**The Atlantic divide in Coronary Heart Disease: Epidemiology and Patient Care in the US and Portugal**

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**Additional Material**

# Regulatory mechanisms of health technologies

The Food and Drug Administration (FDA), in the US, and the *Autoridade Nacional do Medicamento e Produtos de Saúde I.P.* (INFARMED), in PT, represent the official local regulatory agencies of drugs and medical device marketing and post-market surveillance. However, other agencies within the European Union (EU) may articulate with INFARMED for marketing authorization of medicines and devices. Approval of medical devices and drugs follow different pathways and different levels of control in both countries.

## Drugs

**United States** – The FDA approves drugs for marketing based on experimental data supporting safety and effectiveness of the medical product (drug or device) as well as information attesting adequate manufacturing and labelling. Drugs are approved if there is clear evidence that benefits outweigh the risks.1 In order to improve the speed of approval reviews, as of 1992, review fees were introduced with the Prescription Drug User Fee Act and many special approval programs have been created ever since.2-4 Production and marketing of pharmaceuticals is completely privatized but regulated by the FDA, which does not regulate the price of pharmaceuticals.5 Prices result from market forces such as competition, and purchasers and customer negotiation power.5,6 Unlike Portugal and most countries, direct-to-consumer advertising of prescription drugs is allowed in the US provided that the advertisements are accurate and not misleading.5,7

Drug coverage and type of cost-sharing vary among different health plans and insurers.8 However, most employer-based health plans cover outpatient drugs in which employees typically prefer flat rate co-payment cost-sharing.5,9,10 In addition, most outpatient drug coverage plan formularies follow a three-tier reimbursement scheme with lower co-payment for generics and higher co-payments for brand-name drugs with generic equivalent.8,10

**Portugal** – The European Union regulatory system for drug marketing approval, which comprises four possible procedures: centralized, decentralized, mutual recognition or national. Briefly, the centralized procedure is offered by the European Medicines Agency (EMA) and provides authorization for marketing a drug in all EU countries. The centralized procedure is compulsory for some drugs and optional to others. Drugs that fall outside the scope of EMA are approved for marketing using one of the other procedures depending on the countries for which marketing is sought.11,12 In 2012, the EMA accounted for approximately 13% (66/521) of drug marketing approvals in Portugal.13 Regardless of the type of procedure, drugs receive approval for marketing in Portugal, much like in the US, based on experimental data regarding quality, safety and efficacy. INFARMED further regulates standards regarding their manufacturing, distribution and labelling.12

Contrary to the FDA, INFARMED is responsible for price control and reimbursement eligibility of drugs within the NHS. With this purpose, pharmaco-economic and pharmaco-therapeutic reports need to be submitted so that a hospital price or a maximum retail price can be agreed with the pharmaceutical company, before asking the government for a reimbursement rate and then begin marketing.14 Maximum prices are currently determined by INFARMED based on prices practiced in other European countries of similar GDP per capita to PT.15 Outpatient drugs eligible for reimbursement by the NHS are assigned to one of four reimbursement rate categories based on a therapeutic classification.14,16

The use of the national drug formulary is mandatory for doctors prescribing in institutions within the NHS and is also an important guiding instrument for hospitals’ pharmacy departments and their drug formularies.17,18

## Medical devices

**United States** – Approval of medical devices is centralized at federal government under the FDA. Regulations aim to assure the safety and effectiveness of the devices according to a risk-tiered classification (Class I, II and III), where regulatory control increases from Class I to Class III depending on the risk the device poses to the patient but also on its intended use and indications for use.19 Depending on the class assigned to the device, an additional pathway to general controls may be required. This may be either a premarket notification (510(k)), or a premarket approval application (PMA), where the PMA is the strictest and more formal regulatory control. At its inception, review of medical device applications was free of charge but as of 2003, the FDA may charge fees to medical device manufacturers. Additionally, a Third Party Program has been implemented which provides the option to seek private parties to review applications. Such amendments have been implemented to improve the review process, which has been often criticized as a slow and lengthy process.4,20

