Pharmaceutical innovation: impact on expenditure and outcomes and subsequent challenges for pharmaceutical policy, with a special reference to Greece

Karampli E[1,2], Souliotis K[3], Polyzos N[4], Kyriopoulos J[1], Chatzaki E[2]

[1]Department of Health Economics, National School of Public Health, Athens

[2]Medical School, Democritus University of Thrace, Alexandroupolis

[3]Faculty of Social Sciences, University of Peloponnese, Corinth

[4]Department of Social Administration, Democritus University of Thrace, Komotini

Greece

Abstract

Over the recent decades, advances in healthcare technology have led to significant improvements in the quality of healthcare and in population health. At the same time, technological change in healthcare, rising national income and expansion of insurance coverage have been acknowledged as the main determinants of the historical growth in health spending in industrialized countries. The pharmaceutical sector is of particular interest as it constitutes a market characterized by rapid technological change and high expenditure growth rates. The purpose of this article is to provide an overview of research findings on the impact of pharmaceutical innovation on pharmaceutical expenditure growth, total health expenditure and population health outcomes and to bring forward the challenges that arise for pharmaceutical policy in Greece. Hippokratia 2014; 18 (2):100-106.

Key words: Pharmaceutical technology, innovation diffusion, drug costs, pharmaceutical economics, Greece

Corresponding author: Eleftheria Karampli, MSc, Department of Health Economics, National School of Public Health, 196 Alexandras Ave., 115 21 Athens, Greece, tel: +302132010245, fax: +302106449571, e-mail: ekarabli@esdy.edu.gr

Introduction

Advances in healthcare technology have led to significant improvements in the quality of healthcare and in population health and, in parallel, have contributed to increases in real health expenditure in most industrialized countries over the recent decades[1]. The term health technology refers to products such as pharmaceuticals or medical devices, new techniques (for example surgical interventions) as well as systems of organizing healthcare provision[2]. Technological advances in the healthcare industry, rising national income and expansion of insurance coverage have been acknowledged as the main determinants of the historical growth in health spending. Other determinants of health expenditure growth include demographic factors (population growth and aging) and medical prices inflation[3-5].

The pharmaceutical sector is of particular interest as it constitutes a market characterized by rapid technological change and high expenditure growth rates[6]. The purpose of this article is to provide an overview of research findings on the impact of pharmaceutical innovation on pharmaceutical expenditure growth, total health expenditure and population health outcomes and to bring forward the challenges that arise for pharmaceutical policy in Greece. Innovation is defined as "*the technological progress that leads to the creation of an entirely new product or a reduction in the cost of producing or an increase in the therapeutic value of an existing product*"[7]. Pharmaceutical innovation therefore can be seen to include new chemical entities; new formulations; new combinations and new indications for existing products[7]. Although there is controversy on what constitutes innovation in pharmacotherapy[8,9], for the purposes of the present paper, the terms pharmaceutical innovation/pharmaceutical technology correspond to the more generic definition.

The impact of pharmaceutical innovation on pharmaceutical expenditure

Real pharmaceutical expenditure (expenditure adjusted for the effect of inflation) has been increasing at an annual average rate of 5.0% between 1980 and 2005 in the Organization for Economic Cooperation and Development (OECD) countries, a rate higher than the growth rate of all other health expenditure components combined and that of Gross Domestic Product (GDP)[10]. The recent economic crisis and subsequent public expenditure cuts in many OECD countries have slowed the rate of real heath expenditure growth; pharmaceutical expenditure has been decreased as it has been identified as one of the main areas of public spending cuts[11]. There is considerable uncertain-

ty about the magnitude of future health spending growth rates[12,13]. According to a recent OECD publication[14], public spending on health is projected to continue to rise over the next 50 years in OECD countries under either a cost-containment or a cost-pressure scenario.

