A Comparative Study of the Diffusion of Antihypertensive and Antidepressant Medications in Germany and Japan

by

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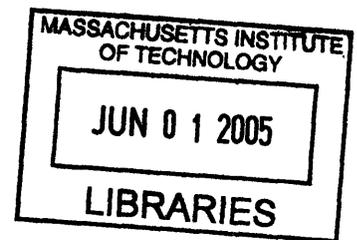in Partial Fulfillment of the Requirements for the Degree of

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Abstract

This thesis analyzes and compares the diffusion of antihypertensive and antidepressant medications in Germany and Japan during the time period of 1992 and 2003. The antihypertensive medications are classified as new, middle and old generations and the antidepressants are classified as new and old generations in this study. The demographic, economic, price, promotional, regulatory, and cultural factors that contributed to the sales level, number of compounds available in the market, and launch time of these medications are also examined using quantitative and qualitative methods at therapeutic class, generation, as well as product levels.

The qualitative analysis includes discussions on the general health care systems, health care polices, and country-specific hypertension- and depression-related cultural backgrounds. Econometric tools (descriptive statistics and linear regression models) are used as means of quantitative analysis. The diffusion of different generations of medications is examined. The degree of the use of branded vs. generic medications are also compared. Finally, Chow-tests are conducted for cross-country and cross-therapeutic-class comparisons.

This study finds that there are significant branded-v-generic, cross-generation, cross-class, cross-country differences in the diffusion of the selected therapeutic classes in the two countries. The factors examined contributed to the diffusion to various extents. Among which, the cultural factor played an important role in the adoption and sales of new medications of both therapeutic classes in both countries, especially the antidepressants in Japan. The promotional factors appear not to be very significant in the sales volumes, partially due to the regulatory settings of the two national-based health care systems.

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Chapter 1 Introduction

1.1 Motivation and objective

In all developed countries, pharmaceuticals are heavily regulated products. However, the regulation of pharmaceuticals varies across countries and therapeutic classes due to variations in regulatory systems, historic traditions, and cultures. The different regulations affect not only the pricing of medications, but also the economic behaviors of pharmaceutical manufacturers in marketing and promotions, and hence the diffusion (the level and the pattern of sales) of pharmaceuticals. It is therefore interesting to investigate the direct and indirect factors affecting pharmaceutical diffusion. This thesis is aimed to compare the diffusion of two selected medications in two countries and to examine the various factors that contributed to the diffusion using both quantitative and qualitative approaches.

Two therapeutic classes are chosen in the analysis – antihypertensives and antidepressants. The reasons for choosing these therapeutic classes are: antihypertensives are a "standard" class, where there is little discrepancy in prescription with regard to syndrome and dosage. Hence there is less noise added for medical practice reasons; the diffusion of antidepressants has demonstrated a distinct pattern in Japan, in part resulting from public and medical professionals' perceptions and manufacturers' advertising strategies.

The countries in this analysis are Germany and Japan. The reason for choosing these countries is that Japan's health care system has its root in the Bismarck's Germany.

Germany has a health care system that covers everything except long-term or permanent care. In 1961, the Japanese government achieved its goal of universal coverage. Hence they are both national-based health care systems [1]. However, the sales of pharmaceuticals have exhibited distinctive differences over time due to other factors such as the particular health care policies and regulations and practice of medicine. The regulatory, economic, and cultural factors contributing to the diffusions will also be analyzed.

The time period in this thesis is between the first quarter of 1992 and the last quarter of 2003. Quantitative (descriptive statistics and econometric models) and qualitative methods are used to analyze and compare the different patterns of diffusion.

There have been a number of studies that have analyzed diffusion of pharmaceuticals using econometric methods. For example, Ramarao Desiraju et al. studied the diffusion of new pharmaceutical drugs in developing and developed nations [2], and John Vernon examined the concentration, promotion and market share stability in the pharmaceutical industry [3]. Few have taken promotion efforts and/or regulatory effects on the sales of pharmaceuticals. These include Ernst Berndt et al. 1997 on the role of marketing, product quality and price competition in the growth and composition of the U.S. antiulcer drug industry [4] and Fabio Pammolli, et al 2002 on the competition after patent expiry in pharmaceuticals. There are also literatures on the economics of antihypertensive and antidepressanat medications, such as Ernst Berndt et al. 1992 on the price indexes for antihypertensive drugs [5], and Ernst Berndt et al. 1996 on tracking the effects on price indexes for antidepressant drugs [6].

