Brief Report

Medicinal Product Regulation: Portugal's Framework

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ABSTRACT

Purpose: The pharmaceutical industry is one of the most tightly regulated sectors, and it is essential to know each country's legal framework to understand the regulation, approval, and marketing of medicinal products for human use. This article describes the main statutes and procedures governing medicinal products for human use in Portugal and the role of the country's National Medicines and Health Products Authority (*Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.*; INFARMED).

Methods: From the most recently available data, an update of requests and approvals concerning marketing authorizations, variations, pricing, and reimbursements is provided. Data were sourced from the INFARMED website, Infomed (database of medicinal products for human use), and periodic reports issued by national authorities. Organic laws, acts, and law decrees published in the government gazette (*Diário da República*) are cited and reproduced as required.

Findings: In 2015 Portugal ranked fifth in the European System of Medicines Evaluation in terms of the number of completed procedures as a reference member state. Approximately 80% of all approved drug applications in Portugal in 2015 were for generic drugs, mostly pertaining to the nervous system. In Portugal, INFARMED monitors drug quality, safety profile, and efficacy in all stages of the drug life cycle, ensuring patients' safety.

Implications: The Portuguese market for medicinal products for human use has been appreciably changed by the advent of generic drugs. There is an increased trend for new request applications for biological and biotechnological substances. (*Clin Ther.* 2016;38: 2118–2126) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: marketing authorization, medicinal products regulation, National Regulatory Agency, Portugal.

INTRODUCTION

The prescription, supply, and use of medicines should center on their rational use, to foster patients' interests and integrity and to promote public health and national economic sustainability. For a marketing authorization (MA) to be valid and a drug marketed in an intended member state (MS), its assessment is based on European Union (EU) standards. Furthermore, it is essential to know the legislative reality for drug approval, regulation, and market evolution in each country.

The pharmaceutical industry is one of the most tightly regulated sectors, with the European Medicines Agency tasked with overseeing such regulation in the EU. Even so, each MS undertakes its own regulation of pharmaceutical products, and in Portugal it is the National Medicines and Health Products Authority (*Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.*; INFARMED) that evaluates, authorizes,

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regulates, and monitors human medicines as well as other health products to ensure quality, tolerability, and efficacy.

However, unlike the European Medicines Agency and national authorities in other MSs, which are responsible for the regulation of both human and veterinary medicinal products, INFARMED is solely responsible for regulating human medicinal products, and this article therefore focuses exclusively on this type of product. The veterinary medicines are regulated by Directorate-General of Food and Veterinary Medicine (*Direção-Geral de Alimentação e Veterinária*).

INFARMED is vested with the required capacity to define and implement policies, legislation, regulations, evaluations, authorizations, postmarketing surveillance, monitoring, and research control and to supervise the production, distribution, marketing, and consumption of medicines, medical devices, and cosmetics. Despite working closely with other national entities, it exercises its own jurisdiction over the entire national territory.[1]

Approval of medicines in Portugal is governed by European guidelines, standards, and legislation, which are transposed into national law. Indeed, one of the main designated objectives of INFARMED's Evaluation and Accountability Board (*Quadro de Avaliação e Responsabilização*) is to promote Portugal as a reference member state (RMS) in the EU and European Economic Area.[2] Furthermore, the INFARMED laboratory is 1 of 4 laboratories selected from around the globe to analyze drugs for the United Nations Development Programme in the fight against HIV-AIDS, tuberculosis, and malaria in 26 countries across Africa, Asia, Europe, the Middle East, and the Americas, something that attests INFARMED's technical competence and ranks it among the best in the world.[2]

The Portuguese Medicine Act (Decree Law 176/2006 of 30 August 2006 *Estatuto do Medicamento,*[3] as amended by Decree Law 128/2013 of 5 September 2013[4] and subsequent alterations) is the reference document that transposes European Community (EC) legislation into domestic law and enables European standards to be followed in Portugal. This Act establishes the legal framework in Portugal and implements existing community legislation governing the life cycle of medicines. Furthermore, it focuses on the regulation and control of quality, tolerability, and efficacy and is an essential tool for enabling health professionals and industries to cope with rapid scientific and technical progress in Portugal and the EC.

In this respect, the Portuguese Medicine Act also transposes European Directive 2004/27/EC, which replaces the original European Directive 2001/83/EC[5] of The European Parliament and of the Council of the EU. Under its terms, no medicinal products may be sold on the market without obtaining an MA. After the introduction of the Portuguese Medicine Act, the legal regime governing human medicines in Portugal has been periodically reviewed to attend to European Legislation.[4]

This article's main focus is thus to provide an overview of the regulation of medicines, the main entities and procedures involved, and an analysis of new MAs and applications recently approved in Portugal.