It is therefore important to understand which factors affect expenditure growth and the extent to which these are amenable to policy. The present paper focuses on pharmaceutical expenditure. The methodological approach adopted in most studies investigating the determinants of pharmaceutical expenditure growth is the decomposition of growth in real pharmaceutical spending into changes in three components: quantity of pharmaceuticals prescribed (measured in Defined Daily Doses-DDDs), prices (using the pharmaceutical price index – PPI) and prescribing choices/therapeutic mix. The latter captures the change in mean price per DDD that results from changes in drug treatment patterns within therapeutic categories and classes of drugs. A negative change in this component indicates a shift on average towards prescribing of less expensive pharmaceuticals and vice versa[15,16]. A summary of study results is presented in Table 1. Although there is variability in the characteristics of the pharmaceutical markets and the study timeframe, researchers conclude that prescribing choices and increases in volume of consumption are the main contributors to the observed increase in real spending for pharmaceuticals[15-21].

With the exception of one study, all studies concluded that the prices of pharmaceuticals (as captured by the price index) decreased during the study period. This relates to the regulation of the pharmaceutical market in these countries[22]. In health systems with statutory price control pharmaceutical prices decrease overtime as a result of policy measures that determine ex-factory prices (e.g. price cuts and reviews, rebates, etc.) as well as wholesaler and pharmacy profit mark-ups[10]. A change in these components will be reflected in the PPI.

Depending on the time period and the country, real pharmaceutical expenditure increased by 9%-119% whereas the change in the prescribing choices component ranged from 4.8% to 67%. In all countries, the quantity of pharmaceuticals consumed increased overtime by 10% to 41% (Table 1). The notable exception is that of Sudan: the largest contributor to pharmaceutical expenditure growth was the increase in the quantity component by 91%, whereas the prescribing choices component decreased by 18.44%. According to Mousnad et al[21] the considerable increase in consumption volume was a result of the increased demand for pharmaceuticals caused by the insurance reform that was implemented in the country. Furthermore, Mousnad et al[21] note that the relative prices for pharmaceuticals increased due to an increase in prices of essential goods owing to the global economic crisis as well as tax increases. The therapeutic mix component, according to the researchers, reflects a shift towards locally produced generics. The researchers also report that since 2007 no new products were introduced in the pharmaceutical market in Sudan[21]. Since prescribing could not be shifted towards more expensive medications, the effect of increased generic prescribing was the dominant driver.

Analysis of patient-specific prescription data in British Columbia, Canada provides a more detailed picture of the underlying dynamics in pharmaceutical expenditure growth[23]. Between 1996 and 2002, real pharmaceutical expenditure per capita increased by 11.6% annually on

Table 1: Percentage change in real pharmaceutical expenditure and its components in selected countries.

Country	Sweden	Sweden	Italy	Taiwan	China	Greece	Sudan
Type of expenditure in the analysis	Outpatient	Inpatient and outpatient		prescription drugs	Inpatient*	inpatient and outpatient	inpatient and outpatient†
Period of study	1990-1995	1990-2000	2000-2001	1997-2001	2003-2007	2000-2004	2006–2010
Authors	Gerdham et al. 1998[15]	Gerdham and Lundin 2004[17]	Addis and Magrini 2002[16]	Hsieh and Sloan 2008[18]	Wu et al. 2013[19]	Lambrelli and O'Donnell[20]	Mousnad et al. 2013[21]
Real pharmaceutical expenditure‡	50%	119%	13.5%	56%	9%	39.5%	66.3%
Price component‡	-9%	-7%	-1%	-18%	-33%	-10%	6.7%
Quantity component ‡ (DDDs)§	27%	41%	9.5%	20%	10%	31%	91.0%
Prescribing choices component‡	30%	67%	4.8%	59%	48%	18%	-18.4%

* anti-infective drugs, † medicine expenditure of the National Health Insurance Fund, ‡% change, §DDDs: Defined Daily Doses.

average. Population aging *per se* explained 0.9% of the annual change. This is in line with findings regarding the effect of population aging on total health expenditure growth[24,25]. The factors explaining most of the growth in pharmaceutical spending were treatment substitution (across and within drug classes) (6%), poly-therapy (increases in the number of therapeutic categories from which patients receive concomitant treatment) (4.5%) and the increase in exposure to pharmacotherapy (the percentage of the population that is treated with drugs) (1.1%). Lower drug prices and increased use of generics had a negative impact on pharmaceutical spending growth[23]. Variations in trends were observed between different age-groups and therapeutic categories of drugs in the Canadian study[23].

