technology, as well as the consequent uncertainty as to the greater claimed relative effectiveness.

In the area of contracting the current SiNATS law provides Infarmed with broad powers that include the following:

1. Contracts may be amended or terminated when facts which represent a change of the requirements for its signature occur or become known, including the reassessment of the State's priorities when allocating financial resources;
2. Termination of the effects of the reimbursement and prior assessment contracts may occur due to a unilateral decision from Infarmed, whenever causes for the exclusion of the reimbursement occur.

SIATS: The Information System for HTA

Alongside the approval of SiNATS, in 2015 the Government also approved the creation of an information system that would allow SiNATS to operate and to gather real-world data that would allow for the ex-post assessment of funded medicines.

Under its powers, Infarmed may request from all departments or bodies and individuals or legal persons intervening in the health system (including MAH) to convey any elements necessary for the operation of SIATS (*Sistema de Informação para a Avaliação das Tecnologias de Saúde*) [10].

Although several databases have been created for obtaining real-world data in some diseases, these have so far been limited to very few diseases, thus staying very short of the original objective initially proposed in 2015.

The SIATS system is currently mainly used to manage the application of price and HTA requests, and it's not to be expected that in the near future it will be able to gain the complexity that was originally planned during the approval of the whole SiNATS system.

Orphan Drugs

In Portugal, no special rules exist for the access of orphan drugs. From a technical point of view, orphan medicines are reviewed and assessed in the same way as other medicines.

Access to orphan medicines is either done at hospital level free of charge (and medicines are reviewed under the prior assessment process) or they are reimbursed under special conditions, solely for that specific population (special reimbursement), usually free of charge.

Although no real difference exists with other medicines, orphan drugs tend to see higher cost-effectiveness thresholds approved than their non-orphan counterparts.

7.4 Mapping of Stakeholders

In order to properly access the market, the MAH has to engage a series of stakeholders whose influence in the overall outcome of the process may vary from none to substantial.

Below are listed some of the stakeholders that must be taken into account when considering the application of any type of public funding for a medicine in Portugal.

Ministry of Health

At the Ministry of Health, only one member is usually responsible for the approval of the reimbursement and prior assessment of medicines. By law the role falls under the supervision of the Minister himself. However, he/she tends to delegate the function to the Health Secretary of State.

Infarmed

At Infarmed, the interaction for pricing and reimbursement or prior assessment of a medicine may occur mainly at three levels:

Executive Board

The Executive Board of Infarmed has a total of three members appointed by the Government. Overall there is a President, a Vice-president and an additional third Member. At the Executive Board one or more members may be responsible for the final negotiation of the market access conditions of the medicines. However, this may change with each executive team, and thus no proper rule exists. Currently, both the President and the Vice-President are actively involved in the negotiation of both reimbursement and prior assessment decisions.

DATS (*Direcção de Avaliação das Tecnologias de Saúde*)

This is the department within Infarmed responsible for managing the whole SiNATS, including the interaction between the MAH, the CATS and also the Executive Board of Infarmed.

CATS (*Comissão de Avaliação de Tecnologias de Saúde*)

The Commission for HTA is a pool of experts that are responsible for the assessment of the clinical and economic value of new health technologies, including medicines. The commission is managed by a President and two Vice-Presidents. The full list of the members of the CATS can be found online [25].

CNFT (National Commission of Pharmaceutical Products)

In 2013 the Ministry of Health created a National Commission of Pharmaceutical Products (*Comissão Nacional de Farmácia e Terapêutica*) in order to define a national list of pharmaceutical products and guidelines for their use. This commission works under the supervision of Infarmed and its members are appointed by the Minister. In a conceptual way, medicines approved for reimbursement or prior assessment should automatically be included in the formulary list. The most current list of members can be found at the Infarmed website [26].

Hospital Administrations and Hospital Therapeutic Commissions

Hospital administrations and Hospital Therapeutic Commissions assume a relevant importance in the case of products that are to be sold to hospitals.

Because the final decision by Infarmed is not binding when positive, hospitals can still refuse to use certain drugs in their environment, if they choose to do so.

Being so, the MAH's negotiation with hospitals for the inclusion of the medicine in the local formulary is an additional step after obtaining the positive prior assessment.

Patients Associations

Patient associations do not have any formal saying in the HTA process or the reimbursement/prior assessment process. However, they may have a political influence, which may influence all decision makers in the process, both at the Infarmed and the Ministry level.

7.5 Major hurdles

Having started in 2015, SiNATS currently suffers from issues that have been transferred from the previous system and which have so far not been properly solved.

Of all the hurdles in place, a few stand out as the most relevant.

Timelines

Although timelines are always established by the law, the truth is that Infarmed and the Government have always had absolutely no respect for them, thus not complying with the law.

Current official timelines for the review and approval of a reimbursement/prior assessment decision have been increased in September 2017 and currently vary between 30 and 180 days, depending on the type of product (new product, new dosage, generic), with an additional 30 business days for negotiation. However, data from the trade association, APIFARMA, show that currently approved medicines needed an average of 18.6 months to get approved, with a median of 16.1 months [27]. Of these products, approved between 2011 and 2016, only 5.9% were approved in less than 6 months, with 27.6% having taken more than 2 years to get approved [27].

Of the currently under evaluation medicines, the values seem to be similar, with an average waiting time so far of 19.7 months and with 23% of the products have been waiting for approval for more than 2 years [27].

Last, important differences seem to exist between the type of product under evaluation, with oncologic drugs (average 28.2 months) taking far more time to be approved than Hepatitis C or HIV drugs (12.8 and 12.4 months, respectively) [27]. Overall, these extremely long and unpredictable timeframes make market access in Portugal a substantial challenge for all MAHs operating in the country.

Lack of Transparency

Transparency is another important aspect of the market access system implemented under SiNATS.

With a strong pressure of the Government to reduce the total overall expenditure with medicines in the country, Infarmed and its structures have, over the years, become ex-

tremely biased in the type of evaluations performed. The tendency is to rarely grant any status of additional added value, thus forcing new medicines to have prices similar or cheaper than the ones already on the market.

The lack of full transparency on the reviewer's positions during the assessment and the lack of appeal mechanisms, when confronted with biased evaluation, are major challenges for MAHs.

Under this scheme, cost-minimization has become more frequent than cost-effectiveness, and budget impact has become determinant for the overall result of the assessment.

Lack of Data

Finally, one last hurdle exists which makes market access quite challenging in Portugal, which is the lack of good data. Portugal lacks availability of statistical and cost data at all levels, with information being sparse and usually limited to specific settings.

National databases are not the norm, and epidemiologic data is often not available.

Although the implementation of SiNATS has come with the promise of the implementation of SIATS and the broad availability of data on costs and effectiveness, the practice is far from the one expected, with serious challenges still existing in obtaining both clinical and economic data.

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