



Apifarma – holistic perspective on the value of medicines in Portugal

August 2018

Executive summary

Intro

- **Objective of this study is to provide an holistic perspective on the value of medicines in Portugal by looking at 3 dimensions:** human value, societal value and economic value
- **8 diseases were selected to quantify and illustrate human and societal impacts:** HIV, Schizophrenia, RA, Diabetes, NSCLC, CHF, CRC, COPD
- **Analyses show that innovative medicines as a whole have added significant value in Portugal**, bringing benefits that are multiple times larger than the country's total spend on pharmaceutical drugs

Human impact

- **Innovative medicines added 2 Mn years of healthy life to Portugal since 1990**, 180k in 2016 alone
- **110,000+ deaths were avoided and life expectancy has been extended by up to 10 years**
- **Innovative medicines increased quality of life** by reducing symptoms and side effects, making treatment options more convenient and helping patients spend quality time with their family

Societal impact

- **Innovative medicines allowed patients to remain productive**, generating €280 Mn/year additional income to families across the 8 diseases (1000€ per month per affected household)
- **Innovative medicines reduced hospitalizations and other direct healthcare cost by €560 Mn every year**
- **€5-7Bn of yearly value of healthy life years saved in 8 diseases**, above €3.8Bn/year of pharma spending

Economic impact

- **Pharmaceutical industry adds €4.3 Bn to Portuguese GDP**, representing 2.3% of the country's GDP, being also a **highly productive industry**, with a 2.1x Input/Output ratio (above average of all sectors)
- **Pharma is a driver of overall GDP growth**, growing slightly faster than the economy (2.7% vs 2.3% p.a.)
- **Pharma is a job creator in Portugal**, employing ~10,000 people directly and ~40,000 in broader definition

Priorities going forward

- **Ways to further accrue value include**
 - **Innovating in patient care:** boosting prevention & diagnosis, integrating care and leveraging technology
 - **Accelerating access to innovative medicines:** streamlining reimbursement approval, ensuring sufficient budgets and resources and potentially establishing outcome-based contracts for selected diseases
 - **Attracting Pharma investment:** by targeting R&D for new modalities, becoming a center of excellence for clinical trials, innovating with cutting edge manufacturing and developing global services center

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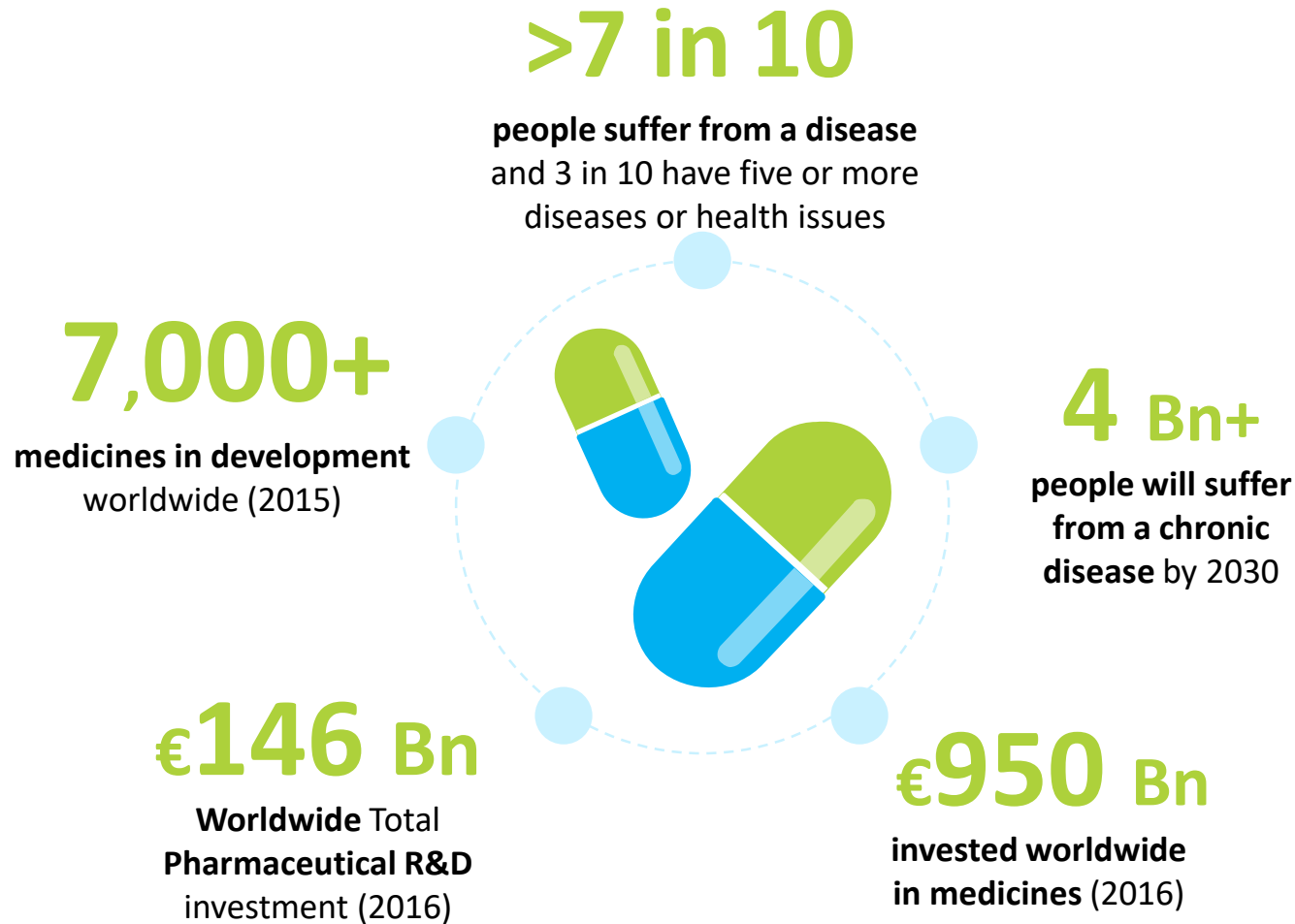
1. Introduction

2. Value of medicines in Portugal

3. Opportunities for the future



Medicines played and continue to play a fundamental role in society



SOURCE: IFPMA, Facts and Figures 2017 (2017); EvaluatePharma, World Preview 2018, Outlook to 2024 (2018); PhRMA, 2016 Profile Biopharmaceutical Research Industry (2016); Center for Managing Chronic Disease website (Jul 2018); Vos et al., Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study (2013)

In this report, we set out to capture what is the value added by medicines in Portugal and explore potential paths forward to further accrue this value

What is the value medicines added to Portugal

Human impact

- To which extent did medicines **improve and save patients' lives** in Portugal?

Societal impact

- How do medicines **benefit the Portuguese society** as a whole?

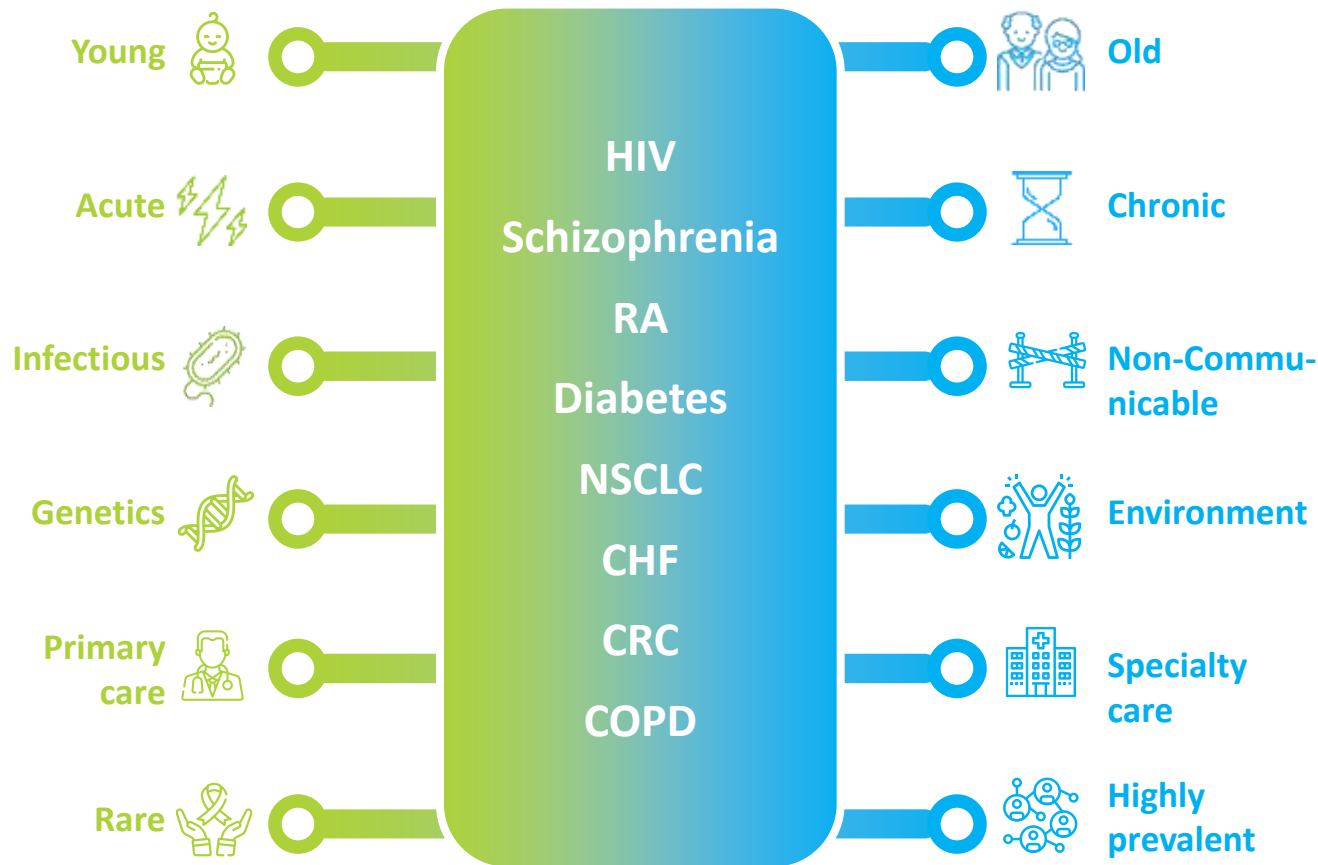
Economic impact

- How important is the role of the Pharma industry **in Portugal's economy**?

How to further accrue this value in the future

- What are potential opportunities to increase this value?
- What should be priorities going forward?

8 diseases that capture the heterogeneity of disease challenges were selected to quantify and illustrate the value of medicines to Portugal



- **Wide range of challenges tackled by medicines**, from the way the disease manifests itself to the patients it affects
- **8 diseases selected capture variety of angles and areas where medicines were:**
 - **Transformative**, able to change the course of a disease
 - Decisive in helping **control or highly diminish effects**
 - **Significant** but despite continuous effort there are **still unmet needs**
- **~15% of overall disease burden** associated with 8 diseases
- **~20% of population affected** by 8 diseases

An extensive range of sources of insight have been leveraged

Sources of insight



Global network of experts and advisory boards (including medical researchers, scientific and patient representatives, regulators, access stakeholders, etc.) – 30+ interviews and discussions specifically on the value of medicine in Portugal



40+ worldwide health databases (e.g., IHME¹ for DALYs calculation and evolution of innovative medicines)



20+ interviews and feedback from local expert representatives from most relevant pharma companies in Portugal



500+ local and international scientific papers to further derive insights and contextualize situation in Portugal (e.g., clinical trials, journal articles and working papers)



Analysis of data from 20+ official sources in the country (e.g., Infarmed's reports, Direção-Geral da Saúde's Diseases National Programs)

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1. Introduction

2. Value of medicines in Portugal

3. Opportunities for the future



Medicines have changed Portugal's landscape by improving patient's lives, generating income and savings to the society and stimulating the economy

A

Human



2 million years of healthy life¹ added to Portugal since 1990, 180 thousand in 2016



110,000+ deaths avoided and increased life expectancy of up to 10 years since 1990



Better quality of life for patients and caregivers e.g., reduced side effects and more convenient treatment options

Impact of medicines in 8 selected diseases

B

Societal



€280 Mn annual additional income to families due to productivity increase using latest treatments



Healthcare system savings of €560+ Mn annually from lower hospitalization rates and avoidance of other direct costs

C

Economic



4.3 Bn yearly value creation to GDP including direct, indirect and induced impacts



Pharma one the **most value creating industries** with a **2.1x Input/Output ratio**