In the case of lipid-lowering drugs, antihypertensive treatment and antidepressants, the dominant driver of increased spending was the increase in exposure to these therapies. Increases in exposure were more pronounced in the 45-64 age-group for antihypertensives and in those over 85 years of age for lipid-lowering drugs. Regarding therapeutic choices, increases in per capita drug spending were driven mostly by a shift in prescribing towards newer therapeutic drug classes in the case of antihypertensives (from b-blockers and diuretics, towards angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers). For antidepressants, prescribing of more expensive drugs both across and within antidepressant drug classes was observed. By contrast, treatment choices were the major driver of the increase in spending on antacids during the study period. Although there was an increase in the level of exposure to antacid treatment, increased prescribing of proton pump inhibitors was the most important driver in all age-groups.

In summary, despite differences in methodology, country setting or study period there is consistency in findings regarding the significant contribution of volume of consumption and changes in treatment patterns on pharmaceutical expenditure growth during the last decades. Where more detailed analysis was performed, increases in the consumption of pharmaceuticals were found to have been driven by a higher proportion of the population receiving pharmacotherapy and poly-therapy.

These trends are the result of the interaction of a multiplicity of factors that may or may not be amenable to policy. Factors that impact the level and mix of pharmaceutical consumption include –but are not limited to– population demographics and health needs, advances in medical knowledge, access to treatment and doctor-patient preferences[17,23,26]. Lipid lowering drugs, antihypertensives, anti-diabetic medications and hormone replacement therapy are examples of drug classes in which these factors were the predominant cost drivers[17,27-29]. Healthcare system reforms also play an important role. Evidence from the US point to the significant effect of insurance. In particular, according to the literature, expanding insurance coverage in the US to include pharmaceuticals contributed to increased pharmaceutical consumption and spending[30,31], a finding that was also reported by Mousnad et al[21] for Sudan. On the other hand, changes in treatment patterns may reflect a shift in prescribing between drug classes of the same therapeutic category and/or a substitution effect between drugs in the same drug class. As Morgan[23] notes, even though in the former case policy intervention may not be required or need be limited to prescribing guidelines, in the latter case policies such as reference pricing or generic substitution have the potential to modify this components' impact on expenditure growth.

The introduction of new pharmaceutical technology impacts pharmaceutical expenditure growth by affecting both the volume and the therapeutic choice components of expenditure. The underlying mechanisms can be described using the framework proposed by Cutler and McCellan[32]. The researchers theorized that new medical technology affects healthcare costs in two ways: by replacing available technology in a group of people (treatment substitution effect) and by making the treatment of more people possible (treatment expansion effect). In the case of pharmaceuticals, the substitution effect is observed when newer agents replace already available ones in the treatment of a given population already receiving pharmacotherapy for a specific condition. The expansion effect takes place when the new pharmaceutical technology makes treatment of more patients possible; for example when a novel agent that covers an unmet need or substitutes other forms of care (e.g. H2 antagonists replaced surgery for stomach ulcer) is introduced or by lowering the treatment threshold[18,33]. In the aforementioned studies both increases in the number of patients treated with medicines (increase in exposure) and changes in therapeutic mix (either across or within drug classes) were among the major contributors to increases in drug spending. As Serra-Sastre and McGuire point out[6], because newly marketed pharmaceuticals are introduced into the market under a price premium, advanced pharmaceutical technology increases pharmaceutical spending also through its impact on unit price.

The effect of pharmaceutical innovation on total health expenditure and population health outcomes

As confirmed by the findings of the previous discussion, new pharmaceutical technology has been a major driver of pharmaceutical expenditure growth. The question that consequently arises refers to its benefits (if any) and the extent to which these justify the additional cost. A growing body of literature attempts to identify and quantify the benefits of new medications. Benefits are more difficult to quantify than costs and may include better quality of pharmacotherapy (higher efficacy, fewer side-effects, ease of administration etc), improvements in health outcomes (reduced mortality and morbidity, improved quality-of-life and work-force productivity), as well as cost-savings in healthcare expenditure[18]. The latter is known as the "new drug cost-offset theory"[34].