**Portugal** – The medical device approval system falls under the decentralized regulatory system implemented at the EU.21,22 The procedure involves a Notified Body, which is private for-profit organization accredited by European authorities, that evaluates whether manufacturers are conforming to the EU’s Medical Device Directives.21 Similar to the FDA system, control requirements depend on the associated-risk group (I, IIa, IIb and III) of the device. This review process has been criticized as having lack of transparency and vague requirements, which allows for different levels of standards between Notified Bodies.20 For example, there is no publicly available list of all approved devices in EU nor of their review application information.23,24 Furthermore, as emphasised by Fraser et al.24 regulations provide detail on how clinical studies of devices should be performed, but they do not specify when they are required.

The Notified Bodies provide a CE (Conformité Européen) mark certification to the medical device if proven that it is safe and functions according to the manufacturer’s intended use, enabling it to enter the EU market.20 High-risk medical devices must be further registered with the INFARMED for commercialization.22

**Table A1: Reference population used for direct standardization of rates – 2010 US population.**

|  |  |  |
| --- | --- | --- |
| **Age** | **Male** | **Female** |
| 20-24 | 11,014,176 | 10,571,823 |
| 25-29 | 10,635,591 | 10,466,258 |
| 30-34 | 9,996,500 | 9,965,599 |
| 35-39 | 10,042,022 | 10,137,620 |
| 40-44 | 10,393,977 | 10,496,987 |
| 45-49 | 11,209,085 | 11,499,506 |
| 50-54 | 10,933,274 | 11,364,351 |
| 55-59 | 9,523,648 | 10,141,157 |
| 60-64 | 8,077,500 | 8,740,424 |
| 65-69 | 5,852,547 | 6,582,716 |
| 70-74 | 4,243,972 | 5,034,194 |
| 75-79 | 3,182,388 | 4,135,407 |
| 80-84 | 2,294,374 | 3,448,953 |
| 85+ | 1,789,679 | 3,703,754 |

Source: Centers for Disease Control and Prevention, National Center for Health Statistics.25

**Table A2. Comparison of health care systems between the US and Portugal, 2000 and 2010.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **US** | |  | **Portugal** | |
| **Variable (Unit)** | **2000** | **2010** |  | **2000** | **2010** |
| **Population** | | | | | |
| Total (million) | 281•2 | 309•3 |  | 10•3 | 10•6 |
| 65 years or older (%) | 12•4 | 13•1 |  | 16•3 | 18•7 |
| Females (%) | 50•9 | 50•8 |  | 51•7 | 52•2 |
| White (%) | 81•0 | 78•3 |  | . | . |
| **Health Coverage** | | | | | |
| Uninsured (%) | 13•1 | 16•3 |  | 0a | 0a |
| **Hospital capacity** (per 1,000 population) | | | | | |
| Total hospital beds | 3•5 | 3•1 |  | 3•7 | 3•4 |
| Beds in public hospitals | 0•9 | 0•8 |  | 2•9 | 2•5 |
| **Health costs** | | | | | |
| Total health expenditure (% of GDP) | 13•1 | 17•0 |  | 9•3 | 10•8 |
| Total health expenditure per capita (US $ PPP) | 4,790•5 | 8,243•5 |  | 1,645•9 | 2,793•1 |
| Government share (% of total expenditure) | 43•0 | 47•4 |  | 66•6 | 65•9 |
| Private Insurance (% of total expenditure) | 35•3 | 33•7 |  | 4•4 | 4•3 |
| Out-of-Pocket (% of total expenditure) | 14•9 | 12•0 |  | 23•4 | 25•8 |
| **Health status** | | | | | |
| All-cause deaths (per 100,000 population, ≥20 years, crude rates) | 1,169•0 | 1,074•7 |  | 1,309•4 | 1,255•3 |
| Males | 1,182•4 | 1,103•8 |  | 1,441•5 | 1,368•8 |
| Females | 1,156•5 | 1,047•4 |  | 1,190•4 | 1,154•9 |
| All-cause deaths (per 100,000 population, ≥20 years, age-sex adjusted rates) | 1,247•5 | 1,074•7 |  | 1291•4 | 1,040•7 |
| Life expectancy at birth (years) | 76•7 | 78•6 |  | 76•9 | 80•0 |
| Males | 74•1 | 76•2 |  | 73•3 | 76•8 |
| Females | 79•3 | 81•0 |  | 80•4 | 83•2 |