~10,000 jobs created directly by Pharma companies and **~40,000 in broader Pharma industry**

Impact of industry overall

¹ By avoiding 2 million DALYs (Disability Adjusted Life Years)

A Medicines have contributed to adding 2 Mn years of healthy life to Portugal, which could be valued at up €80 Bn

 **2 Mn**

**Healthy life years added¹
since 1990**

Healthy life years added in 2016 are **more than 3 times those lost to road injuries**

Valued between

 **€60-80 Bn**

Healthy life years added in 2016 valued at €5-7 Bn², **equivalent to 140-190% of all pharma spend in Portugal (€3.8 Bn)**

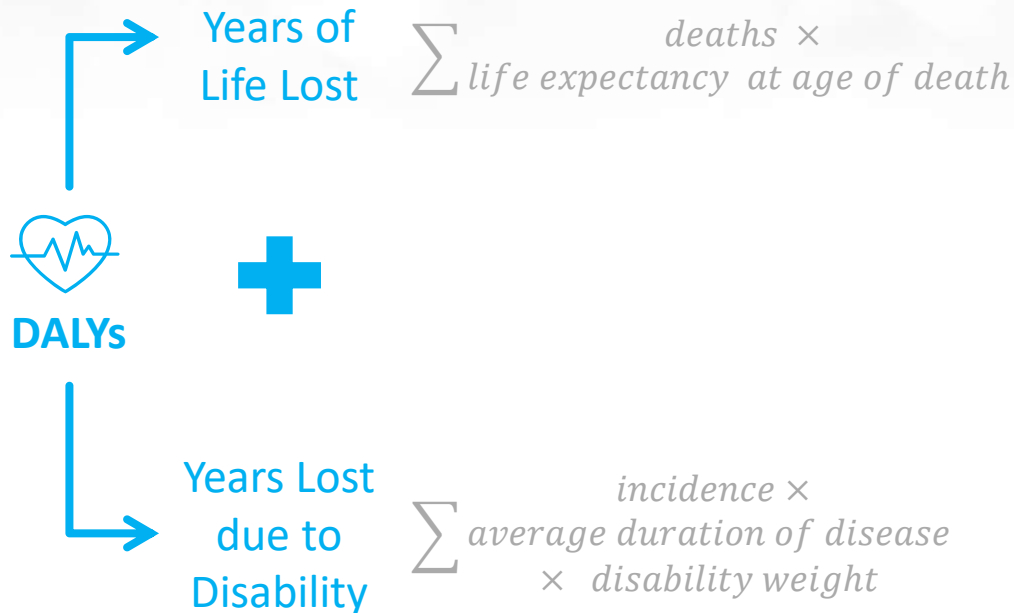
¹ By avoiding DALYs (Disability Adjusted Life Years)

² In 2016, better medicine avoided 181k DALYs

SOURCE: GBD Results Tool website (Jun 2018); Marseille et al., Thresholds for the cost-effectiveness of interventions: alternative approaches (2015); Ochalek et al., Cost per DALY averted thresholds for low- and middle-income countries: evidence from cross country data (2015); Woods et al., Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research (2016); Mendonça et al., Cost-effectiveness of lung transplantation and its evolution: the Portuguese case (2014); Claxton et al., Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold (2015); Yazdanpanah et al., Routine HIV Screening in Portugal: Clinical Impact and Cost-Effectiveness (2013); Sassi F, Calculating QALYs, comparing QALY and DALY calculations (2006); IFPMA, The Pharmaceutical industry and Global Health: Facts and Figures 2017 (2017); IFPMA, The Pharmaceutical industry and Global Health: Facts and Figures 2017 (2017)

A DALYs allow for quantification of the value of medicines through reductions in both disability and mortality using a single, standard metric

What is a DALY¹?



Each DALY can be thought of as **1 lost year of healthy life, due to death or disability**

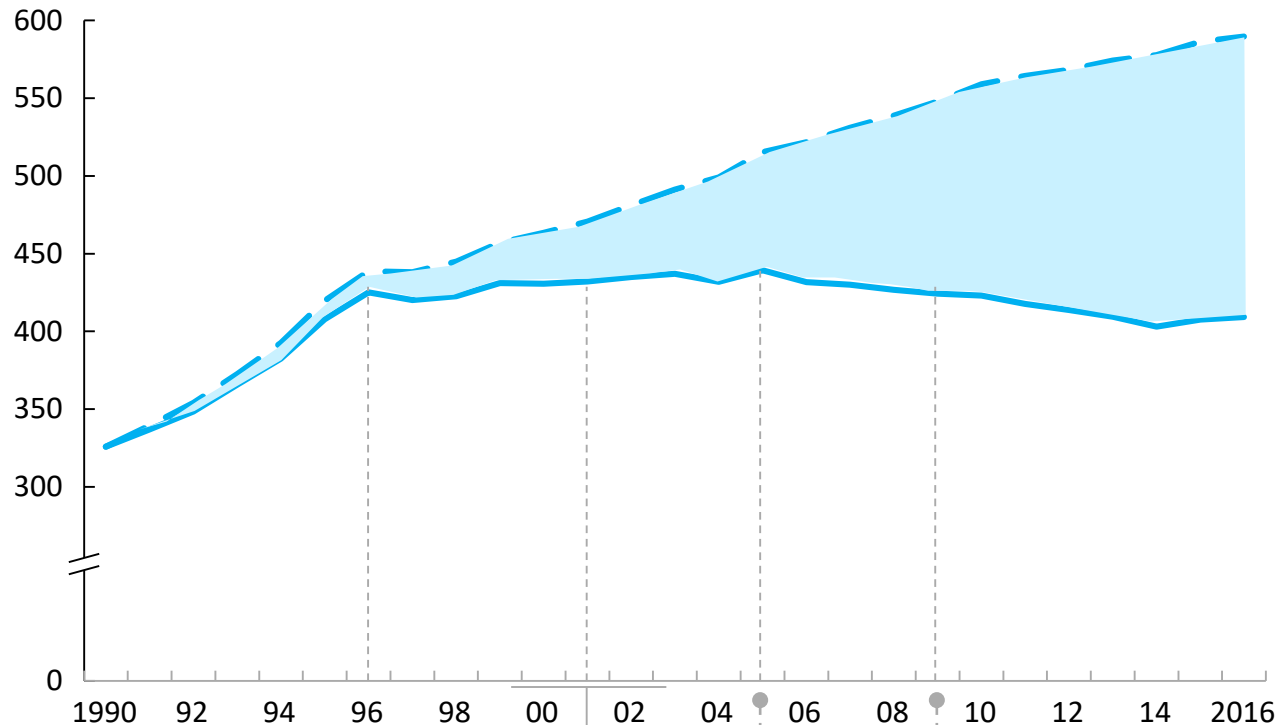
Why use DALYs?

- DALYs allow for **comparisons and aggregation** of data across **different diseases**
- Metric is **widely used by health authorities across countries** and data is widely available
- DALYs **capture disease burden** both in terms of **death and disability caused by disease**
- Research allows to associate **a monetary value to each DALY**, allowing for impact valuation of reduced burden

A Introduction of innovative medicines allowed for 2 Mn DALYs avoided since 1990, valued at €60 to 80 Bn

DALYs¹ evolution for 8 selected diseases², 1990-2016

Thousand DALYs



— PT - DALYs
 - - - PT - DALYs (Projection of DALYs under absence of innovative medicines³)

- **2 Mn DALYs avoided since 1990⁴** mainly due to introduction of innovative medicines
- Number reflects 8 selected diseases, **which represent 15% of total burden in PT**
- **DALYs avoided valued at €60-80 Bn** using DALYs valuation of 30-40k⁵
- **In 2016 alone**, 31% reduction equivalent to 180k DALYs represented €5.4-7.2 Bn, or **~140-190% of all pharma spend in Portugal**

Examples of major medical innovation in Portugal

HIV: ART introduction

CHF: Beta-blockers adoption

Diabetes: DPP-4 adoption

CRC: Angiogenesis inhibitors introduction

¹ Disability-Adjusted Life Years

² HIV, Schizophrenia, Rheumatoid Arthritis, Diabetes, NSCLC, CHF, COPD, CRC

³ Alternative estimate of DALYs evolution for 8 selected diseases excluding introduction of innovative medicines, e.g., ART for HIV in 1996 and Beta-blockers for CHF in early 2000s

⁴ Impact for diseases measured since 1990, except for diseases where DALYs improvement was shown at later stage: HIV (1997), Diabetes (2003) and COPD (2004)

⁵ Calculated average of 7 different DALY valuation methodologies

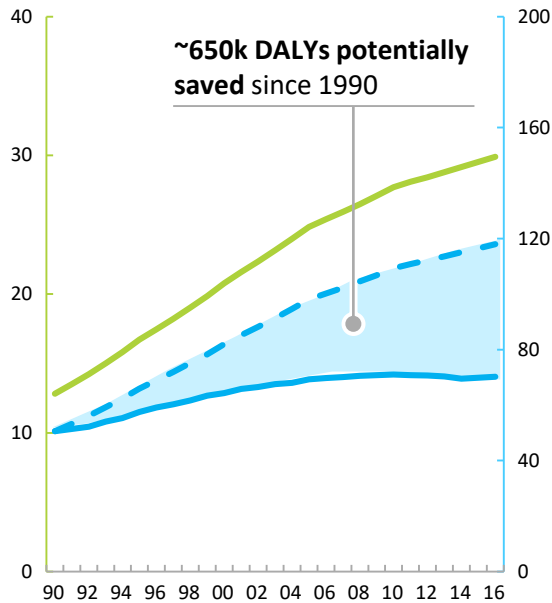
Note: Considering improvements in treatment verified after 1990

A Medicines played a key role in mitigating disease burden, in particular in areas with increasing prevalence, such as CRC, Diabetes & COPD

DALYs¹ and prevalence evolution, Portugal, 1990-2016

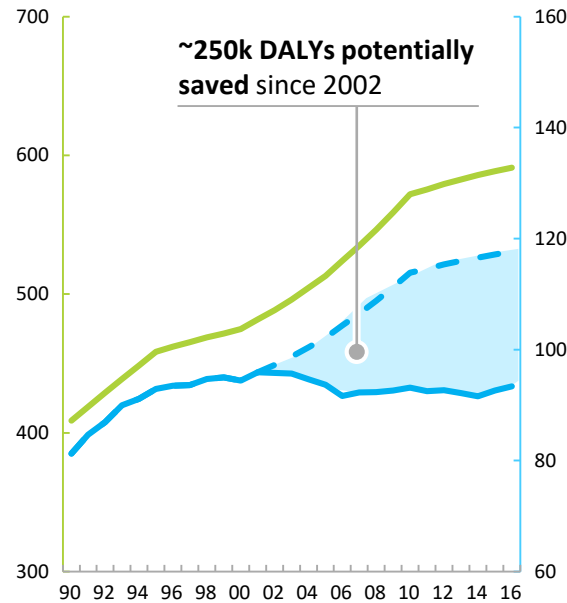
— DALYs
— Prevalence
- - - DALYs (Projection under absence of medical innovation²)

CRC - Advances in medicines were determinant to lessen burden from increased incidence



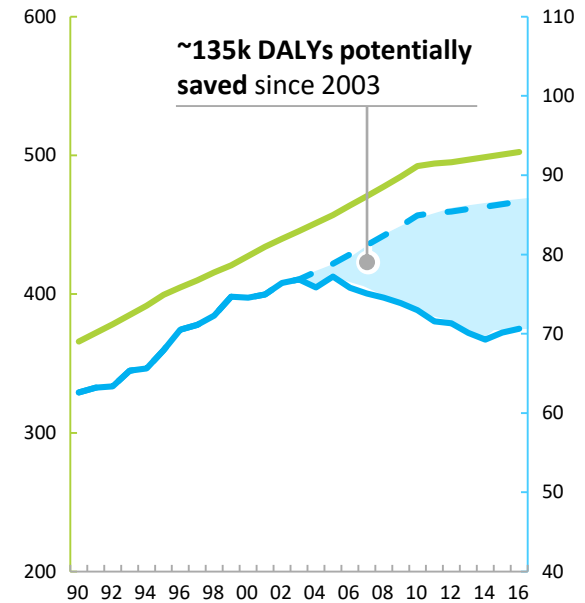
- **Chemotherapy as an adjuvant therapy** (early 1990s) and **Angiogenesis inhibitors introduction** (2006) are among the key innovations in CRC treatment