However, this thesis has a different focus from these previous studies. Firstly, this thesis includes cross-therapeutic-class and cross-country comparisons of the diffusion of particular pharmaceuticals that have not been conducted before; secondly, a broad range of factors that contribute to the diffusion of these pharmaceuticals is analyzed, including demographic, economic, promotional, price, as well as regulatory factors.

1.2 The German and the Japanese health care systems

As mentioned in section 1.1, both the German and the Japanese health care systems are national-based. In this section these two health care systems (especially the financing of the health care) are compared. Then the regulations on pricing and co-payment of pharmaceuticals in Germany and Japan are discussed. After that, the total sales of pharmaceuticals in these two countries are illustrated. Finally, some demographic features (age and gender structures) are presented.

The two health care systems

The German health care system is based on a compulsory insurance scheme [1]. The insurance funds are highly decentralized (more than 1,000 before 1995 and ~380 in 2004) and they cover approximately 90% of the population. Eight percent of the population is covered by private insurance and the rest 2% are mainly government officials that are covered by the Government administers health care plans [7]. German physicians are paid fee-for-service, which gives them an incentive to increase the number of patients they see. However, the reimbursement policy sets a cap on the total amount of all doctors' compensations, which results in a strong competition amongst physicians in their efforts to expand their volume of treatment [1]. In Germany, the patients have free choice of physician. As in the U.S., a general practitioner may refer the patient to a specialist if needed.

Unlike the decentralized German health insurance funds, the Japanese health care insurance funds are highly centralized: the basic categories include Employee Health Insurance (covering ~56% of the population), National Health Insurance and Health Service for the Elderly (covering 36% of the population), and a group of minor government insurance plans for government employees, seamen and private teachers (covering about 8% of the population) [7]. The physicians in Japan are also paid on a fee-for-service basis, among which there is no price competition. These provide the doctors an incentive to treat as many patients as possible, as well as expansion of the volume of drugs prescribed. Unlike in the rest of the world, the Japanese doctors do not

specialize to the extent observed elsewhere. Patients can choose hospitals and physicians.

Regulations on pricing and co-payment of pharmaceuticals

The German health care regulatory body is the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, or BfArm), which handles product approval and health/safety-related matters. The Gemeinsamer Bundesausschuss (Joint Federal Committee) determine the prices of pharmaceuticals. The pricing of pharmaceuticals in Germany is based on a reference price system, introduced in the 1989 Health Reform Act [1]. Under this system the reimbursement levels of medicines are fixed at the reference price and the patient will pay for the difference between the actual price and the reference price. An insured person will pay for the lesser of 10% of retail price or ten Euros [7].

The Ministry of Health, Labor and Welfare (MHLW, or Kosei-roudou-sho in Japanese) manages all health regulatory matters in Japan, a merger of the Ministry of Labor and the Ministry of Health and Welfare in 2001 [7]. The prices of all medicines are regulated by the MHLW based on the innovativeness, cost of R&D, and reasonable profit margins of the product. Almost all of the listed drugs are fully reimbursed minus the patient co-pay (the co-payment rate ranges from 0% to 30% depending on a patient's social and occupational status).

The overall markets of pharmaceuticals

Figures 1.1 and 1.2 illustrate the overall spending and per-capita spending on pharmaceuticals in Germany and Japan over time (1992 - 2003). The sales are in Purchasing Power Parity adjusted U.S. dollars. The figures show that Japan had higher per-capita U.S. dollar sales of pharmaceuticals than Germany (except for 1992), and the difference was enlarged over time.