MEDICINE LIFE CYCLE IN PORTUGAL

In Portugal, INFARMED is the entity responsible both for regulating human medicines throughout their life cycle (Figure 1), from the time of manufacturing of the raw materials to the dispensing and use of the finished product by the patient, and for ensuring that the quality, safety profile, and efficacy standards of any given product are being continuously monitored and updated.

The different actors in the life cycle of medicines (MA holders [MAHs], manufacturers, distributors, prescribers, pharmacists, and end-users) are committed to their rational use, an aspect that is overseen by INFARMED. Once a drug's quality, safety profile, and efficacy have been proved, and it is found to have a favorable benefit–risk ratio, an MA can be granted and the drug can go into the market.

Manufacturers responsible for drug production are entities engaged in medicine and health product manufacture and are subject to industrial licensing, which is jointly coordinated by the Ministry of Economy and the Ministry of Health.[6] INFARMED acts in support, by giving advice to both of these ministries, and regulates the licensing of facilities for drug production and distribution, after ensuring that good manufacturing[7] and distribution[5] practices are in place. INFARMED overviews all stages of good distribution practices, including the collection, storage, and supply of medicinal products to authorized entities.

Patients have the right and duty to seek information and to be informed about their responsibilities for

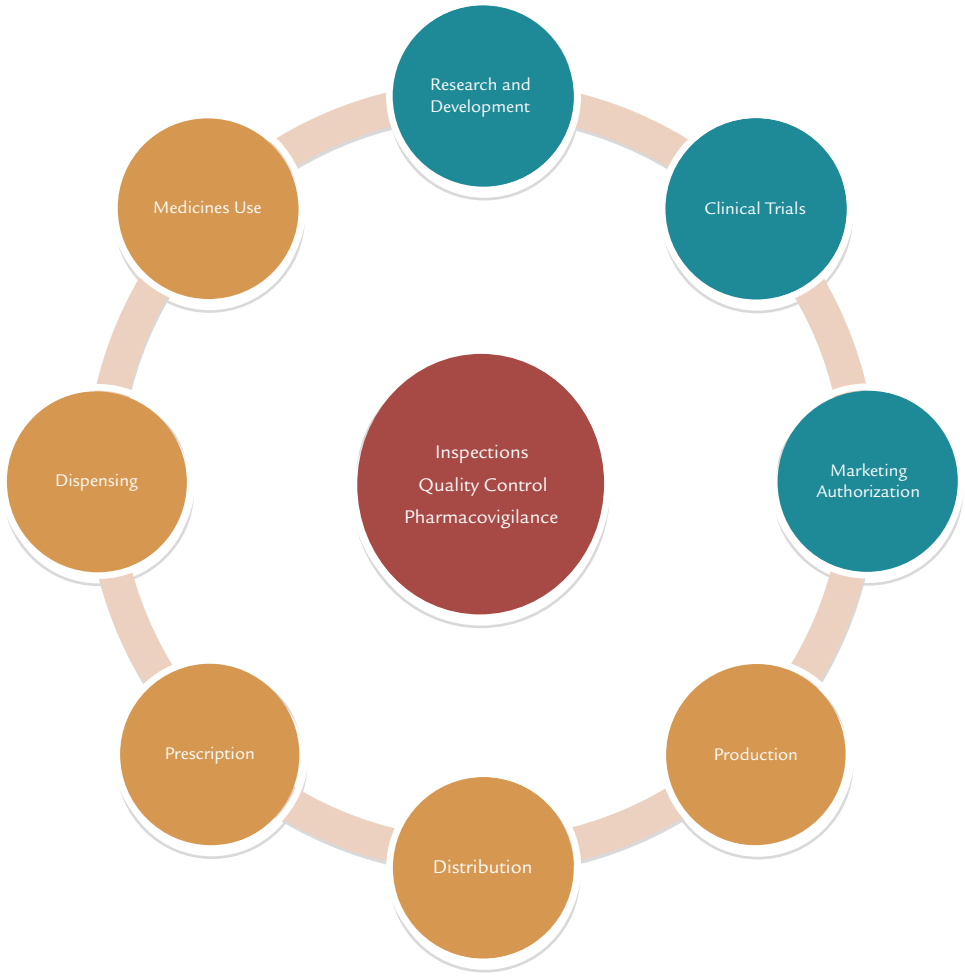

Figure 1. Medicine Lifecycle: blue circles correspond to technical and scientific evaluation; orange circles correspond to economic evaluation and reimbursement. Central processes take place throughout the cycle.

making proper and appropriate use of medications and are likewise responsible for reporting any adverse effects. Notifications from health professionals and patients make up the notification system that underpins Portugal's pharmacovigilance system, which continuously monitors the safety profile of medicines on the market. The health technology assessment is available for patients and health professional, and it has created a discussion forum on this topic: Discussion Forum - Involvement of society, patients, and other stakeholders.