Diabetes - Treatment adoption was crucial to mitigate burden despite increase in prevalence



- **Introduction of DPP-4, GLP-1 and SGLT-2 drug classes and basal insulin regimes** in the 2000s and 2010s complemented Metformin and traditional insulin therapies

COPD - Newest drug-classes and combinations allowed for reduction in disease's burden



- **Introduction of LAMA and LABA/ICS** around 2003 marked the turning point of COPD treatment and consequent burden decrease in Portugal

¹ Disability-Adjusted Life Years

² Alternative estimate of DALYs evolution excluding introduction of innovative medicines, e.g. Angiogenesis inhibitors introduction in 2006 (CRC)

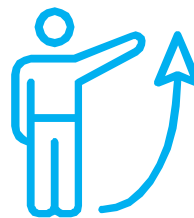
SOURCE: GBD Results Tool website (Jun 2018); Expert interviews

A Medicines have avoided over 110,000 deaths in Portugal since 1990 and contributed to increase in life expectancy by up to 10 years



110,000+

lives saved since 1990



**Up to
10 years**

increased life expectancy²

Premature deaths avoided are **comparable to Setúbal municipality total population in 2017¹**

Equivalent increase in **global life expectancy took humanity almost 4 decades³ to accomplish**

1 Setúbal is estimated to have around 117k inhabitants (2017)

2 For HIV between 1996-99 and 2008-10 (13-15 year period)

3 Global life expectancy increased by 10 years between 1973 and 2009 (60 to 70 years)

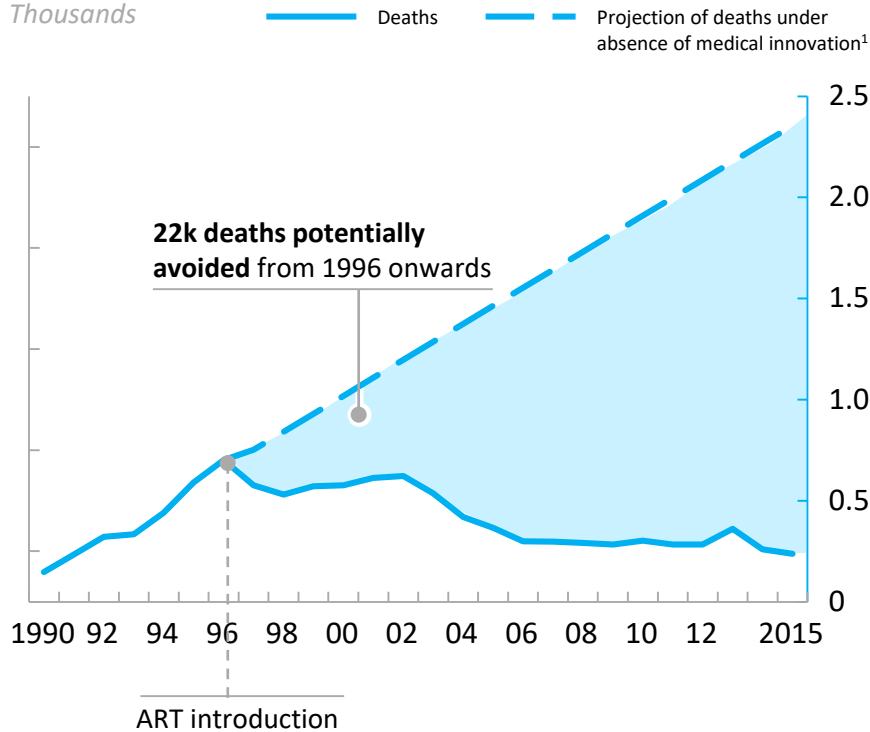
SOURCE: Pordata website (Jul 2018); The World Bank website (Jul 2018)

A Innovative therapies turned HIV from death sentence to a treatable chronic disease and significantly decreased CRC mortality rates

HIV - ART turned a fatal disease into a chronic and manageable illness, saving up to 22,000 lives

No. of HIV/AIDS new infections and related deaths
Portugal, 1990-2015

Thousands

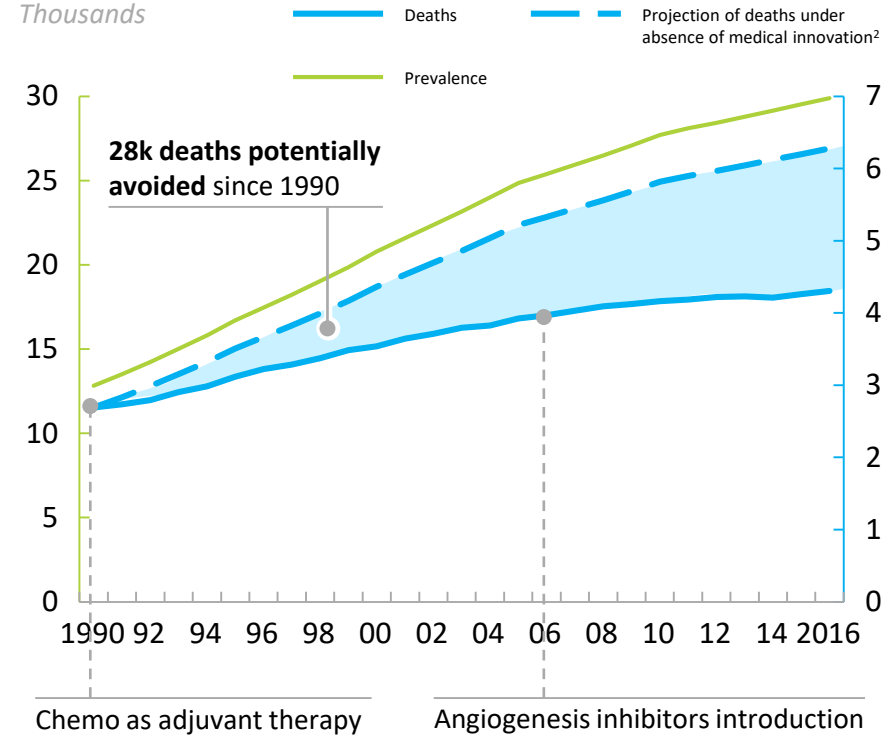


- **~65% decrease in deaths since 1996** due to adoption of Antiretroviral Therapy (ART)

Colorectal Cancer - Advances in medicines allowed for decrease in mortality rates avoiding up to 28,000 deaths

CRC prevalence and no. of related deaths
Portugal, 1990-2016

Thousands



- **CRC related deaths progressed at a lower rate** when compared to prevalence increase, due to advances in medicines

¹ Considering linear evolution of number of death based on 1990-96 values

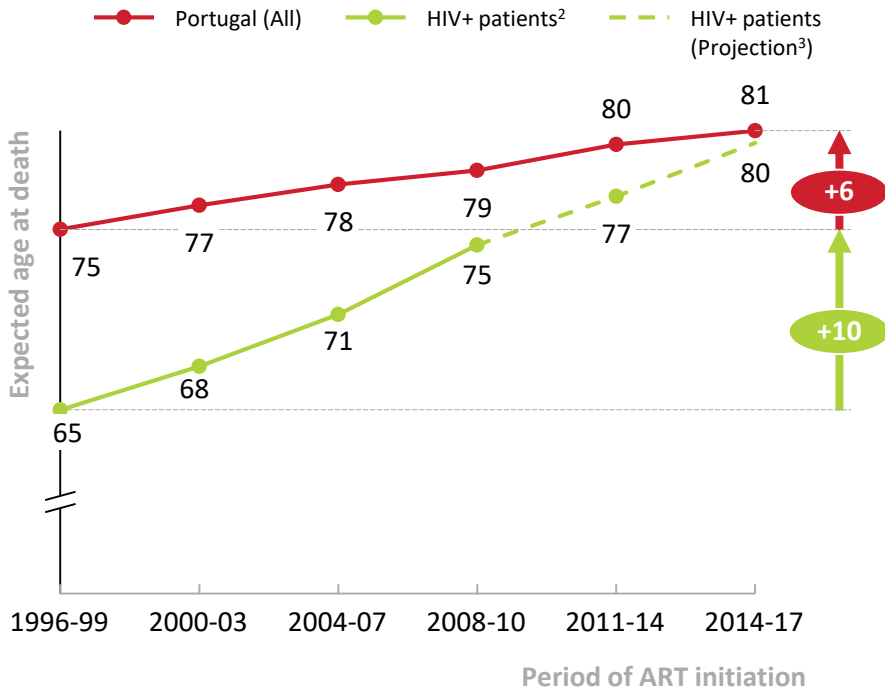
² Considering prevalence evolution from 1990 onwards

SOURCE: Instituto Nacional de Saúde Doutor Ricardo Jorge, Infecção VIH e SIDA: a situação em Portugal a 31 de dezembro de 2016 (2017); GBD Results Tool website (Jun 2018); Expert interviews

A Continuous improvement in treatments increased life expectancy to near normal in HIV patients and ~50% increase in NSCLC survival rates

HIV - Advanced treatments brought patients life expectancy close to standard throughout last decades

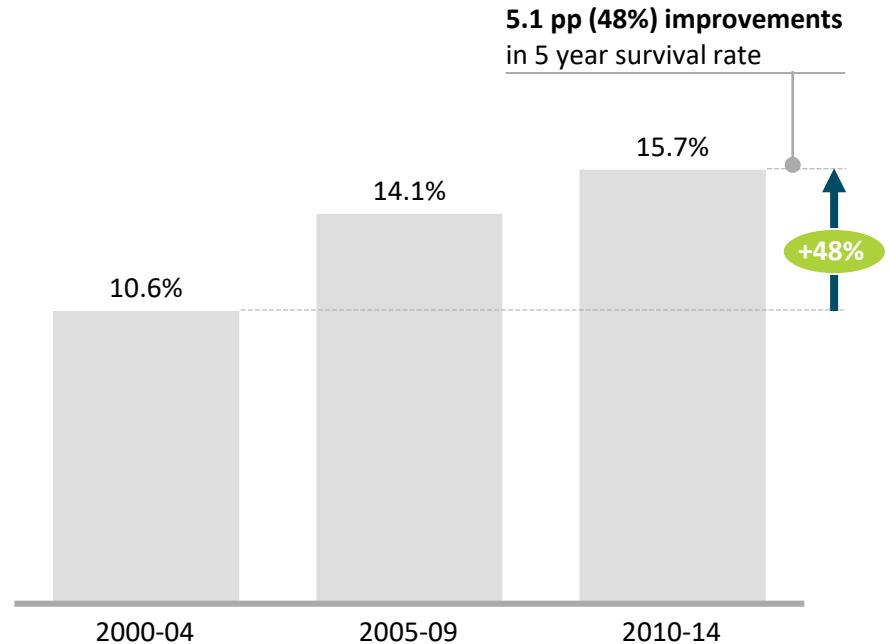
Life expectancy evolution based on calendar period of ART initiation¹ United States and Europe, 1996-2010, 2010-2017 (estimation)



- **~10 years increase** directly attributed to more advanced ART
- **Close to 0% difference** compared to remaining population

NSCLC – New treatments steadily improved patients long-term survival rates by close to 50%

5 year survival rate for NSCLC patients Portugal, 2000-2014



- **Chemotherapy and oncogene targeted therapies** credited as main contributors to 5 year survival rate improvements

¹ Life expectancy evolution for 20 years old HIV patients with 2nd and 3rd follow-up (1st year of successful treatment)

² Average between life expectancy of Men and Women

³ Forecasted based on linear evolution of previous data

SOURCE: World Bank website (Jun 2018); The Lancet HIV, Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies (2017); Allemani et al., Global surveillance of trends in cancer survival: analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers during 2000–2014 from 322 population-based registries in 71 countries (CONCORD-3) (2018)

A Medicines allowed Portuguese patients to live healthier and happier lives



Reduced
symptoms and
side effects

Better medicines controlled diseases and slowed progression, avoiding further complications and side effects



More
convenient
treatment options

Thanks to innovation, patients can take less drugs, less frequently, with less discomfort and without going to the hospital



Family
quality time

Medicines allow patients to do what they love with those they hold dear



A Quality of life has improved significantly for patients with debilitating diseases, helping to manage symptoms and reduce side effects



Schizophrenia

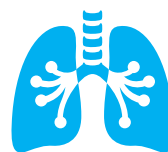
Integration in society



Before antipsychotics, patients had to be institutionalized. With early antipsychotics, patients were heavily sedated, had tremors and needed injections every two weeks



Now, most patients can be treated in their community, severe side effects are infrequent and patients can receive just one injection every 3 months