Total pharmaceutical sales
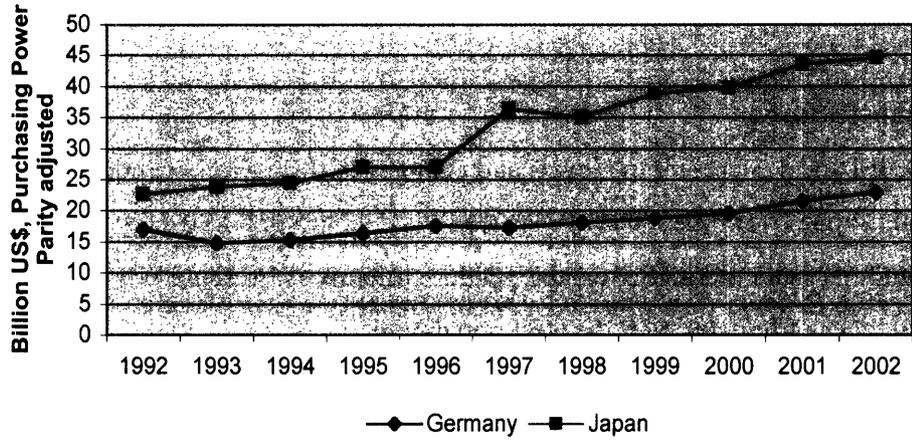
Figure 1. 1 Total pharmaceutical sales in Germany and Japan

Total pharmaceutical sales per capita
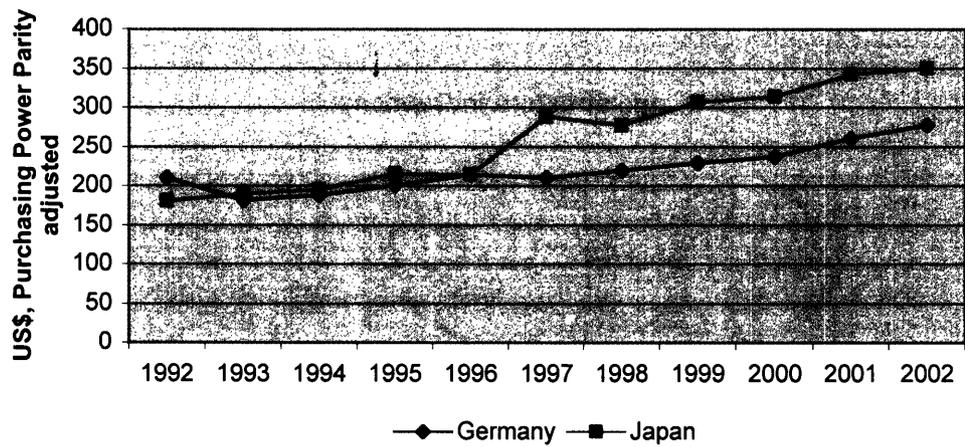
Figure 1. 2 Per capita pharmaceutical sales in Germany and Japan

In terms of the use of generics, Germany has a well-developed generics market, aimed to reduce health care costs. However, in Japan the generics have relatively low penetration rates [7]. This feature will be confirmed to be true for the antihypertensive and antidepressant medications in the econometric analysis in chapters 3 and 4.

Demographic features

Figures 1.3, 1.4 and 1.5 present the levels and changes of the age and gender structures in Germany and Japan over time. The age structure is decomposed to 0-14 years old, 15-64 years old, and 65 years old and over; the gender structure is presented by an illustration of the percentages of females over the total population.

As shown in Figures 1.3 and 1.4, both countries had increased 65-years-and-over percentage over time, and decreased percentages for the other two age groups. Japan had a higher percentage of people over 65 years old at the end of time period than Germany (18.4% vs. 17.3%). In addition, the gender structures show that there is a higher percentage of females in Germany than in Japan (this might be partially resulted from World War II, when numerous German males died.)