INFARMED, patients, and health professionals thus seek to ensure the correct, safe, and effective use of medicines in Portugal. This control process continues uninterruptedly throughout the life cycle of a drug and is an adaptive process aimed at patients' welfare and the sustainability of the National Health System.

MARKETING AUTHORIZATION

For a human medicinal product to be marketed, a MA has to be approved by a national procedure (NP), centralized procedure (CP), mutual recognition procedure (MRP), or decentralized procedure (DP). When approval is sought for marketing exclusively within

Portugal, an NP can be used, in which case the application submission must be addressed to INFARMED.[3]

In a purely national procedure, INFARMED checks the validity of the MA and decides on the application, a process that may take up to 210 days. After an MA application, it is checked by INFARMED within 10 days, and the applicant may be asked to provide more information, explanations, and/or documents.

The CP is currently governed by Regulation 726/2004/EC[8] and enables applicants to obtain an MA that is valid in all EU MSs and recognized throughout the European Economic Area.[8] In the case of new active substances not authorized in the community before 20 May 2004, this procedure is mandatory for drugs to treat AIDS, cancer, neurodegenerative diseases, and diabetes; advanced, genetic, and cellular therapies; biotechnology-derived products, and orphan drugs.[8] The CP is also available for medicines containing innovative active substances used in other conditions, provided that such drugs constitute a therapeutic, scientific, or technical innovation or represent a significant advantage to public health within the EU.[8]

Moreover, the CP allows for greater uniformity in the EC in terms of the summary of product characteristics (SPC) and package leaflet (PL), having become the norm for the introduction of new drugs in the European market.

In cases whereby there is a country in which a product is already being marketed, it is advantageous to use that country as the RMS for obtaining a new MA. The MRP is particularly important when an RMS is regarded as having expertise or being a reference in the therapeutic area of the drug in question, because it makes for a better-grounded drug evaluation.

Directive 2004/27/EC introduced major revisions to this procedure, making it available as an option for medicinal products representing a therapeutic innovation or which are of benefit to society/patients and for generic medicinal products already approved by CP. This directive reinforced the need for formalizing the cooperation between MSs through the creation of coordination group for this procedure. Currently, it is used when an MA is required in more than one MS for a medicine already authorized in at least one other MS, which then becomes the RMS.[9]

The MRP may not be used for drugs subject to compulsory CP, drugs previously rejected by a CP (unless based on a new common technical document [CTD] supplemented with new clinical and nonclinical data), homeopathic preparations, or herbal medicinal products.[9]

When Portugal is an RMS, an assessment report is drawn up (or an existing one updated) in 90 days.[3,5,10] When Portugal acts as a concerned member state (CMS) an opinion is issued in 90 days about the evaluation report prepared by the RMS. After all CMSs have given their approval, a MA is then granted within 30 days.[3,5,10]

The DP is used to obtain MAs in several MSs, in the absence of any MA at the time of MA application.[10] The various MSs for which an application is submitted must approve the RMS' assessment report, SPC, PL, and labelling, which leads to identical dossiers being approved across CMSs. This procedure can be initiated by any applicant when seeking to obtain an MA in more than one MS, or by an MS when receiving an application and verifying that the product in question is already being evaluated by another MS.[10] The MS where a submission is already being evaluated then becomes the RMS.

In Portugal, INFARMED is the authority responsible for receiving and evaluating DP submissions during the national phase of this procedure. During 2012, INFARMED ranked third in the European System of Medicines Evaluation, with 225 evaluation procedures as RMSs; of this total, 30 were by MRP and 195 by DP.[11]

A more in-depth evaluation of the trend in MA applications and approvals can be seen in respect of 2013, based on data published in Portugal in January 2015.[12] The number of MA applications and approvals declined from 2009 to 2013 (by 37% and 46%, respectively), with the exception of MAs granted by CP (Figure 2; see **Supplemental Figure 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.07.171). Despite this, there has been an increase in the number of drugs and new presentations available on the market. Furthermore, most requests and approvals occur by NP.