COPD

Enjoyment of life and greater autonomy



Before first short-acting beta2-agonists, COPD patients lived between their home and hospital bed, and depended on others for simple daily activities



Now, patients can be independent, run errands, spend quality time with family and live ~20 years without major complications

A Pharma innovation keeps on improving patients' lives, making treatments more convenient and effective



Diabetes

Better treatment options



Until recently, monitoring and treatment options caused patients discomfort, leading them to skip treatment and the disease to progress



Now, most patients rate life with treatments as being close to perfect health, thanks to fixed dose oral anti-diabetics, insulin pumps and other innovations



RA

Remission of symptoms



Before DMARDs, patients gradually lost mobility and medicines did little to address the disease beyond managing pain and inflammation



Now, innovative medication slows down and reverses the progression of RA: between 2009 and 2015, share of patients with the disease controlled in Portugal grew from **34% to 46%**

B Medicines have allowed patients to remain active, generating €240 Mn additional income to patients and families

 **€240 Mn**
in additional income
per year



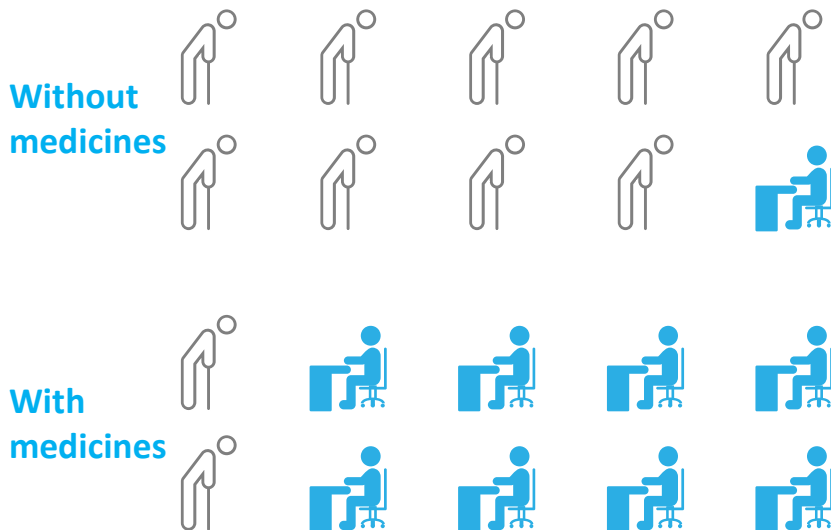
Medicines slow the progress of disease and alleviate symptoms, allowing patients to remain active, avoiding sick days and delaying retirement

Additional monthly income per affected patient of **up to €1,000 per year, enough to cover household costs**

SOURCE: Miranda et al., Finding Rheumatoid Arthritis Impact on Life (FRAIL Study): economic burden (2012); Huscher et al., Evolution of cost structures in Rheumatoid Arthritis over the past decade (2015); Laires et al., The economic impact of early retirement attributed to rheumatic diseases: results from a nationwide population-based epidemiologic study (2016); Apifarma, Importância do Diagnóstico Precoce na Artrite Reumatoide (2018); Halpern et al., Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group (2009); Kanavos et al., Diabetes expenditure, burden of disease and management in 5 EU countries (2012); ADA, Economic Costs of Diabetes in the U.S. in 2017 (2018); Observatório Nacional da Diabetes, Diabetes, Factos e Números, o ano de 2015 (2016); Expert interviews

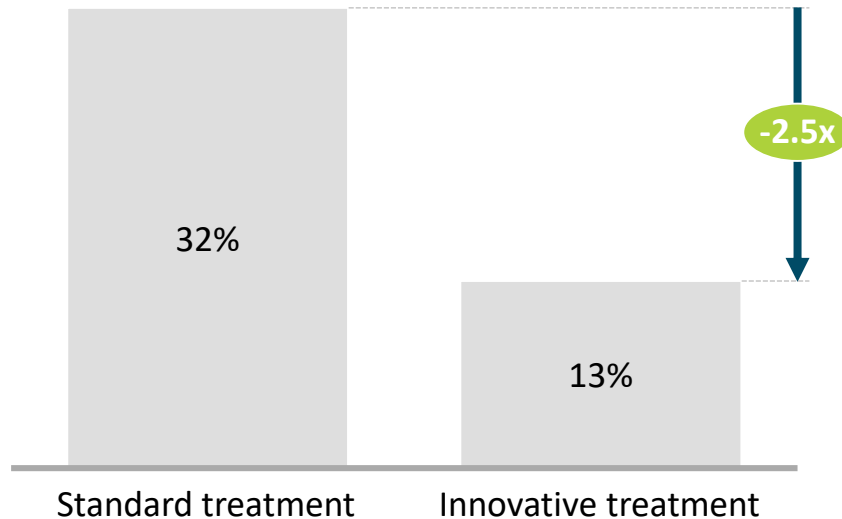
B Innovative medicines allowed RA patients to remain at work and avoid early retirement

RA - Medicines allow 18k patients to generate €240Mn in salaries, supporting themselves and their families



- **Medicines allow RA patients to avoid early retirement** and remain active, instead of being forced to retire approximately 3 years after onset
- **RA patients who remain working estimated ~1 in 10 without medicines and ~8 in 10 with medicines**
- **Impact of medicines is €240 Mn**, equivalent to 18k patients earning ~13k yearly each

RA – Newer drugs allow patients to be ~2.5x more likely to remain working after 2 years



- **Patients receiving biologics are 2.5x less likely to retire** and are able work 31 weeks longer
- **~€8.000 in additional salary earnings per patient** associated in Portugal with additional weeks at work

B Medicines also benefit the Portuguese society by reducing costs in the healthcare system in more than €560 Mn every year



€560 Mn+

**Healthcare System costs
avoided every year**



Healthcare system costs include hospitalizations and other direct medical costs such as outpatient doctor and hospital visits, prescription and OTC drugs

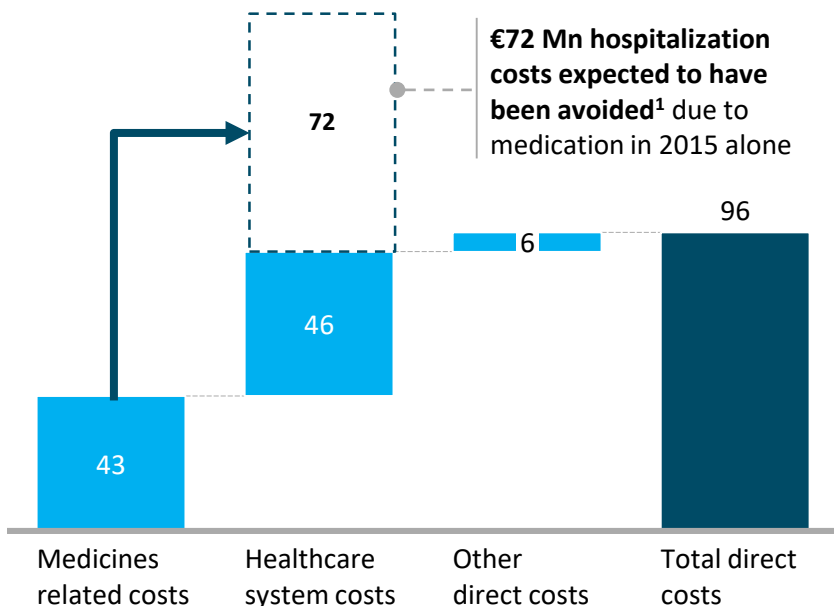
Savings from selected 8 diseases are **enough to cover annual operation costs of Hospital Santa Maria and Pulido Valente¹**

¹ Centro Hospitalar Lisboa Norte includes both Hospital Santa Maria and Pulido Valente, which have operational costs of €395 Mn (2016 data)
SOURCE: Expresso, Hospital de São João tem melhor desempenho do que Santa Maria (Jul 2018)

B Medicines reduce the need for hospitalizations, generating significant savings as seen in Schizophrenia and Rheumatoid Arthritis examples

Schizophrenia – Available antipsychotics allow for Healthcare system savings of €72 Mn every year

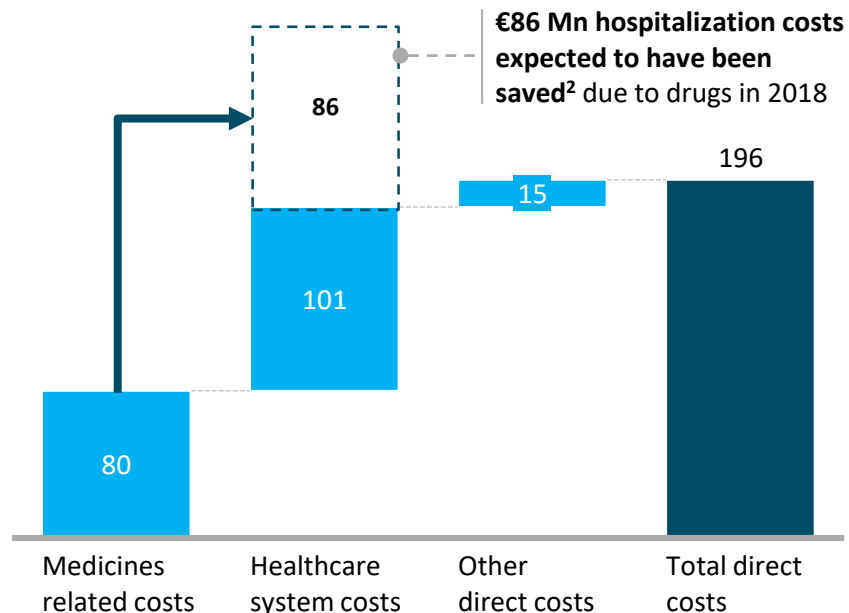
Annual estimated direct costs from Schizophrenia
Portugal, 2015
EUR millions



- Savings result from 61% reduction in Hospitalizations due to positive impact of medicines in control of Schizophrenia symptoms

Rheumatoid Arthritis – Related drugs contribute to slow down of disease, saving €86 Mn costs yearly

Annual estimated direct costs from Rheumatoid Arthritis
Portugal, 2018
EUR millions



- Slow down of disease progress (including remission) as the main cause of decrease in hospitalizations rates and costs

1 Assumes that Healthcare costs are proportionate to hospitalization rate, and that there were -61% hospitalizations, given average effect of antipsychotics against placebo in clinical trials in Leucht et al (2012) meta study

2 Assuming similar trend to Ireland; Harty et al. (2015)

Note: Medicines related costs based on Gouveia et al. for Schizophrenia and Apifarma and Huscher Huscher et al. for Rheumatoid Arthritis

SOURCE: Gouveia et al., The cost and burden of Schizophrenia in Portugal in 2015 (2015); Leucht et al., Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis (2012); Miranda et al., Finding Rheumatoid Arthritis Impact on Life (FRAIL Study): economic burden (2012); Huscher et al., Evolution of cost structures in rheumatoid arthritis over the past decade (2015); Apifarma, Importância do Diagnóstico Precoce na Artrite Reumatoide (2018); Harty et al., Profound reduction in hospital admissions and musculoskeletal surgical procedures for rheumatoid arthritis with concurrent changes in clinical practice (1995-2010) (2015); Expert interviews

B Pharmacological interventions have also impacted positively other medical costs such as outpatients visits, surgeries and drugs