Age structure in Germany
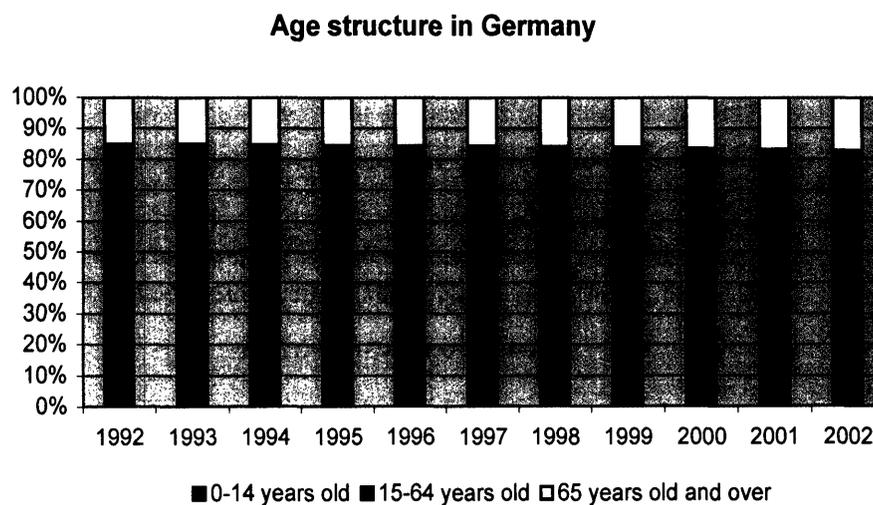
Figure 1. 3 The age structure in Germany

Age structure in Japan

■0-14 years old ■15-64 years old □65 years old and over
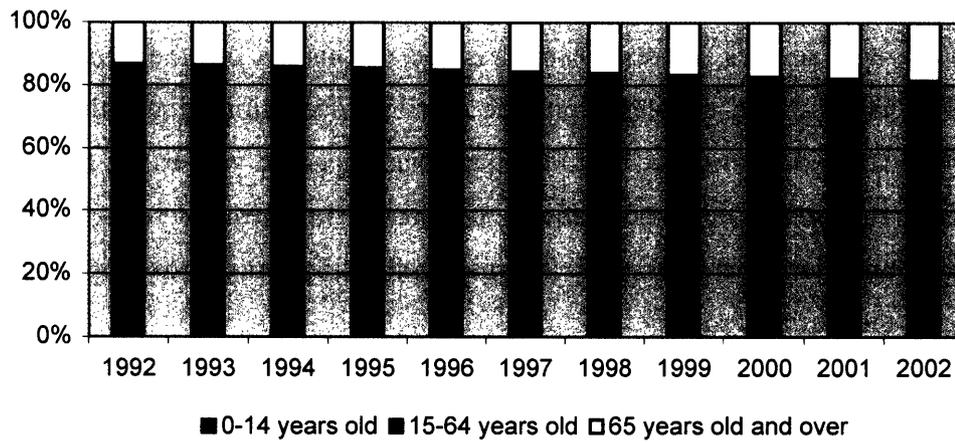
Figure 1. 4 The age structure in Japan

Percentage of females over the total population
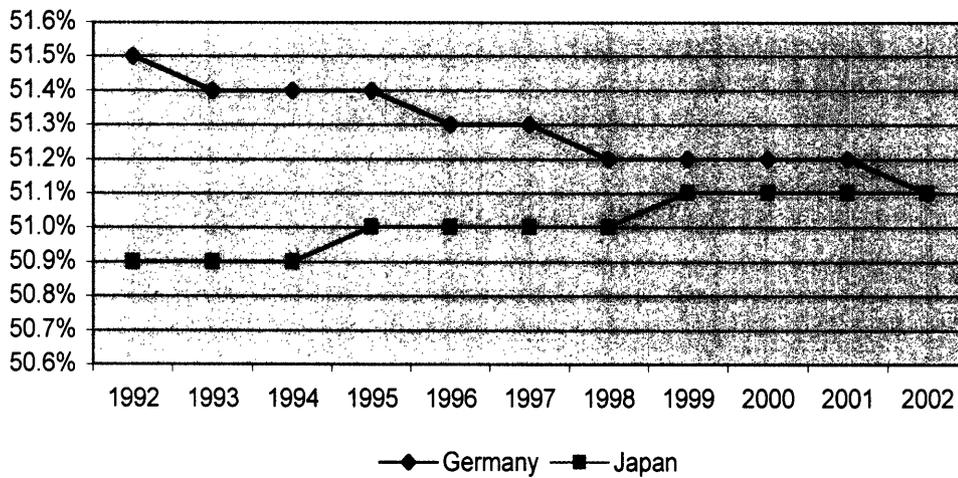
—◆—Germany —■—Japan

Figure 1. 5 The gender structures in Germany and Japan

1.3 Thesis organization

This thesis contains five major sections. Chapter 1 is the introduction, and chapter 2 discusses the data sources, regression models and definitions of the corresponding variables. Chapter 3 and chapter 4 provide detailed discussions about the sales of antihypertensives and antidepressants in Germany and Japan, as well as the factors that contributed to the sales of these medications. Chapter 5 compares the cross-country and cross-therapeutic-class differences of the medications. At the end of chapter 5 a conclusion of the thesis is made.