By the end of this period, 50% of all new MA applications were for generic medicines, and approximately 94% of all human medicines and 96% of all drug presentations already available on the market were prescription drugs.[12] In Portugal, 608 MA procedures were completed during 2014, representing an 8% increase over the previous year.[13]

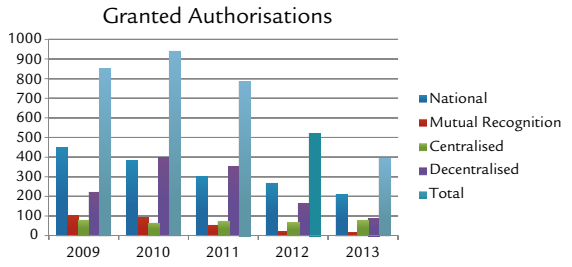

Figure 2. Trend in medicine marketing authorizations granted across the period 2009-2013, according to type of procedure. *Generated from data obtained in INFARMED Medicine Statistics 2013*.[12]

From January to June 2015, Portugal ranked fifth in the number of completed procedures (MRP and DP) as RMS and fourth in the number of initiated procedures.[14] As with other countries, however, the number of MRP- and DP-based submissions in Portugal has also been decreasing (from 225 in 2012 to about 60 in the first 6 months of 2015).[11,14]

VARIATIONS IN AND RENEWALS OF MARKETING AUTHORIZATIONS

An MA is initially valid for 5 years. During renewal, a comprehensive analysis of all Periodic Safety Update Reports (PSURs) is conducted and the benefit–risk balance is assessed. The renewal request must be submitted in CTD format and accompanied by a compact disc with read-only optical memory copy of the updated initial CTD.[15]

The renewal request must be made a minimum of 9 months in advance, and, in the event of it being met by a positive decision, the MA becomes valid indefinitely, unless pharmacovigilance monitoring raises questions about the safety profile of the medicinal product concerned.[3,8] MA renewal also allows for MAHs to update the SPC, PL, and labelling.

If a request is denied, INFARMED notifies the MAH, with instructions to remove the product from the market in 10 or 90 days (depending on the grounds that led to the rejection), running from the date on which the MA expires or other date specified by INFARMED.[15]

Any deviation from the terms of an MA requires prior authorization from INFARMED, which may or may not accept a MA variation, but refusal does not compromise an already existing authorization. These variations can be classified (pursuant to Decree Law 128/2013 of 5 September 2013, which amends Decree Law 176/2006 of 30 August 2006) as minor or type I (IA or/and IB), major or type II, or MAH transfers.[4]

HUMAN MEDICINE PRESCRIBING AND DISPENSING

In terms of dispensing, drugs can be classified as prescription drugs (renewal, special, and restricted prescription) and nonprescription drugs. The dispensing of prescription drugs is restricted to pharmacies, requires a prescription by a medical doctor, and includes drugs that directly or indirectly pose a risk to patients' health if used without medical supervision.[3]

Nonprescription drugs include those that are not classified as prescription drugs, are amenable to self-administration, and are dispensed at licensed stores, with their retail price being set by the free pricing system, that is, fixed at the level of distribution and marketing channels.[3]

Restricted prescription drugs are those whose use is reserved for certain particular situations, such as restricted hospital use, or which must be acquired directly from the hospital pharmacy, even though their use is not restricted to the hospital setting. They include drugs used for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis, plaque psoriasis, cystic fibrosis, HIV, chronic organ failure, transplant rejection, hepatitis C, multiple sclerosis, spastic paraplegia, and certain hormonal deficiencies, among others.[3]

In Portugal, all prescription drugs are prescribed according to a common template, which is mandatory for all prescribers.[16] To facilitate and make this process more uniform, on 1 August 2011, electronic prescription started in Portugal, a procedure performed with the aid of information and communication technologies, using applications certified by the Central Administration of the Health System (*Administração Central do Sistema de Saúde*).[17]

Electronic prescription applies to all prescription drugs, including compounded drugs, narcotic-containing drugs or psychotropic substances, self-administered products for diabetes mellitus and

dietary products, and reimbursable drugs dispensed at community pharmacies, as well as to some nonprescription drugs.[17] Only in cases of computer system failure, unsuitability justified by the prescriber, home prescription, or other situations up to a maximum of 40 medical prescriptions per month, may prescriptions not be made out electronically.[18]

Since the law was revised in 2012, electronic medicine prescriptions must be in accordance with the International Common Denomination,[19] pharmaceutical form, dosage, and presentation, and dosages must be properly indicated.[18] Exceptionally, electronic prescriptions can be made by reference to trade names in the following cases[18]: (1) drugs with a narrow therapeutic index or narrow therapeutic margin, (2) in cases of intolerance or adverse reactions reported to INFARMED concerning another commercial product containing the same active substance, and (3) medicines for continuity treatments lasting longer than 28 days.