Research findings on the effects of newer drugs on

health spending are conflicting. Lichtenberg[35,36] analyzed data from the 1996 Medical Expenditure Panel Survey (MEPS) in the US and concluded that, controlling for patient characteristics and conditions, patients that were prescribed newer drugs for a given condition had fewer hospitalizations, shorter length of stay in the hospital and lower total non-drug (hospital, emergency room, outpatient, office-based, dental,home health) medical expenditures associated with that condition. Drug vintage was calculated using the number of years since the active ingredient was first approved by the Food and Drug Administration (FDA)[35]. Although Zhang and Sumerai[37] consider that the cost-reducing effects in Lichtenberg's analyses are overstated, another study adopting the same definition of drug novelty but US State level panel data[38] supports the existence of a cost-offsetting effect at the State level. As however their findings refer to the effects of newer drugs across individuals and across diseases, the researchers[38] note that significant heterogeneity across disease categories and drug classes might be present.

Other studies have focused on the effects of selected drugs and/or drug classes. Karaca and Wiggins[39] analyze MEPS data based on the methodology proposed by Lichtenberg[35], but adopt a different criterion of drug novelty and limit their analysis on selected drug classes that are acknowledged as "break-through" in clinical practice (they constitute "*a novel approach to therapy or a unique mode of action*"). In specific, they investigate the impact of selective serotonin reuptake inhibitors (SSRIs), statins, angiotensin-converting-enzyme (ACE) inhibitors, H2 antagonists, proton pump inhibitors (PPIs), calcium channel blockers, and fluoroquinolones on individuals' drug and non-drug expenditures for selected conditions from 1996 to 2001. Their results suggest that pharmaceuticals substitute other forms of care. For all drug classes but ACE inhibitors, per capita drug expenditure for regular users of each class of new drugs increased; but the increase was off-set by significant reductions in total non-drug expenditures in all break-through drug classes but fluoroquinolones. Similar conclusions are reported on highly active antiretroviral therapy (HAART)[40].

On the other hand, there are studies that do not confirm the cost-offset hypothesis. This is the case for antidiabetic agents in Taiwan[41] and newer therapies for colorectal cancer in the US[42]. In both studies, diffusion of newer drugs increased drug outpatient spending mainly through the effect of treatment substitution. Utilization of these drugs did not result in reduced demand for other types of medical care during the study period (1 year); hence, adoption of pharmaceutical innovation was expenditure-increasing in the short-term. It must be noted that the studies discussed so far explore the effect of newly marketed drugs on non-drug health expenditure, as this is the focus of the present paper. The substitutability between pharmaceutical care in general (which would include all drugs) and other types of care is not in the scope of our analysis.

Research on the effect of pharmaceuticals on health outcomes is dominated by F. Lichtenberg's work. In most of his studies, Lichtenberg evaluated the impact of new pharmaceutical technology on longevity[43,44], quality of life[45] and work productivity[35]. Defining drug novelty as described above, his findings suggest that utilization of new active substances had a positive effect on patient health outcomes.

With regards to the impact of specific drugs and/or drug classes on health outcomes, newer antiretroviral therapy, new cancer drugs (e.g. for breast and colorectal cancer), statins, pharmaceutical treatment for acute myocardial infarction, new asthma medications and newer orphan medications are examples of pharmaceutical technologies which significantly contributed to improved health outcomes in patients suffering from the related conditions[33,46-50]. Furthermore, new pharmaceutical technologies such as influenza vaccines, migraine medications and newer antipsychotic agents have been linked to improved economic outcomes (increased productivity and higher employment rates)[33].

Implications for pharmaceutical policy: a balance act?

The research findings discussed in the previous paragraphs bring forward the challenges faced by policy-makers internationally in an effort to contain costs while ensuring patient access to valued pharmaceutical innovation. Furthermore, current decisions regarding pharmaceutical innovations (reimbursement, prices) are among the policy variables that influence future R&D investments[10]. Biologic drugs as well as personalized treatments which target chronic, debilitating or life-threatening conditions are illustrative examples of the challenges faced by pricing and reimbursement authorities and the pharmaceutical industry.