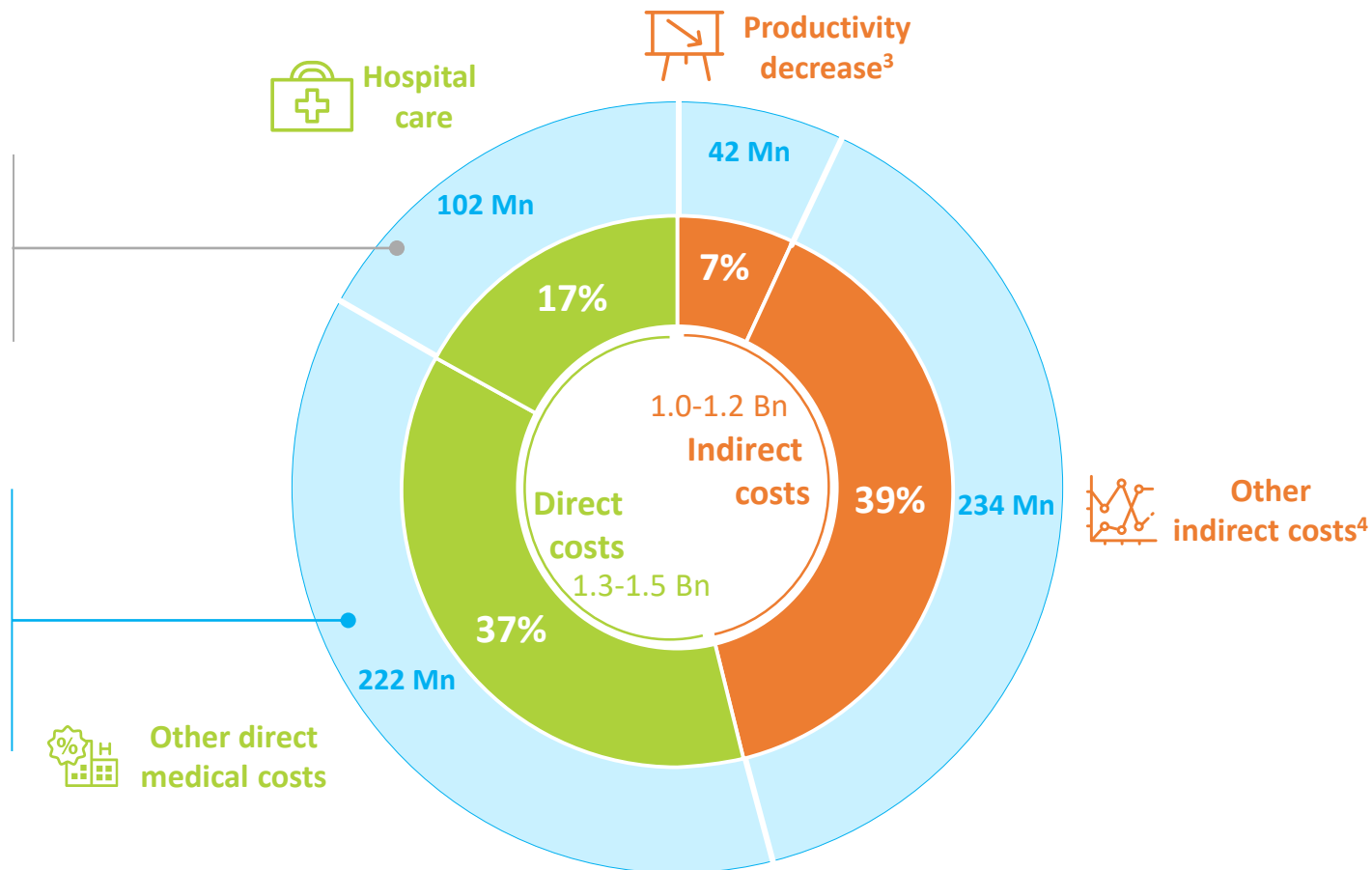
DIABETES - Total economic impact cost estimation¹

Portugal, 2015, Percentage of total costs

○ Avoided costs²

€102 Mn avoided in Hospitalization costs, e.g., less hyperglycemic events (through better control of glycemia)

€222 Mn avoided in other direct medical costs as result of better control of comorbidities (e.g., avoided surgeries and drugs for diabetic foot and retinopathy)



¹ Indirect burden inferred based on international studies: US in 2017: 28% of overall costs, including death, absenteeism and productivity loss; and 5 European countries in 2010: 52% of all costs in 2010: absenteeism, early retirements and social benefits (Kanavos et al. and ADA)

² Total of €600 Mn; Forecast assuming DALYs increase based on prevalence growth rate from 2002 onwards

³ Employed and unemployed people; ⁴ Including e.g., Early retirement/unemployment disability, Absenteeism, Deaths and Social benefits

SOURCE: Kanavos et al., Diabetes expenditure, burden of disease and management in 5 EU countries (2012); ADA, Economic Costs of Diabetes in the U.S. in 2017 (2018); Observatório Nacional da Diabetes, Diabetes, Factos e Números, o ano de 2015 (2016)

C Total impact of Pharma industry to Portugal's economy is a sum of its direct, indirect and induced contribution



1 Direct contribution

Value creation by Pharma through its innovation, direct production, revenues and jobs

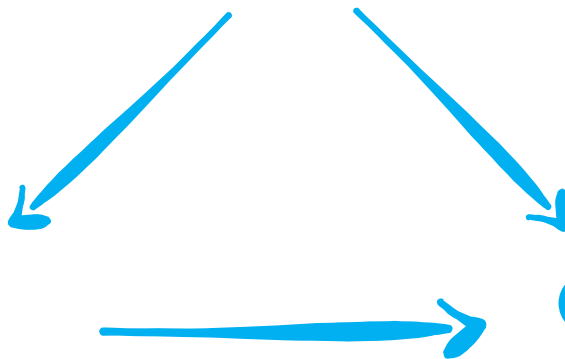


2 Indirect contribution

Indirect value creation by Pharma through the value chain it impacts (e.g., chemicals, advertising, office supplies)

3 Induced contribution

Induced value creation by Pharma through increased demand (i.e., spending from wages in Pharma and its value chain)



C Input-Output tables are robust impact assessment tools, allowing for the estimation of Pharma's value creation through other industries

Description



Nobel prize winning input/output analysis methodology introduced by Harvard economist Wassily Leontief



IO tables describe how much each industry buys and sells from/to every other, how much it pays in wages and profits and how much it contributes to GDP

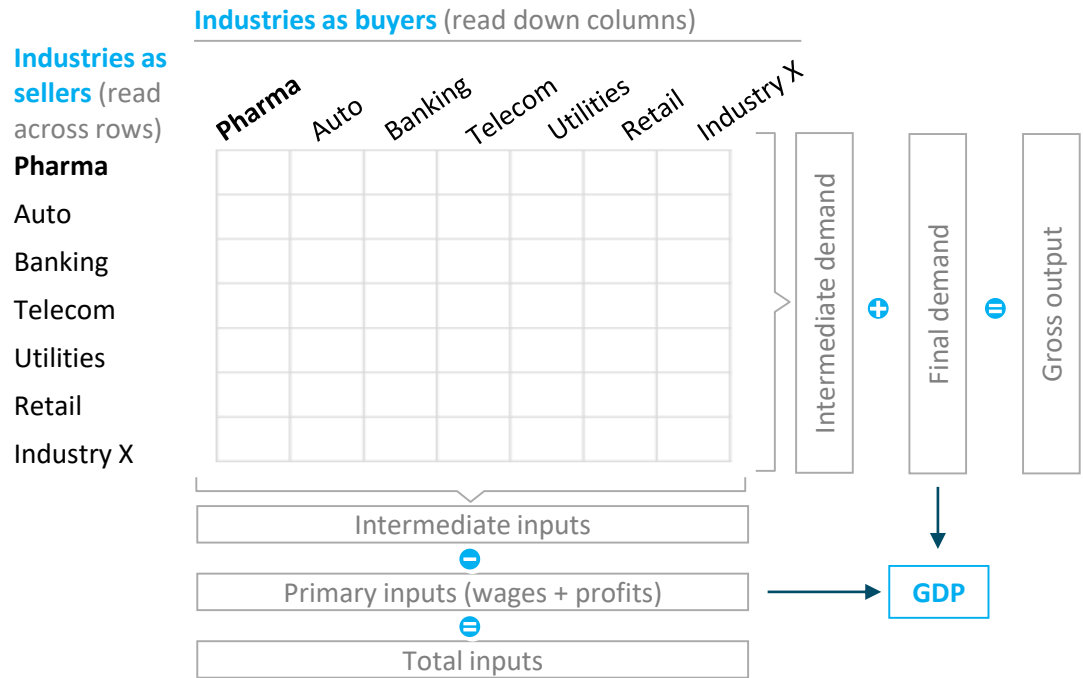


Based on real-world company data for hundreds of institutions, covering all their purchases of goods, services, labor and capital



IO tables allow estimation of GDP multipliers, describing how much production in Pharma generates in other industries through business purchases (indirect) and consumer demand (induced)

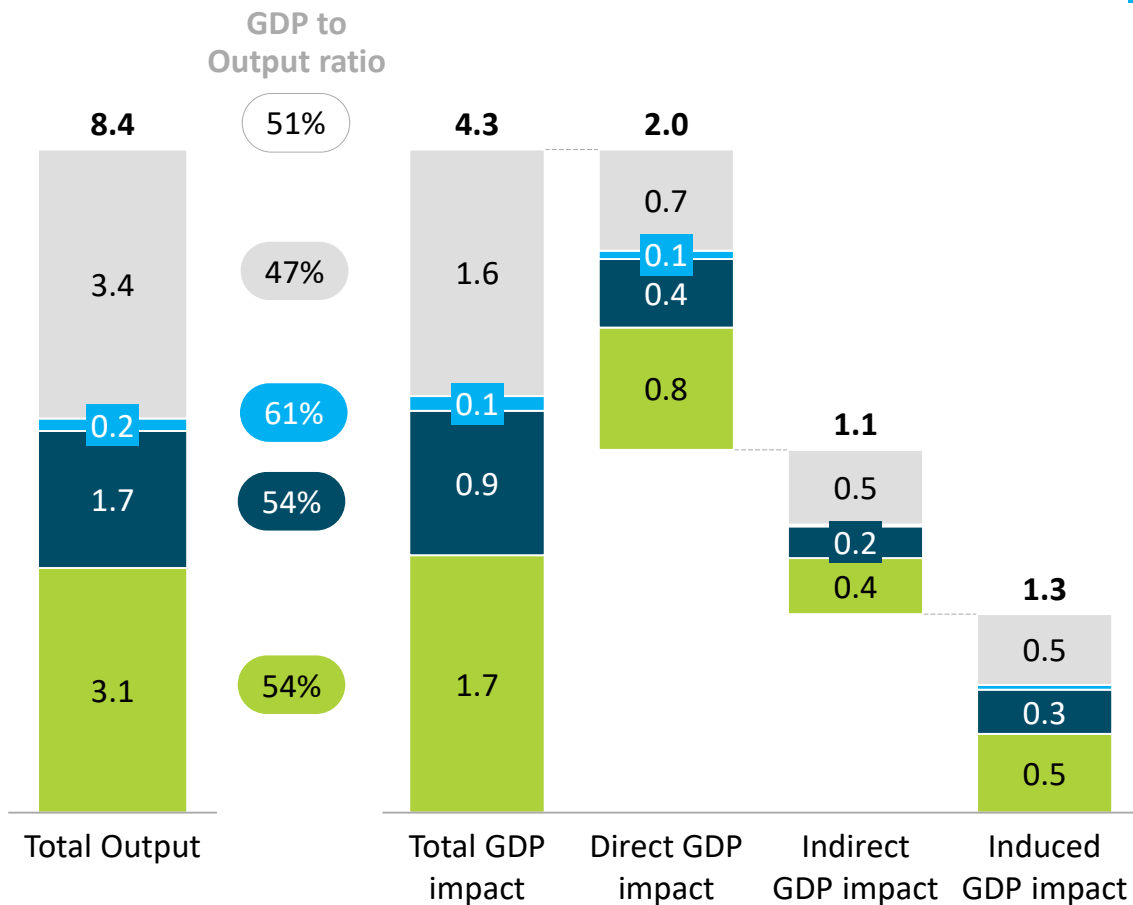
Conceptual view of Input-Output table



C Pharma contributes over €4 Bn to national GDP, mostly by generating demand in other industries

Estimated GDP impact in Portugal

EUR Bn, 2016



- **€4.3 Bn of GDP impact**, measuring net value creation, out of €8.4 Bn of output – which also includes the value of inputs other than labor and capital
- **€2 Bn of value added to GDP directly by Pharma** through production, research and sales of domestic and imported medicines
- **€1.1 Bn added indirectly and €1.3 Bn of induced impact** through business purchases and consumer demand respectively