Under the new legislation, pharmacies are required to keep in stock at least 3 of the lowest priced medicines belonging to each homogeneous group, and users have the right to be informed about which of these is the cheapest. Furthermore, users can choose which medicine to buy unless the prescriber identifies it as "narrow therapeutic index," "adverse reaction," or "treatment continuity greater than 28 days."[18]

Although electronic prescriptions are normally valid for a 30-day period, they can also be issued as renewable, in which case they become valid for 6 months.[17] Up to 4 different drugs, and up to 2 packages per drug can be prescribed in each prescription. However, in the case of drugs whose packaging contains a unit dosage form for a single administration, up to 4 packages can be prescribed.[17]

At the time of prescribing and dispensing human medicines, physicians and pharmacists must, respectively, inform patients about the existence of generic drugs similar to those prescribed and about cheaper alternatives.

PRICING

In Portugal, pricing is subject to approval processes, annual reviews, and extraordinary reviews. During the approval process, the retail price of nongeneric drugs (generally drugs to be introduced into Portugal for the first time) is based on the average of the ex-factory price/wholesale price in the 3 reference countries or, if not available, based on identical or essentially similar medicinal products.[20] In 2016, the reference countries are Spain, France, and Slovakia.[21] Reference countries are chosen by similarity of per capita gross domestic product, comparable purchasing power parity, or lower drug price level.[20]

The maximum (wholesale and pharmacy) profit margins, marketing fees, and taxes are added to the wholesale price, and the retail price is then calculated as follows[20]: $PVP_w/VAT = (PVA + MgA + feeA + MgF + feeF + Inf\ Tax) \times 1.06$ where PVP is the retail price; MgA is the wholesaler's share (%), based on PVA; MgF is the pharmacy's share (%), based on PVA; *fee* A is the fixed amount added to wholesaler's percentage margin; *fee* F is the fixed amount added to pharmacy's percentage margin; Inf Tax is the marketing fee (0.4%), based on the $PVP_{wo/VAT;}$ 1.06 is the factor that reflects the tax rate (6%); PVA is the ex-factory price/wholesale price; and VAT is the value-added tax. The margins and fixed values to be added will vary according to the price levels set under Ordinance 195-C of 2015, Article 12, according to the Article 10 of Decree Law 97/2015.[22]

When there is no reference product with a national MA, a reference price is calculated on the basis of the price-setting rules in place.[22] Price-setting rules apply to generic drugs with or without a homogenous group (see the next section).[20] These rules provide that the retail prices of generic drugs are to be calculated on the basis of a reference product.[20] The retail price must be lower than the PVP of a reference product having equal dosage (or, when it does not exist, the closest dosage) and the same pharmaceutical form, by at least 50% or, alternatively, by at least 25% if it costs less than €10 in all its presentations.[22] Prescription drugs restricted to hospital use are not subject to the approval requirement set out in Article 1 of Decree Law 97/2015.[22]

Nongeneric drugs available on the ambulatory market are subject to annual price reviews and are compared with international reference country prices, unless their retail price is either less than €5 or, alternatively, falls below €5 or rises by any amount as a result of the review.[22,23] Generic drugs are subject to annual price reviews and are compared with national reference products, unless their retail price is less than €3.25 or increases as a result of the annual review process.[22]

Finally, a medicinal product may also be subject to an extraordinary price review for reasons of public interest or at the initiative of an MAH/legal representative.[20]

However, a caveat must be sounded here. Although the above processes yield the maximum prices that can be charged, these do not necessarily correspond to the prices that are actually applied because the MAH may reduce the price.[20]

REIMBURSEMENT

In Portugal, drug retail price reimbursement varies by group, with the relevant group categories being established by reference to use indications, the entity entitled to issue the prescription, and specific increases in consumption envisaged for patients experiencing certain diseases.

On the ambulatory market, medicines prescribed are subject to the general rules on reimbursement and are co-paid by the state and the end-user.[20] In contrast, the hospital market includes drugs reserved solely for treatment in hospitals and other medicinal products subject to restricted medical prescription, all of which are fully paid by the state and subject to an evaluation process before being introduced into the market.[20]

Drugs on the ambulatory and hospital markets are subject to reimbursement and prior evaluation, respectively, with the latter entailing assessment of such drugs' clinical and economic impact on society.