US $ PPP – Purchasing Power Parity in US dollars

a Implicit from universal coverage

Sources: OECD, US Census Bureau, CDC Wonder, Portugal Statistics, Eurostat.26-30

Sex-age-adjusted death rates were computed using the 2010 US population as reference.

**Table A3a: Sample characteristics of studies used for discussion of prevalence of risk factors.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **AMALIA31** | **PHYSA32** | **VALSIM33** | **Sardinha *et al.*34** | **Carreira *et al.*35** |
| **Time period** | October 2006 to February 2007 | November 2011 to December 2012 | April 2006 to November 2007 | 2008 and 2009 | - |
| **Type of study** | Cross-sectional study, using a structured questionnaire in a direct interview. | Cross-sectional survey with protocol-based interviews and examinations. | Cross-sectional study based on questionnaire on sociodemographic, clinical and laboratory data. | Cross-sectional study based on measurements of body mass, stature, and waist circumference. | Systematic review of nationally representative samples, published and available in Pubmed until 211 |
| **Sampling**  **Method** | The sample was stratified by gender, age-group and region and includes individuals of both genders, aged 40 years or more and resident in Portugal. | A multistage-stratified (by age and sex) cluster random sampling method was used to select a nationally (Portugal continental) representative sample of the general population aged 18-90 years based in 2001 recent National census data. Community local health service centers were the basis for recruitment | Stratified distribution and proportional to the population density of each region of mainland Portugal and the islands of Madeira and the Azores treated at primary health care centers. | Sample selection followed a multi-stage proportionate stratified cluster sampling procedure, considering population gender, age and geographical distribution. Controlled quota sampling was calculated taking into account the demographic data reported by National Census. | - |
| **N** | 38893 | 3720 | 16,856 | 2539 |  |
| **Age range** | ≥40 years | 18-90 years | 18-96 years | ≥18 yeas | - |

Sources: Methods of studies describing the CHD risk factors for PT31-35.

**Table A3b: Definitions used of risk factors in studies for discussion of prevalence of risk factors.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **AMALIA31** | **PHYSA32** | **VALSIM33** | **Sardinha *et al.*34** | **Carreira *et al.*35** |
| **Overweight** | Declared weight, height as indicated on identity card | 25≤BMI<30, BMI =weight/height^2 based on actual measurements of height and weight | 25≤BMI<30, BMI =weight/height^2 based on actual measurements of height and weight | 25≤BMI<30, BMI =weight/height^2 based on actual measurements of height and weight | - |
| **Obesity** | Declared weight, height as indicated on identity card | BMI ≥30M; BMI =weight/height^2 based on actual measurements of height and weight | BMI ≥30M; BMI =weight/height^2 based on actual measurements of height and weight | BMI ≥30M; BMI =weight/height^2 based on actual measurements of height and weight | - |
| **Hypertension** | Self-reported hypertension (“high blood pressure”); treatment and monitoring of each of the above conditions when present | Hypertension was defined as a systolic blood pressure (BP) of at least 140mmHg or diastolic BP of at least 90mmHg, or if the participant reported a history of hypertension, or if the participant reported taking antihypertensive medication in any moment of their life. Awareness of hypertension was defined as participant's self-reported of any previous diagnosis of hypertension by a healthcare professional (except if only during pregnancy). The treatment of hypertension was defined as self-reported use of a prescription medication for the treatment of hypertension in the past 2 weeks.  Blood pressure was estimated as the average of three readings or the average of the two last readings if there was a difference of at least 10mmHg of BP from the first reading to the second; | Hypertension (HTA) was defined by a previous diagnosis of HTA or the presence of systolic BP >140 mmHg or diastolic BP >90 mmHg. BP was based on actual measurements. | - | - |
| **Hypercholestero-lemia** | Self-reported hypercholesterolemia ("Blood cholesterol") was defined treatment and monitoring of each of the above conditions when present | Self-perceived hypercholesterolemia was defined by "participant's awareness of these conditions or current use of antidyslipidemic drug" | HDL cholesterol<40mg/dL | - | - |
| **Diabetes** | Self-reported diabetes; treatment and monitoring of each of the above conditions when present | Self-perceived diabetes was defined by "participant's awareness of these conditions or current use of antidiabetic drug" | Diabetes was defined as a previous diagnosis or fasting glucose of >126 mg/dl, and impaired fasting glucose as fasting glucose 110-125 mg/dl. | - | - |
| **Smoking** | Smoking status was classified as: never smoked, ex-smoker (how long quit smoking? Smoked for how long? Cigarettes per day?), current smoker (how long smoker? Cigarettes per day?) | Smoking status was classified as: current, ex-smoker (not for at least 1 year), and non-smoker. | Self perceived; Smoker, Ex-smoker, Non-smokers | - | MISSING |