1 Domestic production of pharmaceuticals (e.g., transformation of chemicals into medicines, packaging)

2 Research and development of medicines (e.g., laboratories, clinical trials)

3 Trade and transport of domestically produced pharmaceuticals (e.g., wholesalers, delivery services, pharmacies)

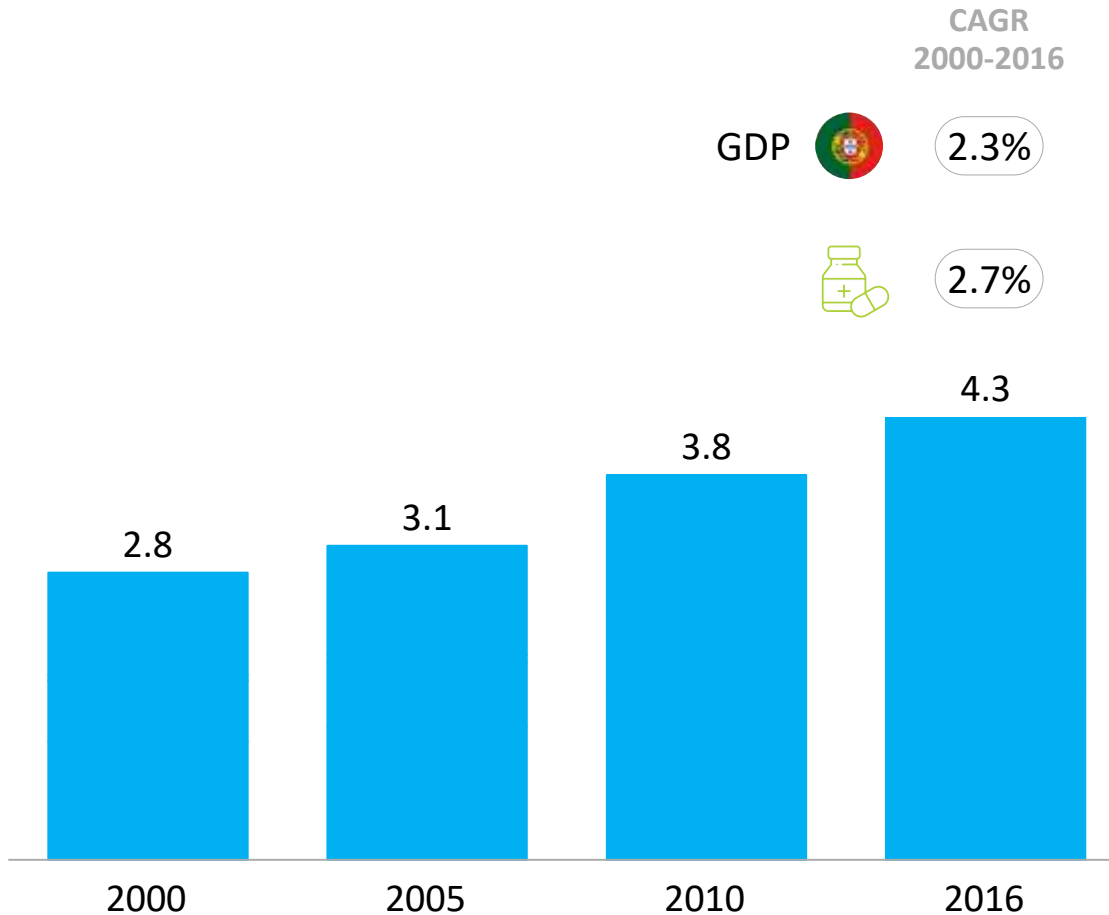
4 Trade and transport of imported pharmaceuticals (e.g., wholesalers, delivery services, pharmacies)

SOURCE: World Input-Output Database website (Jul 2018); IHS MARKIT 2016

C Pharma has been a driver of overall GDP growth, growing slightly faster than the Portuguese economy

Evolution of Pharma's overall GDP contribution

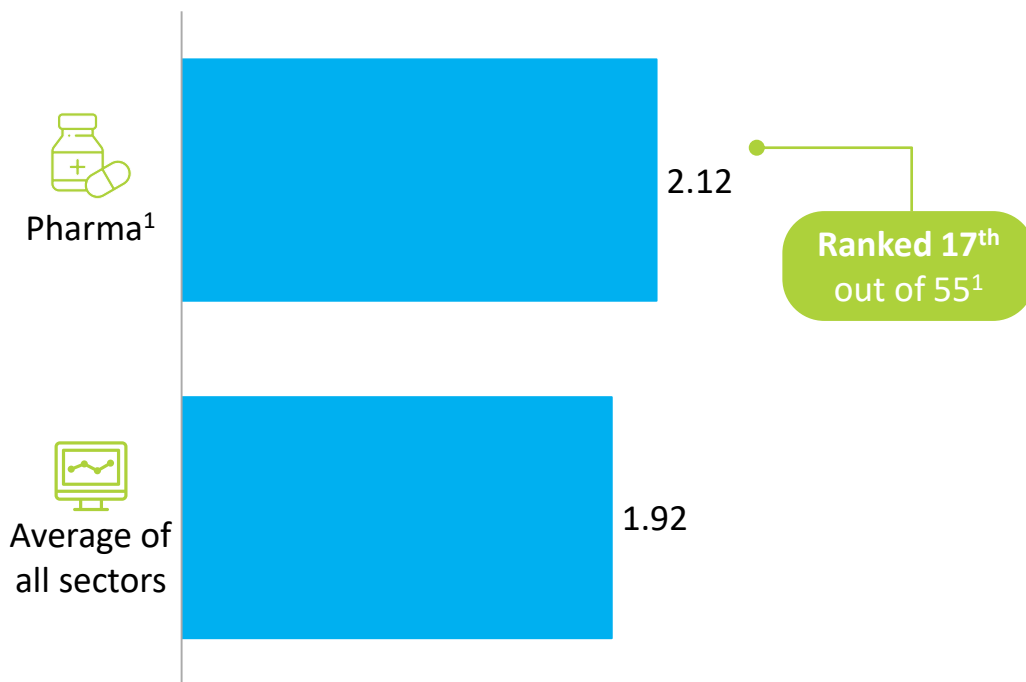
EUR Bn, 2000-2016



- **Pharma added €1.5 Bn more to Portuguese GDP in 2016** than it did in 2000 – enough to cover the entire budget for Science, Education and Technology
- **Pharma's contribution grew slightly faster than the overall economy** (2.7% vs 2.3% p.a.), helping drive growth

C Pharma is a highly productive industry, generating more value relative to input than the average across all industries

Comparison of output to input ratio



- **Pharma overall and pharma manufacturing add more value per input than average of all sectors** – €2.1 and €1.8 of output per euro of input respectively
- **Pharma adds more value and uses knowledge and human talent** to transform commodity chemicals into life-saving medicines
- **Services in general have higher productivity**, since they also incorporate knowledge and talent – but cannot contribute positively to PT trade balance

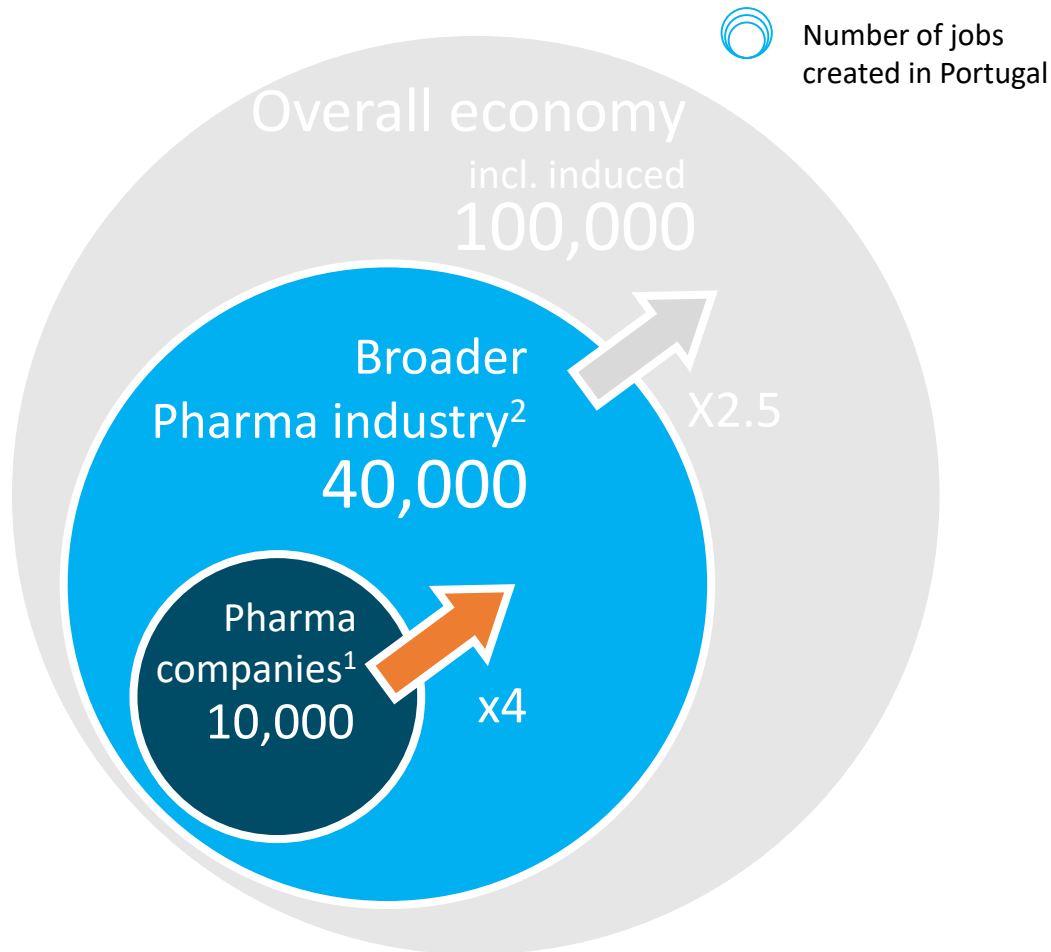
¹ Includes Manufacturing, R&D, Commercial/Retail and Imports

² Ranking of value adding industries by decreasing Output to Input ratio (all industries)

³ Ranking of value adding industries by decreasing Output to Input ratio (manufacturing industries)

SOURCE: World Input-Output Database website (Jul 2018); IHS MARKIT 2016

C Pharma is a job creator in Portugal, employing ~10,000 people directly in Pharma companies and ~40,000 across broader industry value chain



- **~10,000 people employed by Pharma companies**, including innovative and generics companies
- **~40,000 people employed by entire Pharma industry in a broad definition**, including transportation and trade of pharmaceuticals
- **~100,000 total jobs created in overall economy by Pharma**, including suppliers (indirect effect) throughout the value chain and elsewhere, as people in Pharma and value chain boost demand through wages (induced effect)

¹ Estimation based on people employed by Pharma companies associated to Apifarma (8,000) and their market share (80%); includes innovative Pharma companies and generics companies

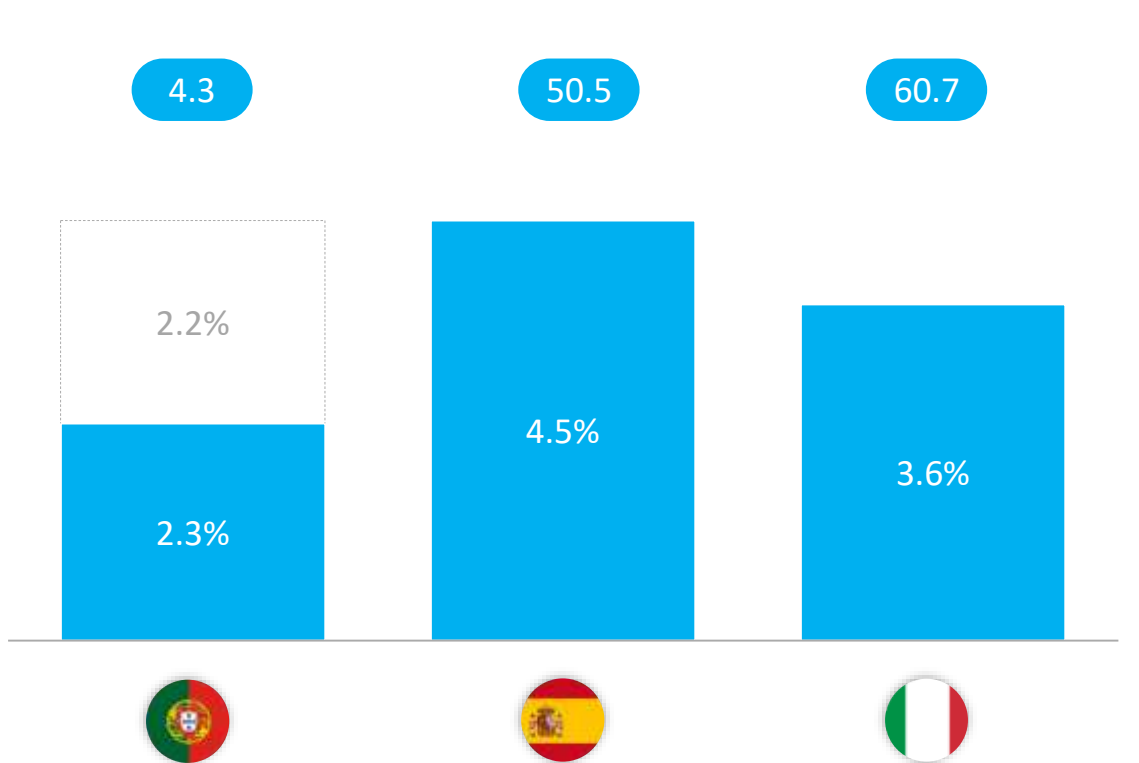
² Includes people employed by Pharma companies and people employed and self-employed in manufacturing, R&D, transportation and trade of pharmaceuticals. For example, clinical trials, researchers in independent pharma labs, wholesalers, truck drivers, logistics personnel, pharmacy technicians and pharmacists