Chapter 2 Data and Regression Models

2.1 Overview of the data

The original data directly obtained from databases for the descriptive analysis and econometric analysis in this study includes: 1) quarterly sales and promotion of the antihypertensive and antidepressant medications in Germany and Japan, 2) annual demographic data (age structure), 3) annual macroeconomic data (gross domestic product (GDP) per capita), and 4) annual number of physicians per capita as a health care system indicator. All of the data cover the time period from the first quarter of 1992 to the fourth quarter of 2003.

The sales and promotion data was obtained from the IMS International database. IMS is a Philadelphia-based firm, which independently collects data on the sales and marketing of pharmaceuticals. The IMS quarterly sales data is collected at presentational form (for example, bottles of 50 tablets of 100-mg pills). The sales data used in this thesis is in patient days, which were calculated by IMS from the total grams sold divided by recommended daily dosage of that medication. In the analyses, the data is further aggregated at product-country-quarter and higher levels. The sales data is also reported in monetary values – national currencies and U.S. dollars converted from exchange rates. Here the U.S. dollar values are used in the analyses for the German and Japanese markets, each deflated by Producer Price Index (PPI). The prices per patient day of the drugs were then calculated from the PPI-adjusted dollar values divided by number of patient days at the appropriate levels. (The detailed definitions of variables will be introduced in section 2.2.)

Table 2. 1   Number of molecules in the sample

Country	Antihypertensives	Antidepressants
Germany	56	35
Japan	62	20

Table 2. 2   Number of products in the sample

Country	Antihypertensives	Antidepressants
Germany	18004	9425
Japan	6717	1465

The products in the sample cover 56 antihypertensive molecules and 35 antidepressant molecules in Germany, 62 antihypertensive molecules and 20 antidepressant molecules in Japan. The number of molecules is shown in Table 2.1 and the number of products is shown in Table 2.2.

IMS collects three kinds of promotion data and reports the data at aggregated local-product level: detailing, journal advertising and advertisement through mail. Detailing means the visits that the sales representatives of pharmaceutical companies pay to physicians. In this research, the number of detailing counts will be used to denote promotional efforts for three reasons: 1) detailing is the most effective (and expensive) means of promotion; 2) the journal and mail advertising data is unavailable for the Japanese market; 3) detailing tends to be a very short visit (usually a few minutes), so it is reasonable to use the number of detailing visits to measure the promotion intensity without considering the variance in the length of each visit.

For most countries in the IMS International database, IMS reports the sales of pharmaceutical products in the retail sector because the retail sales count for the majority of the pharmaceutical market (for example, Germany). However, the data for Japan includes the sales in the retail sector and those in hospitals. This is because in Japan physicians are allowed to dispense medications. As a result, the hospital sales are at a

similar level and of a similar pattern to the retail sales[1]. Hence in this study the retail sales data is combined with the hospital sales data for Japan to represent the Japanese market.

In addition, the IMS database also provides time-invariant information such as each product's manufacturer, launch time, and license type. In the regression models, the license type is used as dummy variables. The IMS data has 4 license types: Originator ("O"), Licensee ("L"), Other Brand ("B"), Generics ("G") and "NA". The products with license "O", "L" or "B" are grouped as branded drugs; and products with license "G" or "NA" are grouped as generic drugs. Table 2.3 lists the number of branded and generic antihypertensive and antidepressant drugs in Germany and Japan. (Note that in both countries there are more branded products than generic products.)

The demographic, economic[2], and health care system data are obtained from the 2004 Organization of Economic Cooperation and Development (OECD) Health Database. The data in the OECD Health Database is obtained from OECD member countries every year.

Table 2. 3   Number of branded and generic products in the sample

Country	Branded/generic	Antihypertensives	Antidepressants
Germany	Branded	13466	6982
	Generic	4538	2443
Japan	Branded	5965	1407
	Generic	752	58

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[1] I have examined and compared the sales levels and patterns of the Japanese retail and hospital sectors. They are consistent the statement here.