Sources: Definitions in studies analyzing CHD risk factos for PT31-35.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table A3c: Prevalence of main CHD risk factors (%) - additional studies to characterize the risk of the PT population.** | | | | | | | | | | | | | | | | | |
| **Country** | **US** | | | **PT** | | | | | | | | | | | | | |
| **Study** | **NHANES** | | | **AMALIA31** | | | **PHYSA32** | | | **VALSIM33** | | | **Sardinha *et al.*34** | | | **Carreira *et al.*35** | |
| **Risk factor** | Crude  rate | Age-adjusted rate | | Crude  rate | Age-adjusted rate | | Crude  rate | Sex-adjusted rate | | Crude  rate | Age-sex-adjusted rate | | Crude  rate | Age-sex-adjusted rate | | Crude  rate | Age-sex-adjusted rate |
| **Overweight/Obesity** | | | | | | | | | | | | | | | | | |
| Both sexes | 71,6 | | 71,6 | 51,6 | | 51,3 |  | | 51,6 | - | |  | 64,99 | | 62,07 | - |  |
| Males | 77,8 | | - | | 53,1 | | - | |  | 67,35 | | - |  |
| Females | 66,1 | | - | | 50,1 | | - | |  | 63,22 | | - |  |
| **Hypertension** | | | | | | | | | | | | | | | | | |
| Both sexes | 32,8 | | 33,7 | 23,5 | | 22,8 |  | | 40,9a | 65,46 | | 43,52 | - | |  | - |  |
| Males | 30,3 | | 21,8 | | 44,4 | | 62,48 | | - | |  | - |  |
| Females | 35,1 | | 24,9 | | 40,2 | | 58,63 | | - | |  | - |  |
| **Hypercholesterolemia** | | | | | | | | | | | | | | | | | |
| Both sexes | 48,1 | | 48,1 | 19,7 | | 19,4 |  | | 33,2 | 27,46 | | 39,46 | - | |  | - |  |
| Males | 50,0 | | 18,6 | | 29,1 | | 47,74 | | - | |  | - |  |
| Females | 46,4 | | 20,7 | | 37,0 | | 34,29 | | - | |  | - |  |
| **Diabetes** | | | | | | | | | | | | | | | | | |
| Both sexes | 12,3 | | 12,6 | 8,9 | | 8,5 |  | | 10,3 | - | |  | - | |  | - |  |
| Males | 12,1 | | 8,5 | | 11,4 | | - | |  | - | |  | - |  |
| Females | 12,4 | | 9,3 | | 9,2 | | - | |  | - | |  | - |  |
| **Smoking** | | | | | | | | | | | | | | | | | |
| Both sexes | 20,3 | | 19,8 | 16,3 | | 17,1 |  | | 15,1 | - | |  | - | |  | - | 17,28 |
| Males | 22,6 | | 25,3 | | 16,1 | | - | |  | - | |  | - |
| Females | 18,3 | | 8,8 | | 14,1 | | - | |  | - | |  | - |

a age-sex-adjusted rate,

NHANES – National Health and Nutrition Examination Survey

Sources: Crude rates retrieved from31-36.