Drug reimbursement requests can be approved in the following scenarios[20]: innovative drugs with greater efficacy, effectiveness, or tolerability compared with the therapeutic alternatives; new drugs, with qualitative composition identical to that of other already marketed and reimbursed drugs, and presenting economic gains; drugs presented with new dosage form, dosage or presentation, presenting with it therapeutic and economic gains; new drugs that do not constitute a significant therapeutic innovation but with economic advantages.

The reference pricing system in Portugal covers reimbursed medicines available on the ambulatory market with generic drugs already on the market.[24] The reference pricing system sets the maximum reimbursable amount on which the state reimbursement is applied, and this maximum reimbursable amount varies according to a given medicine's homogenous group.[20] A homogenous group is defined as a group of medicines with the same qualitative and quantitative composition in active substances, dosage form, dosage, and route of administration, in which at least one generic drug already on the market is included.[25]

Depending on a given medicine's homogenous group, a specific margin (eg, 90%, 69%, 37%, 15%) on its retail price is co-paid by the state and is applied either to the calculated retail price or to a reference price (whichever is the lower of the two).[24] This reference price is calculated by averaging the 5 lowest prices of medicines included in the same homogenous group.[20]

According to the above information, category A drugs are subject to a 90% reimbursement rate, a group that includes hormones and drugs used in the treatment of endocrine disorders, drugs used in ocular affections, and antineoplastic and immunomodulatory drugs. Category B drugs include anti-infective drugs and drugs used in the nervous and cardiovascular system, with 69% of the price being reimbursed by the state. Drugs belonging to category C are, among others, those used in genitourinary and musculoskeletal systems, and allergy medications, which are subject to a 37% reimbursement rate. New drugs, drugs with adjusted reimbursement, or medications covered by a transitional reimbursement system belong to category D and are subject to a 15% reimbursement rate.[24]

Reimbursements for medicines included in category A are increased by 5%, although those included in categories B, C, and D are increased by 15% for pensioners whose total annual income does not exceed 14 times the minimum wage in force in the preceding calendar year, or 14 times the social support value in force.[26] For patients with particular diseases or belonging to special groups, the drug price reimbursement rate can rise as high as 95% for all categories, if its retail price is equal to or less than the fifth lowest price of the corresponding homogeneous group.[27]

DATA AVAILABLE ON APPROVED APPLICATIONS

Data retrieved from Infomed for the period 1 January 2015 to 30 September 2015 found 1085 newly approved applications (linked to new active substance, dosage form, or strength). Approximately 80% of all

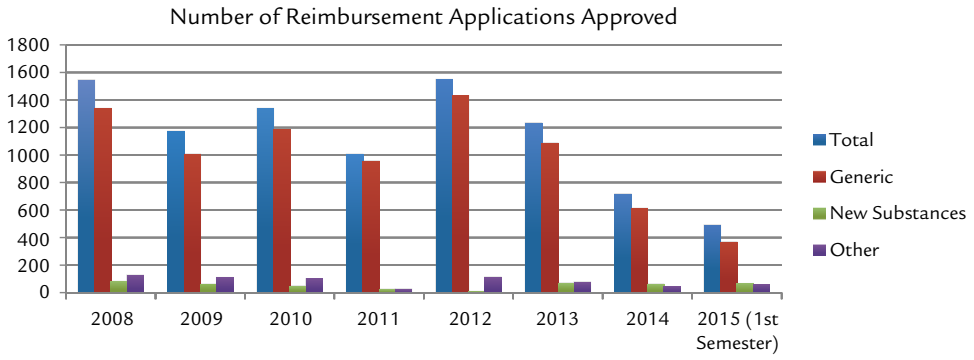

Figure 3. Graphical representation of the number of reimbursement applications approved in Portugal, by product type: 2008 to first half of 2015. New substances correspond to those under subparagraphs a), d), e) and f) of Article 6 of Decree Law 118/2000, as amended. *Generated from data drawn from activity indicators relating to assessment of drug reimbursement applications - periodic update, INFARMED.*[11]

approved drug applications in Portugal across this period were for generic drugs.

Among these 1085 accepted applications, 5 of the 6 most frequently listed International Common Denominations corresponded to drugs for the nervous system (aripiprazole, duloxetine, pregabalin, quetiapine, and fixed combinations of levodopa + carbidopa + entacapone) and those containing perindopril (see **Supplemental Figure 2** in the online version).

At year-end 2013, approximately 38% of all human medicines were eligible for reimbursement, a number that has remained relatively constant.[12] Reinforcing the trend seen in recent years, most reimbursement applications submitted and approved in Portugal in the first half of 2015 also corresponded to generic drugs[11] (depicted in Figure 3; see **Supplemental Figure 3** in the online version, from 2008 to the first half of 2015).