SOURCE: Apifarma, Indústria Farmacêutica em Números (2017); European Federation of Pharmaceutical Industries and Associations, The Pharmaceutical Industry in Figures - Key Data 2017 (2018); World Input-Output Database website (Jul 2018); International Federation of Pharmaceutical Manufacturers and Associations, The Pharmaceutical Industry and Global Health: Facts and Figures 2017 (2017); INE website (Jul 2018)

C Contribution of Pharma to GDP in Portugal lags behind peers; matching pharma in Spain would add extra €4 Bn to GDP

Share of GDP associated with Pharma¹ contribution in Portugal, Spain and Italy

% of GDP



X GDP contribution (EUR Bn)

- Share of GDP associated with Pharma in Portugal is half that of Spain and a third less than Italy
- Pharma industry creates x12 more value in Spain and x14 more value in Italy than in Portugal
- Another 2.2% of GDP (€4 Bn) could be generated with additional investment in Pharma, matching Portugal with neighboring countries

¹ Includes Manufacturing, R&D, Commercial/Retail and Imports)
 SOURCE: World Input-Output Database website (Jul 2018); IHS MARKIT 2016

Contents

1. Introduction

2. Value of medicines in Portugal

3. Opportunities for the future



To further accrue the value of medicines in Portugal, priority areas to focus on are integrated care, access to innovation and attracting investment

Themes

Focus areas

Vision

Innovating in patient care

- a Boosting **prevention and diagnosis**
- b Increasing **integrated patient care**
- c Leveraging **healthcare technology**

- Be ahead of the prevalence curve and capture full value of innovative medicines by **treating earlier, better and smarter**

Accelerating access to innovative medicines

- d **Streamlining and facilitating reimbursement approval**
- e Ensuring sufficient **allocation of budgets and resources**
- f **Establishing outcome-based contracts** for selected diseases

- **Provide best-in-class treatments to patients in a timely manner**, reducing access lead-time to below WE average

Attracting Pharma investment

- g **Targeting R&D** for new modalities and **therapeutic innovation**
- h Becoming **center of excellence for clinical trials innovation**
- i Innovating with **cutting edge manufacturing** (e.g., biologics)
- j Developing expertise **as global pharma services center**

- **€4Bn additional GDP impact by leveraging Portugal's assets** to be recognized as a global center of pharma innovation and services

a Boosting disease prevention and early diagnosis reduces disease burden and allows for the full value of innovative medicines to be captured

High prevalence of risk factors and late diagnosis are driving disease burden

Simple changes can have significant impact in disease prevalence and treatment efficiency

Prevention



DIABETES: 41% more patients in PT than OECD, **+80% of which are overweight or obese**



NSCLC: Smoking is the most important risk factor, and **22% of PT population smokes**

- Promoting **lifestyle changes** in people with modifiable risk factors (e.g. smoking, high salt intake)
- Setting **treatment plans for early manifestations of disease** (e.g. pre-diabetes, colon polyps) to avoid or delay onset
- Providing **basic health education** to empower patients with information on healthier choices

Diagnosis



CRC: Risk of death reduced by 67% with screening, in PT **only 19% of high-risk population is screened**



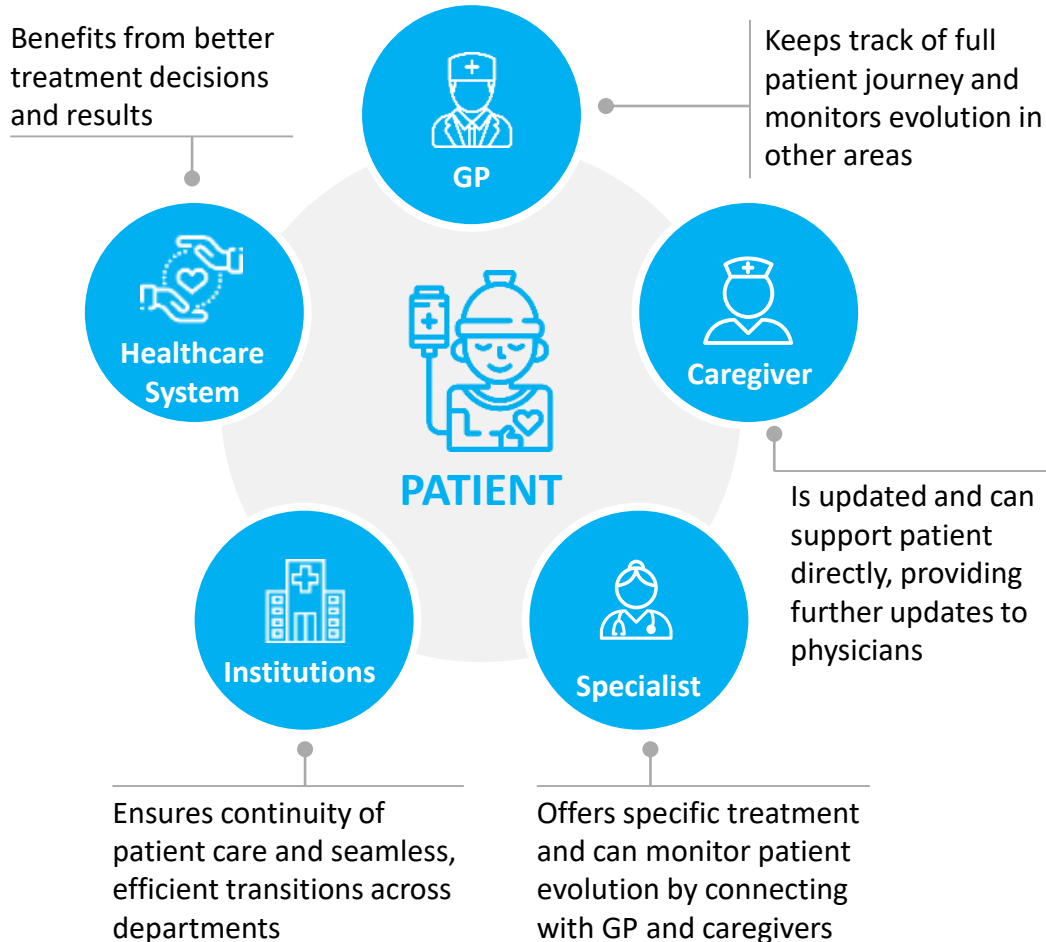
RA: Remission increased by 80% if diagnosed early, in PT **diagnosis on average after 2 years**

- Establishing target **diagnosis and treatment rates** across diseases (e.g. HIV 90-90-90 plan)
- Promoting **early diagnosis campaigns** targeted at high-risk populations (e.g. smokers, family of cancer patients)
- Improve **compliance with existing screenings** by educating patients on the importance of early diagnosis and treatment

SOURCE: Apifarma (2018) "Importância do Diagnóstico Precoce na Artrite Reumatoide"; Martins et al., DAS28, CDAI and SDAI cut-offs do not translate the same information: results from the Rheumatic Diseases Portuguese Register Reuma.pt (2015); OECD, Health at a Glance (2017); Barreto et al., Prevalence, awareness, treatment and control of diabetes in Portugal: Results from the first National Health examination Survey (2018); Global Smoking Prevalence and Cigarette Consumption 1980-2012 (2013); Molina et al. Non-Small Cell Lung Cancer: Epidemiology, Risk Factors, Treatment, and Survivorship; DGS, Programa Nacional para as doenças oncológicas (2017); Doubeni et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study (2018)

b Enabling more efficient integration between patient care touchpoints improves patient well-being and generates better treatment results

The benefits of integrated health care extend to patients, caregivers, providers and the larger health care system



Integration on all levels



Information

Exchanging medical records and prescription information among health professionals



Continuous care

Guiding patient's transitions between primary and specialty care, ensuring treatment compliance and continuation













Medical decision making

Bringing different care providers together to more informed medical decisions based on patient needs and condition

C Healthcare technology can be further leveraged to enable more cost-effective and efficient care while improving patient experience

Examples of how technology can transform patient care and results

	What it looked like in the past	What happens now and in the near future
Diagnosis	 <p>Disease prevention through regular screening</p>	<p>Genetic profile analysis to assess risk of developing disease</p> 
Prescription	 <p>Treatment prescriptions only by consulting in physician's office</p>	<p>Video-consultation and remote interactions for prescription or treatment/dose adjustments</p> 
Treatment	 <p>Standard treatments prescribed to patients with same indications</p>	<p>Personalized treatment catered towards patient's metabolism and biological characteristics</p> 
Delivery	 <p>Patients might need to prepare and administer medicines several times across day and night</p>	<p>Patient can receive medicine continuously through automatic infusion device or patch. Apps monitor body and send reminders</p> 
Monitoring	 <p>Disease monitoring through 6m or yearly doctor appointments and physical exams</p>	<p>Real-time disease monitoring with wearable body sensors (e.g. glucose monitor, heart-rate tracker)</p> 

d Portugal lags behind most EU countries in access to innovative medicines, with patient access taking up to 38 months

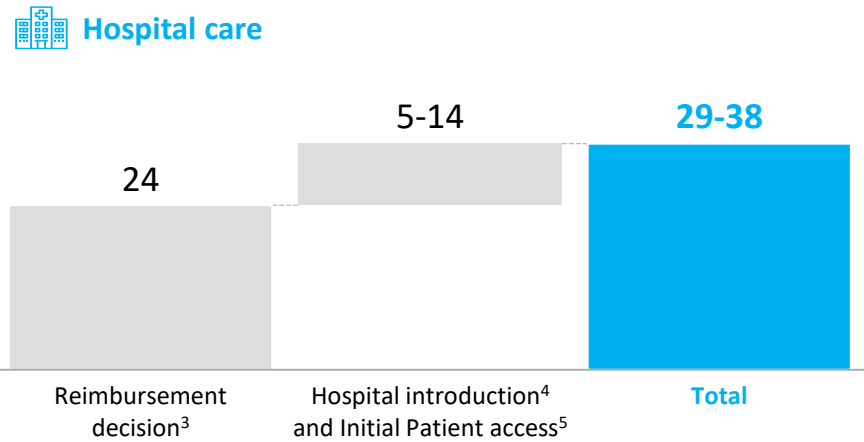
Reimbursement approval for innovative medicines¹ takes 21 months², longest period in Western Europe...



EFPIA's methodology for comparison among countries includes time for process review, stop-clocks and price negotiation plus initial time to request submission²

- **Extended review process and price negotiations** among main causes for prolonged reimbursement approval duration
- **Recently reimbursement decision activity has been improving** with increasing number of dossiers decided

... contributing to significant delays, such as 29-38 months for initial access³ to Hospital medicines



- **Delays in hospital introduction also contribute significantly** to late initial access of innovative medicines
- **Initial access to ambulatory drugs is usually granted at a faster pace**, 21-22 months in total

Earlier access could reduce disease burden in 9%⁴, avoiding 7k DALYs/year valued in €210-280 Mn (8 diseases alone⁵)

1 New active substances and 1st indications only (excluding further indications, generics and biosimilars) methodology, which subtracts initial request submission, stop-clocks and price negotiations

2 Sample of products approved by EMA between 2014–2016. Differs from Informed

3 Initial patient access involves Reimbursement decision, Hospital introduction and Initial Marketing Authorization and request submission); Includes both approvals and refusals by Informed in the 2015–17 interval. Different from Informed methodology, which subtracts time until initial request submission, stop-clocks and price negotiations

4 Average for 50%-100% of relevant hospitals to introduce innovative medicines (medicines with reimbursement approval within Jan 2014 and Mar 2018; based on Hospital introduction questionnaire, n = 8 Pharma companies, 39 medicines). Doesn't include refusals.