[2] The GDP per capita was adopted as the economic factor. Percentage of post-secondary education degree holders as well as the total health care spending per capita were tested and they resembled similar effects to that of the GDP per capita variable.

Lastly, the antihypertensive medications are classified into new, middle, and old generations; and the antidepressant medications are classified into new and old generations, based on the earliest launch time and the mechanism of action of each compound. The necessary information for classification was obtained from the online database PubMed [8], a service of the National Library of Medicine and the consultation with Professor Ernst R. Berndt and Dr. Dirk M. Hentschel [9].

All of the original data are processed using SAS program. The final results of the descriptive analysis (graphs) and the econometric analysis (regression models) are presented in the forms of Microsoft Excel charts and SAS regression outputs respectively.

2.2 Variables and regression models

There are eight linear regression models used throughout the study. In this section these models are explained and the variables in the models are defined. The regression models are aimed to examine numerically the relationship between the sales volume of medications (in patient days per capita) and economic, health care system, promotion, price, and competition factors at therapeutic class, generation, and product levels. The first four equations are used for data that is separated by country and therapeutic class; the last four equations are used for pooled data that includes both countries and therapeutic classes. Firstly, a list and definitions of all the dependent variables and explanatory variables used in the regression models is shown in Tables 2.4 and 2.5.

Table 2. 4   Dependent variables in regression models

Variable name	Variable definition
tot_pd_capita	Total patient days per capita at country-therapeutic class-time level
gen_pd_capita	Number of patient days per capita of each generation at country-therapeutic class-time level
share_new_pd	Share of number of patient days of the new generation out of total at country-therapeutic class-time level
prod_pd_capita	Number of patient days per capita at country-therapeutic class-product-time level

Table 2. 5   Explanatory variables in regression models

Variable name	Variable definition
income_1Kcapita	GDP per 1,000 population at country-time level
phys_1Mpop	Number of physicians per 1 million population at country-time level
pct0_14	Percentage of population that is between age 0 and 14
pct65p	Percentage of population that is older than 65 years old
time	Quarterly time trend variable, where first quarter in 1992 = 1
price_class	Average price of the drugs at country-therapeutic class-time level
price_gen	Average price of the drugs at country- therapeutic class-generation-time level
price_ratio	Price ratio of the new generation and combined old & middle generation. Prices are averaged at country- therapeutic class-generation-time level
price_prod	Price of individual products at country-therapeutic class-product-time level
num_compound	Number of all compounds at country- therapeutic class-time level
num_new_compo und	Number of new compounds at country-therapeutic class-time level
share_num_newc mpnd	num_new_compound divided by num_compound
tot_detail_capita_ lag1	Lagged total detailing counts per capita at country-therapeutic class-time level, lagged by 1 quarter
tot_detail_capita_ lag4	Lagged total detailing counts per capita at country-therapeutic class-time level, lagged by 4 cumulative quarters
gen_detail_capita _lag1	Lagged detailing counts per capita at country-therapeutic class-generation-time level, lagged by 1 quarter
gen_detail_capita _lag4	Lagged detailing counts per capita at country-therapeutic class-generation-time level, lagged by 4 cumulative quarters
rel_detail_lag1	Lagged ratio of new to old-and-middle detailing counts at country-therapeutic class-time level, lagged by 1 quarter
rel_detail_lag4	Lagged ratio of new to old-and-middle detailing counts at country-therapeutic class-time level, lagged by 4 cumulative quarters
prod_detail_lag1	Lagged detailing counts per capita at country-therapeutic class-product-time level, lagged by 1 quarter
prod_detail_lag4	Lagged detailing counts per capita at country-therapeutic class-product-time level, lagged by 4 cumulative quarters
new	Dummy variable for the new generation
middle	Dummy variable for the middle generation
generic	Dummy variable for generic drugs
timenew	Variable "time" times dummy variable "new"
timemiddle	Variable "time" times dummy variable "middle"
oldgen	Dummy variable "old" times dummy variable "generic"

The details of generations of medications are presented in sections 3.2 and 4.2. Also note that tot_detail_capita_lag1 and tot_detail_capita_lag4 are used separately in all of the equations because they have high pair-wise correlation (>0.9). In addition, in the logarithm form, pct0_14, pct65p, time trend variable and dummy variables are not logged. Lastly, a 95% confidence level is used in all of the parameter estimates in the regressions to assess statistical significance. The following is a list of the eight regression models with the variables defined above.