Several policy measures have been introduced with the purpose of addressing these challenges such as Health Technology Assessment (HTA), product-specific pricing agreements for high-cost pharmaceuticals or performance-based schemes[51]. HTA is a multidisciplinary process in which various aspects of a new health technology and its impact on the health system and society in general (ethical issues, economic and organizational implications etc.) are assessed[1]. In pharmaceuticals, HTA is used to inform decisions on pricing, reimbursement and the development of prescribing guidelines[52]. It is also considered that HTA can provide incentives to the manufacturers for the development of new technologies that are of value to the health system[10]. In pricing agreements, the unit price of a specific product is linked to its "value" in terms of health gains or to its volume of consumption[10]. Performance-based schemes (risk-sharing agreements, coverage with evidence development, etc.) are put in place when available clinical evidence is insufficient to inform a decision on a new pharmaceutical[53]. In this case, regulators aim to minimize risk and, at the same time, ensure patient access. Coverage is restricted to specified patient populations and is provided with the obligation to develop new evidence[10,53].

The introduction of the aforementioned policy measures as part of a comprehensive pharmaceutical policy, as well as exploitation of international experience is important for Greece. During the previous years, pharmaceutical expenditure growth in Greece was driven by increases in quantity of drugs prescribed and treatment substitution[20]. Lambrelli and O'Donell[20] analyze OECD data on pharmaceutical expenditure and consumption for the period from 2000 to 2004 and conclude that the increase in real pharmaceutical expenditure during this period can be attributed primarily to increases in volume of prescribed pharmaceuticals and secondarily to the effect of treatment substitution (Table 1). However, they note that OECD data may overestimate the effect of the quantity component as they include parallel exports of pharmaceuticals. Using prescription data from the main health insurance fund (IKA) and for the period 1991-2006, Lambrelli and O'Donell find a significant effect of the prescribing choices component and a smaller effect of the quantity component on pharmaceutical expenditure increase[20]. It can therefore be concluded, that pharmaceutical expenditure growth in Greece follows the pattern observed in other developed countries with increases in the volume of consumption and changes in therapeutic mix being the determinants of growth. The trends observed in the Greek market can be attributed to the introduction in clinical practice of a large number of new pharmaceuticals that were considered important innovations by physicians[20,54], as well as the lack of measures to promote cost-effective use of pharmaceuticals (such as prescription guidelines), promotion of generics and management of the diffusion of new drugs[20,55,56]. As was discussed earlier, new pharmaceutical technology impacts expenditure growth through both the expansion and the substitution effect. In parallel, pharmaceutical innovation contributes to improved patient health outcomes. A recent study by Lichtenberg[57] provides an estimation of the benefits related to the introduction and use of pharmaceutical innovation in Greece. Lichtenberg[57] assessed the impact of pharmaceutical innovation (measured by drug vintage) on the 2000-2009 longevity change in 30 developing and high-income countries. He concludes that, controlling for other determinants of longevity change, 73% of the population-weighted mean increase in life expectancy at birth in these countries can be attributed to the change in vintage of pharmaceuticals sold (increase in the percentage of drugs sold that corresponds to those marketed after 1990)[57]. Greece was among the top 5 countries in drug vintage (measured as the quantity-weighted-mean fraction of drugs sold in 2009 that were marketed after 1990). Comparing the top five and the bottom five countries in drug vintage, Lichtenberg attributes 37% of the difference in life expectancy at birth (9.1 years) between the two country groups to the differences in the vintage of drugs consumed in their markets[57].

The conditions created by the economic crisis and the requirement to contain public pharmaceutical expenditure growth, intensify the problems faced by policy-makers in Greece. The introduction of measures to promote efficiency in pharmaceutical expenditure and ensure patient access to pharmacotherapy is considered imperative[55,58]. Regarding newly marketed pharmaceuticals, institutionalization of HTA, introduction of novel pricing schemes, development of patients' registries which would facilitate monitoring and forecasting of consumption as well as further diffusion of prescribing guidelines in clinical practice can contribute to the aforementioned goals. Given that the adoption and rate of diffusion of new pharmaceuticals in clinical practice affect both pharmaceutical expenditure through the substitution and expansion channels and patients'access to innovative drugs[59], research on the determinants of pharmaceutical innovation diffusion in Greece can inform the development of policies promoting optimum technology diffusion and use.

Conflict of Interest
Authors declare no conflict of interest.