Age-sex-adjusted rates were computed using the US 2010 population as the reference population.

**Table A4. Health technologies access lag between the US and Portugal per medical device class in selected interventional cardiology procedures.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Technology** | | **Country** | **First approved device**  **(Model, Manufacturer)** | **Date (mm/dd/yy)** | |
| **Procedure name** | **Device class** | **Approval** | **Difference: US-PT (months)** |
| Percutaneous Coronary Intervention (PCI) | PTCA Balloon Catheter | PT | Unknown | May 1984f | -47 |
| US | Unknown | 1980d |
| Bare-Metal Stent (BMS) | PT | Palmaz Schatz stent, Johnson & Johnson | 6/21/90f | 33 |
| US | Gianturco-Roubin coronary flex-stent, Cook, inc. | 06/03/93a |
| Drug-Eluting Stent (DES) | PT | Cypher sirolimus drug eluting stent, Cordis | 05/31/02d,f | 11 |
| US | Cypher sirolimus drug eluting stent, Cordis | 04/24/03a |
| Cutting Balloon Catheter (CBC) | PT | Cutting Balloon, Interventional Technologies Inc. | 1995c | 58 |
| US | Flexatome Cutting Balloon, Boston Scientific | 04/18/00a |
| Drug-Eluting Balloon Catheter (DEB) | PT | SeQuent Please, B Braun Melsungen AG | 06/30/09c | 67 |
| US | N/A | Not approved |
| Percutaneous Ventricular support | Impella - catheter-based VAD | PT | Impella® 2.5, Abiomed | 09/30/04c,f | 44 |
| US | Impella Recover LP 2.5 Percutaneous Cardiac Support System, AbIomed Inc. | 05/30/08b |
|  | Percutaneous Ventricular Assist Device (PVAD) | PT | TandemHeart System, CardiacAssist Inc. | 02/26/01c | -12 |
|  | US | AB-180 XC System, Cardiac Assist Inc. | 02/25/00c,a |
| Embolic Protection | N/A | PT | PercuSurge Guard Wire, PercuSurge Inc. | 08/11/98c | 29 |
| US | PercuSurge GuardWire Temporary Occlusion and Aspiration System, PercuSurge Inc. | 06/01/01b |
| Atherectomy | Rotational Atherectomy | PT | Rotablator, Boston Scientific Corp. | 1999c | -73 |
|  | Rotablator®, Boston Scientific Corp. | 05/28/93a |
| Directional Coronary Atherectomy (DCA) | PT | Unknown | 10/23/91f | -13 |
| US | Simpson Coronary Atherocath, Devices for Vascular Intervention, Inc. | 09/14/90a |
| Coronary Thromboaspiration | Manual | PT | Diver CE, Invatec S. p. A. | 07/06/01c | 17 |
| US | Export Aspiration Catheter, Medtronic Vascular | 10/29/02b |
| Mechanical | PT | Angiojet Series 3000 Rheolytic Thrombectomy Syste, Possis Meical Inc. | October 1997c | 25 |
| US | AngioJet Rheolytic Thrombectomy System, Bayer Medical Care Inc. | 03/12/99a |
| Coronary Brachytherapy | Intravascular Radiation Delivery System/Device | PT | Novoste Beta-Cath System, Novoste Corp. | 1999d | 17 |
| US | Novoste Beta-Cath System, Novoste Corp. | 12/13/00a |
| Transcatheter Aortic Valve Replacement (TAVR) | Balloon expand | PT | Sapien TransCatheter Aortic Valve Edwards LifeSciences | September 2007c | 50 |
| US | Sapien TransCatheter Aortic Valve Edwards LifeSciences | 11/22/11a |
| Self-expand | PT | The CoreValve System, Medtronic | May 2007c,e | 82 |
| US | The CoreValve System, Medtronic | 02/04/14a |
| Percutaneous Reduction of Mitral Regurgitation | Percutaneous Mitral Repair System | PT | MitraClip, Abbott Vascular | March 2008c | 67 |
| US | MitraClip, Abbott Vascular | 10/24/13a |
|  |  |  | **Mean difference:** | | **22** |
|  |  |  | **Median difference:** | | **27** |