Equation 1: class-level model

$tot\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_class + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_compound + \beta_9 \cdot tot\_detail\_capita\_lag1$

$tot\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_class + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_compound + \beta_9 \cdot tot\_detail\_capita\_lag4$

(where β_0 is the intercept term.)

Equation 2: generation-level model

$gen\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_gen + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_new\_compound + \beta_9 \cdot gen\_detail\_capita\_lag1 + \beta_{10} \cdot new + \beta_{11} \cdot timenew + \beta_{12} \cdot middle + \beta_{13} \cdot timemiddle$

$gen\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_gen + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_new\_compound + \beta_9 \cdot gen\_detail\_capita\_lag4 + \beta_{10} \cdot new + \beta_{11} \cdot timenew + \beta_{12} \cdot middle + \beta_{13} \cdot timemiddle$

(Dummy variable old is omitted. For the antidepressants, there is no middle generation or timemiddle.)

Equation 3: share of new model

$share\_new\_pd = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_ratio + \beta_7 \cdot share\_newcmpnd + \beta_8 \cdot rel\_detail\_lag1$

$share\_new\_pd = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_ratio + \beta_7 \cdot share\_newcmpnd + \beta_8 \cdot rel\_detail\_lag4$

Equation 4: product-level model

$prod\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_prod + \beta_7 \cdot num\_new\_compound + \beta_8\, generic\cdot + \beta_9 \cdot prod\_detail\_capita\_lag1 + \beta_{10} \cdot new + \beta_{11} \cdot middle$

$prod\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_prod + \beta_7 \cdot num\_new\_compound + \beta_8\, generic\cdot + \beta_9 \cdot prod\_detail\_capita\_lag4 + \beta_{10} \cdot new + \beta_{11} \cdot middle$

(Dummy variable *old* is omitted. For the antidepressants, there is no middle generation.)

Equation 5: pooled class-level model

$tot\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_class + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_compound + \beta_9 \cdot tot\_detail\_capita\_lag1 + \beta_{10} \cdot Germany + \beta_{11} \cdot antihypertensives$

$tot\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_class + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_compound + \beta_9 \cdot tot\_detail\_capita\_lag4 + \beta_{10} \cdot Germany + \beta_{11} \cdot antihypertensives$

(Dummy variables *Japan* and *antidepressants* are omitted.)

Equation 6: pooled generation-level model

$gen\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_gen + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_new\_compound + \beta_9 \cdot gen\_detail\_capita\_lag1 + \beta_{10} \cdot new + \beta_{11} \cdot timenew + \beta_{12} \cdot middle + \beta_{13} \cdot timemiddle + \beta_{14} \cdot Germany + \beta_{15} \cdot antihypertensives$

$gen\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_gen + \beta_7 \cdot price\_ratio + \beta_8 \cdot num\_new\_compound + \beta_9 \cdot gen\_detail\_capita\_lag4 + \beta_{10} \cdot new + \beta_{11} \cdot timenew + \beta_{12} \cdot middle + \beta_{13} \cdot timemiddle + \beta_{14} \cdot Germany + \beta_{15} \cdot antihypertensives$

(Dummy variables *Japan* and *antidepressants* are omitted. For the antidepressants, there is no middle generation or timemiddle.)

Equation 7: pooled share of new model

$share\_new\_pd = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_ratio + \beta_7 \cdot share\_newcmpnd + \beta_8 \cdot rel\_detail\_lag1 + \beta_9 \cdot Germany + \beta_{10} \cdot antihypertensives$

$share\_new\_pd = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_ratio + \beta_7 \cdot share\_newcmpnd + \beta_8 \cdot rel\_detail\_lag4 + \beta_9 \cdot Germany + \beta_{10} \cdot antihypertensives$

(Dummy variables *Japan* and *antidepressants* are omitted.)