References
1. Sorenson C, Drummond M, Kanavos P. Ensuring value for money in health care. The role of health technology assessment in the European Union, European Observatory on Health Systems and Policies, Copenhagen, 2008, 3-4.
2. Facey K. INAHTA Health Technology Assessment (HTA) Glossary [Internet]. Topfer L, Chan L(eds), INAHTA Secretariat, Cologne, DE, 2006. Available from: http://www.inahta.net/Glossary/, last accessed 2012 Nov 1.
3. Przywara B, Projecting future health care expenditure at European level: drivers, methodology and main results [Internet], European Commission, Brussels, 2010. Available from: http://ec.europa.eu/economy_finance/publications/economic_paper/2010/pdf/ecp417_en.pdf, last accessed 2013 Feb 24.
4. Smith S, Heffler SK, Freeland MS. The Impact of Technological Change on Health Care Cost Spending: An Evaluation of the Literature [Internet], Health Care Financing Administration, Centers for Medicare and Medicaid Services, Baltimore, MD,2000. Available from: http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/tech_2000_0810.pdf, last accessed 2012 Feb 21.
5. Karampli E, Chatzaki E, Polyzos N, Souliotis K, Kyriopoulos J. Determinants of health expenditure growth in developed countries. Iatriki. 2013; 102: 281-289.
6. Serra-Sastre V, McGuire A, Diffusion of health technologies: evidence from the pharmaceutical sector. Joan C-F, Courbage C, McGuire A (eds),The Economics of New Technologies: incentives, organization, and financing, Oxford University Press, New York, 2009, 53-74.
7. Charles River Associates, Innovation in the pharmaceutical sector. A study undertaken for the European Commission [Internet], European Commission, Directorate General Health & Consumers, Brussels, 2004. Available from: http://ec.europa.eu/health/files/pharmacos/docs/doc2004/nov/eu_pharma_innovation_25-11-04_en.pdf, last accessed 2014 Jan 14.
8. Morgan S, Lopert R, Greyson D. Toward a definition of pharmaceutical innovation. Open Med. 2008; 2: e4–e7.

9. Motola D, De Ponti F, Poluzzi E, Martini N, Rossi P, Silvani MC, et al. An update on the first decade of the European centralized procedure: how many innovative drugs? Br J ClinPharmacol. 2006; 62: 610-616.

10. OECD, Pharmaceutical Pricing Policies in a Global Market, OECD Publishing, Paris, 2008, 29.

11. OECD, Health spending continues to stagnate, says OECD [Internet], Organisation for Economic Co-operation and Development, Paris, 2013. Available from: http://www.oecd.org/els/health-systems/health-spending-continues-to-stagnate-says-oecd.htm, last accessed 2013 Jun 30.

12. Ryu AJ, Gibson TB, McKellar MR, Chernew ME. The slowdown in health care spending in 2009-11 reflected factors other than the weak economy and thus may persist. Health Aff (Millwood). 2013; 32: 835-840.

13. Kaiser Family Foundation. Assessing the Effects of the Economy on the Recent Slowdown in Health Spending [Internet], Kaiser Family Foundation, Menlo Park, CA, 2013. Available from: http://kff.org/health-costs/issue-brief/assessing-the-effects-of-the-economy-on-the-recent-slowdown-in-health-spending-2/, last accessed 2013 Aug 31.

14. de la Maisonneuve C, Oliveira Martins J, Public spending on health and long-term care: a new set of projections [Internet], OECD Publishing, Paris, 2013. Available from: http://www.oecd.org/eco/growth/Health%20FINAL.pdf, last accessed 2013 Aug 31.

15. Gerdtham UG, Johannesson M, Gunnarsson B, Marcusson M, Henriksson F. The effect of changes in treatment patterns on drug expenditure. Pharmacoeconomics. 1998; 13: 127-134.

16. Addis A, Magrini N. New approaches to analysing prescription data and to transfer pharmacoepidemiological and evidence-based reports to prescribers. Pharmacoepidemiol Drug Saf. 2002; 11: 721-726.

17. Gerdtham UG, Lundin D. Why did drug spending increase during the 1990s? A decomposition based on Swedish data. Pharmacoeconomics. 2004; 22: 29-42.