5 Average for initial access after reimbursement approval (medicines launched within Jun 2015 and Jun 2017 for Diabetes, COPD & Asthma and CHF); Subsequent adoption follows a linear tendency Doesn't include refusals

SOURCE: EFPIA, Market access delays analysis (2018 & 2017); Apifarma (Jul 2018); Apifarma, Hospital introduction questionnaire (Jul 2018); IMS Database (Jul 2018); GBD Results Tool website (Jun 2018); Informed, O Informed em 2017 (2018); Apifarma, Survey regarding innovative medicines public financing (May 2018); Expert interviews; Team Analysis

d Suggestions on how to overcome delays in access involve combined efforts and close collaboration among key stakeholders



NOT-EXHAUSTIVE

Suggestion on how to overcome delays in access of innovative medicines



Stimulate reflection on current HTA¹ and reimbursement process prioritization and criteria to adopt assessment methodologies that account for new challenges, e.g., segmenting and streamlining reimbursement decisions and negotiations



Promote more efficient end-to-end process, namely in formal introduction of new medicines in hospitals, e.g., by simplifying, reducing bureaucracy and increasing transparency of current process



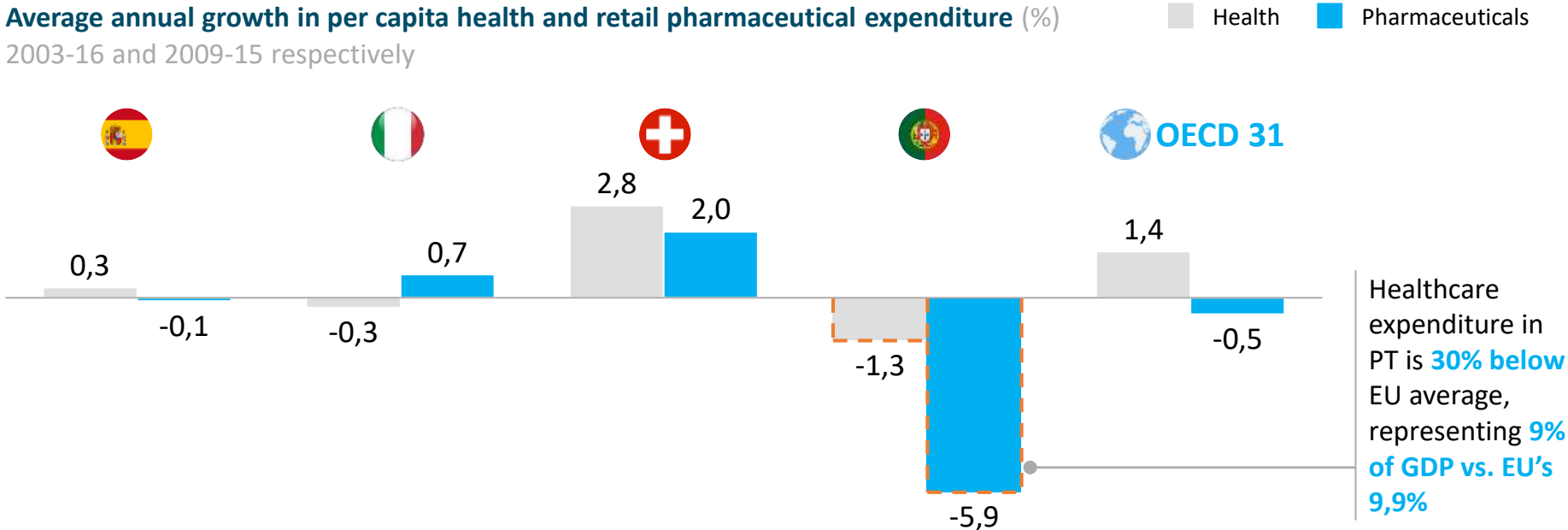
Foster utilization of innovative medicines by further promoting key stakeholders awareness and by eliminating all informal adoption barriers

Accelerating access to innovative medicines can also be promoted by ensuring sufficient budget and resources allocation, and by establishing outcome-based contracts for selected diseases (detailed next)

e Ensuring sufficient allocation of budget and resources to medicines would bring opportunities to improve healthcare

Portuguese investment allocated to healthcare and pharmaceuticals has been decreasing faster than in other countries

Average annual growth in per capita health and retail pharmaceutical expenditure (%) 2003-16 and 2009-15 respectively



Ensuring sufficient budget allocation brings opportunities to improve overall healthcare



Providing patients with faster and easier access to innovative medicines as a result of reduced budget constraints in hospitals and other institutions



Allowing for earlier and broader diagnosis of multiple conditions with widespread use of new diagnosis campaigns, tools and resources



Supporting better treatment for all patients with the adoption of more convenient treatments (e.g. long acting medicines, digital delivery devices)

f Sharing responsibility through outcome-based contracting allows for better and more cost-effective treatment for priority diseases

By establishing outcome-based contracts, companies and hospitals agree on payment and reimbursement plans based on medicine's performance and treatment results

3 steps to start outcome-based contracting in Portugal

1st Collect patient data from electronic health records, local disease registries, pharmacy prescriptions



2nd Analyze treatment results with anonymized, privacy compliant data



3rd Define priority diseases or patient groups to establish first outcome-based contracts



Canadian example

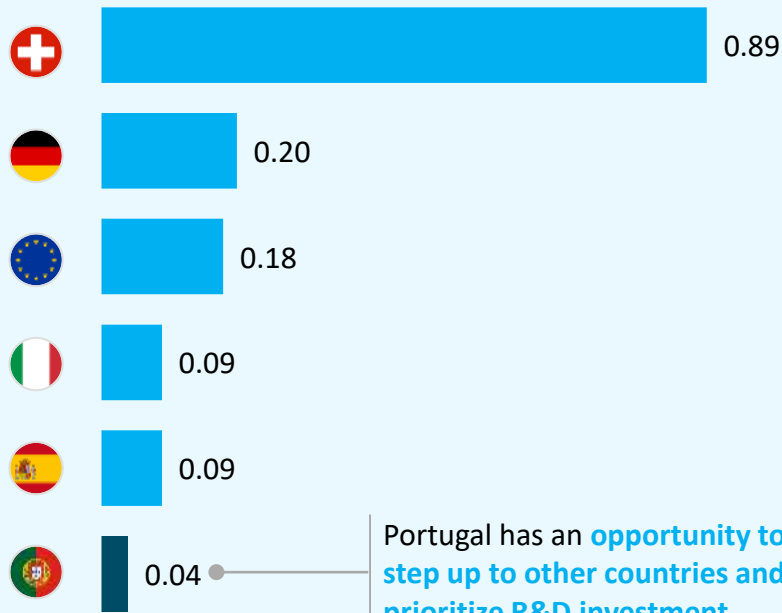
- After setting outcome-based contract, **manufacturer supplies medicines at temporary price**
- Review board evaluates **impact based on treatment results and incidence of adverse reactions**
- **Based on improvement, board sets price ceiling for new drug** by categorizing it into 4 levels, from slight improvement to breakthrough

g Targeted R&D is a strategic area to leverage Portuguese strengths and attract Pharma investment

R&D is a major stepping stone for development and Portugal is not yet playing a relevant role

Pharmaceutical R&D investment

As percentage of GDP, 2015



Within PT Pharma, **R&D has the highest GDP productivity ratio (61%)**, compared to industry average of 51%

Portugal has potential to become a specialized center for pharma R&D



Strong academic participation

Important advances coming from university labs, leveraging cooperation with local hospitals and companies



Skilled labor readily available

124k students graduate with Health or Technology degrees every year



Structured data collection already in place

Near complete adoption of electronic health records and electronic prescription methods

Targeted R&D in Portugal can start by leveraging strengths and focusing on strategic targets



Harnessing power of data analytics

to optimize research (e.g., finding new drug targets, predicting treatment risks, improving existing formulations)



Researching treatment options for **conditions with high prevalence in Portugal** (e.g. Diabetes, HIV)



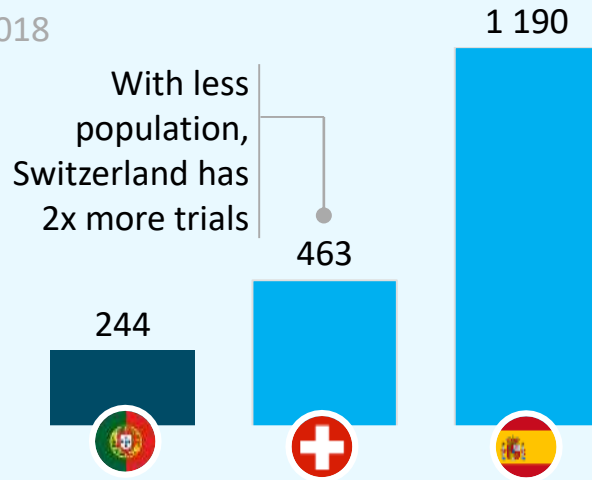
Developing innovative solutions for **future pharma challenges** (e.g. antibiotic resistance, gene therapies)

h Establishing Portugal as a go-to place for clinical trials brings economic opportunity and sets stepping stone for future partnerships

Portugal can embrace potential of clinical trials innovation

Number of active clinical trials

Jul 2018



Investment in clinical trials unlocks valuable social and economical benefits

- Provides early access to innovative medicines to patients participating in trials
- Promotes country development in clinical innovation and scientific research
- Increases presence of international players in Portugal leading to potential future investments



Strict compliance with proprietary law



Concentration of healthcare institutions across small territory



Prevalence of various diseases and favorable setting for recruiting patients



Revision of current legislation to reduce time between submission of trial request and beginning of recruitment, a limiting factor of the activity in Portugal



Improving cooperation between academic, public and private institutions and incentivizing involvement of patients and professionals in clinical trial activity



Developing core capabilities in trial execution and management (e.g., training specialized staff, implementing tools for trial data processing and patient monitoring)

Portuguese strengths to be leveraged

Key steps to become global center of excellence for clinical trials

i Pharmaceutical manufacturing is shifting from pill production to biologics and tech-based products

3D printing – using 3D printing technology to create personalized medical solutions (from prostheses to drugs and human tissue)

Drug eluting implants – active implants that induce medication on top of regular support task (e.g. coronary stents, prosthetics)

Biologics – highly specific medicines synthesized from biological resources (e.g. cells, proteins, antibodies)

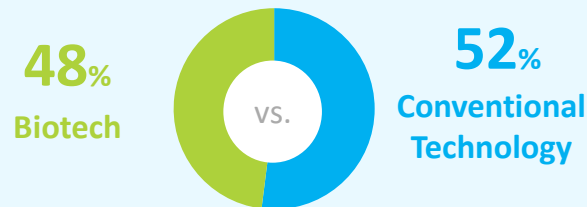
Wearable body sensors – devices implanted in patient to monitor body functions and adjust medication

Extended release devices – capsules or transdermal patches that release medication throughout long periods

Biologics manufacturing is the logical next step in pharma

- Biotech medicines will represent **48%** of the pharmaceutical market volume in 6 years
- **37.8%** of drugs in R&D pipeline are biotech-based and will reach manufacturing soon

Worldwide Pharmaceutical Market
2024 prediction



Portugal can leverage strong presence of healthcare and high-tech

~7.5% of all companies in Portugal directly related with healthcare

€1.8 Bn in Technology services exports in 2017 (15% growth since 2016)

123k jobs in high tech manufacturing and services

Kickstarting biologics manufacturing will require strategic planning



Evaluating future manufacturing potential of different biological segments in R&D pipeline



Prioritizing products that have potential global impact and local availability of knowledge and materials



Building or adapting facilities to meet specialized requirements for cell culture and purification

j Portugal can develop strategies to establish global reputation as the center of excellence for pharmaceutical shared services

Other countries have implemented economic strategies to promote shared services business






Ireland – promotes corporate relocation with diverse financial incentives

- Low corporate tax rate at 12.5%
- Effective zero tax for foreign dividends
- 73 established bilateral tax treaties

Poland – attracts shared services by offering incentives in different stages of development

- Grants and tax exemption during investment phase
- Funding for staff training and purchasing and implementing new technologies

Portugal has competitive advantages that make it a relevant potential player

-  Highly educated workforce
-  Proficiency in multiple languages
-  Proximity to European high-demand centers and use of GMT time zone
-  Stable economy, low risk political scenario
-  Favorable labor costs

Attracting investment in Portugal requires developing strategic incentives



- Offering deals to pilot with pioneer corporations establishing first shared services offices in PT (e.g. financing location, funding staff training)
- Creating **financial incentives** for companies that transfer shared services to Portugal (e.g. tax incentives, grants)
- Establishing long term deals for **gradual transition of entire corporate internal processes**, starting with one function or department