N/A: Not available until February 13, 2015.

Sources:

a FDA Premarket Approval (PMA)37

b FDA Premarket notification 510(k)38

c Personal communication with MD industry representatives/press release/EUCOMED39-43

d Scientific journal44-46

e Personal communication with an interventional cardiology from Centro Hospitalar de Vila Nova de Gaia (Portugal)

f First use in Santa Cruz Hospital47

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table A5. Health technologies access lag per active in selected therapeutic uses between the US and Portugal.** | | | | | | |
|  | | | | | | |
| **Therapeutic use** | **Active substance** | **Country** | **Approved drug (Brand name)** | **Date (mm/dd/yy)** | | |
| **Approval** | **Marketinga** | **Difference between**  **marketing dates:**  **US-PT (months)** |
| Platelet inhibitor | Ticlopidine | PT | Tiklyd | 05/15/81 | 03/21/07 | -185 |
| US | Ticlid | 10/31/91 | |
| Clopidogrel | PT | Plavix | 07/15/98 | 04/29/03 | -65 |
| US | Plavix | 11/17/97 | |
| Prasugrel | PT | Efient | 02/25/09 | 04/01/14 | -57 |
| US | Effient | 07/10/09 | |
| Ticagrelor | PT | Brilique | 12/03/10 | 12/19/11 | -5 |
| US | Brilinta | 07/20/11 | |
| GP IIb/IIIa inhibitor - Abciximab | PT | Reopro | 02/12/96 | 03/21/07 | -159 |
| US | Reopro | 12/16/93 | |
| GP IIb/IIIa inhibitor - Eptifibatide | PT | Integrilin | 07/01/99 | 03/21/07 | -106 |
| US | Integrilin | 05/18/98 | |
| GP IIb/IIIa inhibitor - Tirofiban | PT | Aggrastat | 06/30/99 | 03/21/07 | -106 |
| US | Aggrastat | 05/14/98 | |
| Anticoagulant | Bivalirudin | PT | Angiox | 09/20/04 | 06/23/10 | -114 |
| US | Angiomax | 12/15/00 | |
| Rivaroxaban | PT | Xarelto | 09/30/08 | 01/28/09 | 29 |
| US | Xarelto | 07/01/11 | |
| Apixaban | PT | Eliquis | 05/18/11 | 08/01/14 | -19 |
| US | Eliquis | 12/28/12 | |
| Dabigatran etexilate | PT | Pradaxa | 03/18/08 | 05/01/10 | 6 |
| US | Pradaxa | 10/19/10 | |
| Antianginal | Nicorandil | PT | Dancor | 08/03/96 | 03/21/07 | 95 |
| US | N/A | N/A | |
| Ivabradin | PT | Procoralan | 10/25/05 | 11/01/07 | 87 |
| US | N/A | N/A | |
| Ranolazine | PT | Ranexa | 07/09/08 | N/C | -109 |
| US | Ranexa | 01/27/06 | |
| **Mean difference:** | | | | | | **-51** |
| **Median difference:** | | | | | | **-61** |

N/A – Not available until February 13, 2015

N/C – Not commercialized until February 13, 2015

a Personal communication with INFARMED

Sources: US – FDA48; PT – INFARMED49

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