18. Hsieh CR, Sloan FA. Adoption of pharmaceutical innovation and the growth of drug expenditure in Taiwan: is it cost effective? Value Health. 2008; 11: 334-344.

19. Wu J, Yue N, Xu W. Increasing Anti-Infective Drug Expenditure in Tianjin, China: A Decomposition Analysis. Value Health Regional Issues. 2013; 2:37-42.

20. Lambrelli D, O'Donnell O. The impotence of price controls: failed attempts to constrain pharmaceutical expenditures in Greece. Health Policy. 2011; 101: 162-171.

21. Mousnad MA, Shafie AA, Mohamed Ibrahim MI. Determination of the main factors contributing to increases in medicine expenditures for the National Health Insurance Fund in Sudan. J Pharm HealthServ Res. 2013; 4: 159-164.

22. Mossialos E, Mrazek MF, Walley T (eds). Regulating Pharmaceuticals In Europe: Striving For Efficiency, Equity, And Quality, Open University Press, Berkshire, 2004, 12.

23. Morgan SG. Booming prescription drug expenditure: apopulation-based analysis of age dynamics. Med Care. 2005; 43: 996-1008.

24. Reinhardt UE. Does the aging of the population really drive the demand for health care? Health Aff (Millwood). 2003; 22: 27-39.

25. Busse R, van Ginneken E, Normand C, Re-examining the cost pressures on health systems, Figueras J, McKee M (eds), Health Systems, Health, Wealth and Societal Well-being: Assessing the case for investing in health systems, Open University Press, Berkshire, 2012, 37-60.

26. Morgan SG, The determinants of prescription drug expenditure…and what to do about them [Internet], University of British Columbia, Centre for Health Services and Policy Research, Vancouver, BC, 2008. Available from: http://amcp.org/WorkArea/DownloadAsset.aspx?id=13234, last accessed 2013 Mar 3.

27. Teixeira IJ, Escoval A, Schiappa M. Lipid-lowering drugs: use and expenditure in Portugal (1995-2004). Rev Port Cardiol. 2007; 26: 475-493.

28. Jackevicius CA, Cox JL, Carreon D, Tu JV, Rinfret S, So D, et al. Canadian Cardiovascular Outcomes Research Team. Long-term trends in use of and expenditures for cardiovascular medications in Canada. CMAJ. 2009; 181: E19-E28.

29. Dubois RW, Chawla AJ, Neslusan CA, Smith MW, Wade S. Explaining drug spending trends: does perception match reality? Health Aff (Millwood). 2000; 19: 231-239.

30. Danzon PM, Pauly MV. Health Insurance and the Growth in Pharmaceutical Expenditures. J Law Econ. 2002; 45: 587-613.

31. Zhang Y, Donohue JM, Lave JR, O'Donnell G, Newhouse JP. The effect of Medicare Part D on drug and medical spending. N Engl J Med. 2009; 361: 52-61.

32. Cutler DM, McClellan M. Is technological change in medicine worth it? Health Aff (Millwood). 2001; 20: 11-29.

33. Productivity Commission (AU), Impacts of Advances in Medical Technology in Australia [Internet], Commonwealth of Australia, Melbourne, 2005. Available from: http://www.pc.gov.au/__data/assets/pdf_file/0003/17193/medicaltechnology.pdf, last accessed 2013 Feb 10.

34. Santerre RE. National and International Tests of the New Drug Cost Offset Theory. South Econ J. 2011; 77: 1033-1043.

35. Lichtenberg FR. Are the benefits of newer drugs worth their cost? Evidence from the 1996 MEPS. Health Aff (Millwood). 2001; 20: 241-251.

36. Lichtenberg FR. Benefits and costs of new drugs: an update, National Bureau of Economic Research, Cambridge, MA, 2002. Available from: http://www.nber.org/papers/w8996, last accessed 2013 Feb 10.

37. Zhang Y, Soumerai SB. Do newer prescription drugs pay for themselves? A reassessment of the evidence. Health Aff (Millwood). 2007; 26: 880-886.

38. Civan A, Köksal B. The effect of newer drugs on health spending: do they really increase the costs? Health Econ. 2010; 19:581-595.