Most reimbursement applications approved in Portugal in the first half of 2015 corresponded to new medicines having a qualitative composition identical to that of other already marketed and reimbursed drugs. Furthermore, the number of reimbursement applications approved in Portugal and not classifiable according to national legislations has been steadily declining.

CONCLUSION

In Portugal, medicines are regulated by INFARMED, in accordance with European guidelines. As in other European countries, medicines in Portugal are tightly regulated at each phase of their life cycle to assure drug quality, tolerability, and efficacy with the patient's safety as the main goal.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

MTH and FR planned the research. MTH, PDB, ATR and FR performed literature search, data collection, data interpretation and writing. PDB created figures.

SUPPLEMENTARY MATERIAL

Supplemental figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.07.171.

REFERENCES

1. Regulation (CE) 765/2008 of the European Parliament and of the Council of the European Union of 9 July 2008. *Off J Eur Union*. 2008:30–47.
2. Ministry of Health. Deliberation 50/CD/2015. *Activities Report from 2014*. 2015.
3. Ministry of Health. Decree Law 176/2006 of 30 August 2006. *Diário da República*. 2006.

4. Ministry of Health. Decree Law 128/2013 of 5 September 2013. *Diário da República*. 2013.
5. Directive 2001/83/EC of 6 November 2001 of the European Parliament and the Council of the European Union. *Off J Eur Communities*. 2001.
6. Ministry of Economic and Innovation. Decree Law 209/2008 of 29 October 2008. *Diário da República*. 2008.
7. Directive 2003/94/EC of 8 October 2003 of the Commission of the European Communities. *Off J Eur Union*. 2003.
8. Regulation (CE) 726/2004 of the European Parliament and of the Council of 31 March 2004. *Off J Eur Union*. 2004.
9. Directive 2004/27/CE of 31 March 2004 of the European Parliament and the Council of the European Union. *Off J Eur Communities*. 2004.
10. European Commission. Notice to Applicants Volume 2A Procedures for marketing authorisation. *Heal Food Saf Dir*. 2015.
11. INFARMED. Indicators relating to assessment of drug reimbursement applications - periodic update, from 2008 to 2015. http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AVALIACAO_ECONOMICA_E_COMPARTICIPACAO/MEDICAMENTOS_USO_AMBULATORIO/INDICADORES_DIVULGACAO_PERIO DICA. Accessed April 20, 2016.
12. INFARMED. Medicine statistics from 2013. http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ESTATISTICA_DO_MEDICAMENTO/ESTATISTICA_DO_MEDICAMENTO_ANTERIORES/Estat_Medic_2013.pdf. Accessed April 20, 2016.
13. INFARMED. Activities Report from 2014 to 2014. http://www.infarmed.pt/portal/page/portal/SOBRE_O_INFARMED/DOCUMENTOS_INSTITUCIONAIS/PMD. Accessed April 20, 2016.
14. The Coordination Group for Mutual Recognition and Decentralised Procedures - Human. Statistics for New Applications (MRP/DCP), Variations and Referrals. 2015.
15. INFARMED. *Marketing Authorisations by National Procedure*. 2010.
16. INFARMED. *Dispatch 15700/2012 of 30 November 2012*. 2012.
17. Ministry of Health. Ordinance 198/2011 of 18 May 2011. *Diário da República*. 2011.
18. Assembly of the Republic. Legislation 11/2012 of 8 March 2012. *Diário da Republica*. 2012.
19. Ministry of Health. Ordinance 137-A/2012 of 11 May 2012. *Diário da República*. 2012.
20. Ministry of Health. Decree Law 97/2015 of 1 June 2015. *Diário da República*. 2015.
21. Ministry of Health. Ordinance 12682-A/2015 of 10 November 2015. *Diário da República*. 2015.
22. Ministry of Health. Ordinance 195-C/2015 of 30 June 2015. *Diário da República*. 2015.
23. Assembly of the Republic. Legislation 159-C/2015 of 30 December 2015. *Diário da Republica*. 2015.
24. Ministry of Health. Ordinance 195-D/2015 of 30 June 2015. *Diário da República*. 2015.
25. Ministry of Health. Ordinance 195-B/2015 of 30 June 2015. *Diário da República*. 2015.
26. Ministry of Health. Decree Law 48-A/2010 of 13 May 2010. *Diário da República*. 2010.
27. Ministry of Health. Ordinance 1319/2010 of 28 December 2010. *Diário da Republica*. 2010.

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SUPPLEMENTARY MATERIAL

See Below Figures S1–S3.