39. Karaca Z, Wiggins SN. The Impacts of Break-Through Drug Classes on Total Health Expenditures: Empirical Evidence from the 1996-2001 Medical Expenditure Panel Surveys, Social Science Research Network, Rochester, NY, 2006 . Available from http://ssrn.com/abstract=947603, last accessed 2013 Feb 10.

40. Bozzette SA, Joyce G, McCaffrey DF, Leibowitz AA, Morton SC, Berry SH, et al. HIV Cost and Services Utilization Study Consortium. Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. N Engl J Med. 2001; 344: 817-823.

41. Liu YM, Hsieh CR. New drugs and the growth of health expenditure: evidence from diabetic patients in Taiwan. Health Econ. 2012; 21: 496-513.

42. Karaca-Mandic P, McCullough JS, Siddiqui MA, Van Houten H, Shah ND. Impact of new drugs and biologics on colorectal cancer treatment and costs. J OncolPract. 2011; 7: e30s- e37s.

43. Lichtenberg FR. Sources of U.S. longevity increase, 1960-1997,National Bureau of Economic Research, Cambridge, MA, 2002. Available from: http://www.nber.org/papers/w8755, last accessed 2013 Feb 10.

44. Lichtenberg FR, Duflos G. Pharmaceutical innovation and the longevity of Australians: a first look, National Bureau of Economic Research, Cambridge, MA, 2008. Available from: http://www.nber.org/papers/w14009, last accessed 2013 Feb 10.

45. Lichtenberg FR, Virabhak S. Pharmaceutical-embodied technical progress, longevity, and quality of life: drugs as 'Equipment for Your Health'. Manage Decis Econ. 2007; 28: 371-392.

46. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998; 338: 853-860.

47. Lichtenberg FR. The effect of new drug approvals on HIV mortality in the US, 1987-1998. Econ Hum Biol. 2003; 1: 259-266.

48. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer. 2008; 44: 1345-1389.

49. Mestre-Ferrandiz J, Garau M, O'Neill P, Sussex J. Assessment of the Impact of Orphan Medicinal Products on the European Economy and Society [Internet], Office of Health Economics, London, 2010. Available from:http://www.europabio.org/sites/default/files/report/assessment_of_the_impact_of_orphan_medicinal_products.pdf, last accessed 2013 Oct 5.

50. Lichtenberg FR. The impact of new (orphan) drug approvals on premature mortality from rare diseases in the United States and France, 1999-2007. Eur J Health Econ. 2013; 14:41-56.

51. OECD. Value for money in health spending. OECD Publishing, Paris, 2010, 167-173.

52. Karampli E, Athanasakis K, Kyriopoulos J. Pharmacoeconomics and decision-making in health care: current situation and future trends. Iatriki. 2010; 98: 354-362.

53. Kanavos P, Vandoros S, Irwin R, Nicod E, Casson M. Differences in costs of and access to pharmaceutical products in the EU [Internet], European Parliament, Brussels,2011. Available from: http://www.europarl.europa.eu/document/activities/cont/201201/20120130ATT36575/20120130ATT36575EN.pdf, last accessed 2013 Oct 28.

54. Athanasakis K, Konstantinou E, Thireos E, Kyriopoulos J. The relative value of medical innovations on population health status: Physicians' views in Greece. Archives of Hellenic Medicine. 2010; 27: 963-969.

55. Vandoros S, Stargardt T. Reforms in the Greek pharmaceutical market during the financial crisis. Health Policy. 2013; 109: 1-6.

56. Contiades X, Golna C, Souliotis K. Pharmaceutical regulation in Greece at the crossroad of change: economic, political and constitutional considerations for a new regulatory paradigm. Health Policy. 2007; 82: 116-129.

57. Lichtenberg FR. Pharmaceutical innovation and longevity growth in 30 developing and high-income countries, 2000-2009. Health Policy Technol. 2014; 3: 36-58.

58. Souliotis K. A (repeated) proposal for pharmaceutical policy reform in Greece. Archives of Hellenic Medicine. 2013; 30: 520-521.

59. Murtagh J. Foerster V, Managing Technology Diffusion, Canadian Agency for Drugs and Technologies in Health, Ontario, 2009. Available from: http://www.cadth.ca/media/policy_forum_section/Managing_Technology_Diffusion_e.pdf, last accessed 2013 Oct 28.