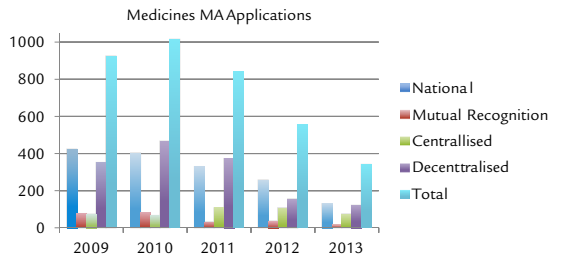

Figure S1. Evolution of Medicines Marketing Authorizations Applications from 2009 until 2013 by procedure type. *Generated from INFARMED Medicines Statistics 2013. (Data available in:* http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ESTATISTICA_DO_MEDICAMENTO/ESTATISTICA_DO_MEDICAMENTO_ANTERIORES/Estat_Medic_2013.pdf).

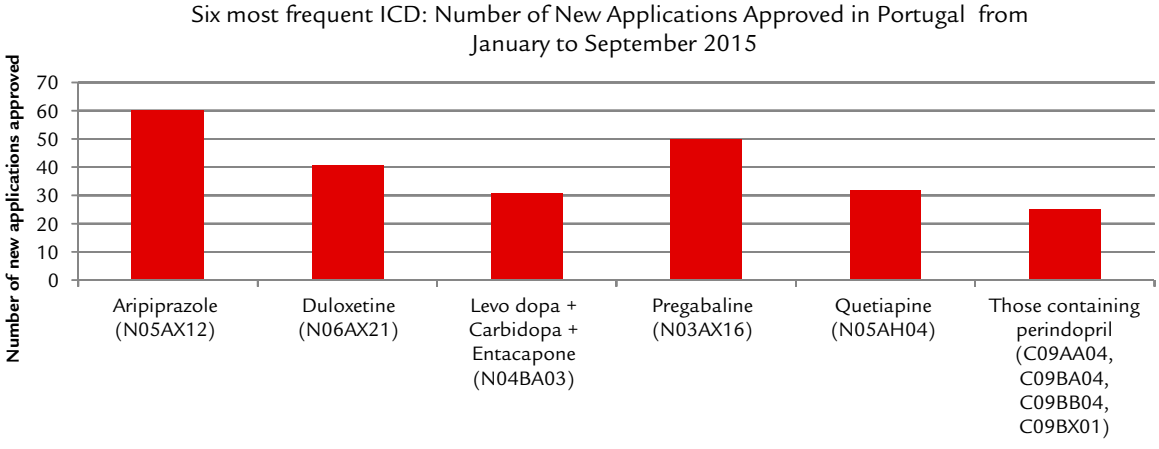

Figure S2. Graphical representation of the six most frequent international common denominations (ICD) new drug applications approved in Portugal from January to September 2015. A presentation corresponds to a new active substance, strength, or dosage form. *Generated from data available at Infomed. (Data available in:* http://www.infarmed.pt/infomed/pesquisa.php).

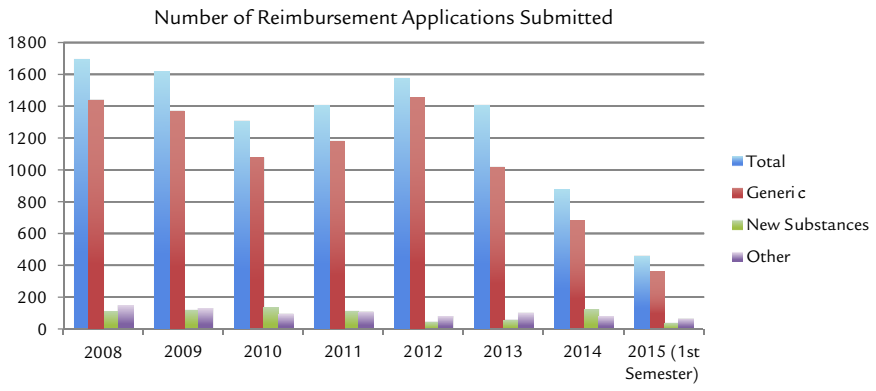

Figure S3. Graphical representation of Number of reimbursement applications submitted in Portugal by product type from 2008 to 1st semester of 2015. New Substances correspond to those under subparagraphs a), d), e) and f) of Article 6 of Decree Law 118/2000, as amended. *Generated from data abstracted from Activity indicators relating to the assessment of drug reimbursement applications - periodic disclosure, INFARMED. (Data available in:* http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AVALIACAO_ECONOMICA_E_COMPARTICIPACAO/MEDICAMENTOS_USO_AMBULATORIO/INDICADORES_DIVULGACAO_PERIODICA).