Equation 8: product-level model

$prod\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_prod + \beta_7 \cdot num\_new\_compound + \beta_8 \, generic \cdot + \beta_9 \cdot prod\_detail\_capita\_lag1 + \beta_{10} \cdot new + \beta_{11} \cdot middle + \beta_{12} \cdot oldgen + \beta_{13} \cdot Germany + \beta_{14} \cdot antihypertensives$

$prod\_pd\_capita = \beta_0 + \beta_1 \cdot income\_1Kcapita + \beta_2 \cdot phys\_1Mpop + \beta_3 \cdot pct0\_14 + \beta_4 \cdot pct65p + \beta_5 \cdot time + \beta_6 \cdot price\_prod + \beta_7 \cdot num\_new\_compound + \beta_8\ generic \cdot + \beta_9 \cdot prod\_detail\_capita\_lag4 + \beta_{10} \cdot new + \beta_{11} \cdot middle + \beta_{12} \cdot oldgen + \beta_{13} \cdot Germany + \beta_{14} \cdot antihypertensives$

(Dummy variables *Japan* and *antidepressants* are omitted. For the antidepressants, there is no middle generation.)

Equations 4-8 allow the intercepts to be different between the two countries and the two therapeutic classes. However, in order to examine whether there is statistically significant cross-country and cross-therapeutic-class differences in the estimated parameters, Chow-tests are performed following the regression models in chapter 5. The null hypothesis is that there is no cross-country or cross-therapeutic-class difference in the parameter estimates. The Chow-statistic follows an F-distribution and is calculated from the sum of squared residuals of semi-constrained and unconstrained models (SSR_r and SSR_u). In this case, the unconstrained models are the regressions separated by country and therapeutic class (Equations 1-4), and the semi-constrained models are the pooled regression models (Equation 5-8). The Chow-test is conducted at the therapeutic class level, generation level, and product level respectively.

$$Chow\ statistic = [(SSR_r - SSR_u)/\ SSR_u] \times [(N\text{-}k)/q] \sim F_{q,\ N\text{-}k}$$

where $SSR_u = \sum SSR_{u,\ i}$, N is the total number of observations in the constrained model, k is the total parameter estimates in the unconstrained models (including the intercept terms), and q is the difference of k and the number of estimated parameters in the constrained model.

The Chow-statistic follows an F-distribution with q and N-k degrees of freedom. If the Chow-statistic is greater than the critical value of $F_{q,\ N\text{-}k}$ at 5% significance level, the H_0 hypothesis is rejected; otherwise the H_0 hypothesis cannot be rejected.

Chapter 3 Antihypertensives in Germany and Japan

In this chapter, a background discussion on hypertension and antihypertensive medications is introduced. Following that, descriptive analyses of the antihypertensives at the class, generation and product level are presented. Then econometric models are used to quantify and compare the factors that contribute to the sales of antihypertensives during 1992-2003 in Germany and Japan. A cross-generation comparison of the medications is also included. Finally, a summary based on the descriptive and econometric analyses is presented.

3.1 Symptoms and causes of hypertension

Hypertension, also called high blood pressure, is a condition occurring when the systolic and diastolic pressures remain abnormally high (a reading of 140/90 mm Hg or higher) [10]. Most people with high blood pressure usually do not have noticeable symptoms. Albeit over time, untreated high blood pressure can damage organs, such as the heart, kidneys, or eyes by forcing the heart and blood vessels to overwork. This may lead to chest pain (angina), heart attack, stroke, kidney (renal) failure, peripheral vascular disease, eye damage (retinopathy), or abnormal heartbeat [11]. Studies have shown that hypertension is causally involved in nearly 70% of all stroke cases [12].

The factors that can cause high blood pressure are multi-faceted. They include obesity, drinking three or more alcoholic beverages a day, high salt intake, aging, a sedentary lifestyle, stress, low potassium, magnesium, and calcium intake, and resistance to insulin [13].

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The degree of economic development, culture, traditions, geography and the composition of certain natural resources can all affect the size of high-blood-pressure population through food intake, lifestyles and genetics. Among developed countries, scientists have discovered some cross-country differences in the prevalence of hypertension. For example, a study conducted in 2003 showed that the average hypertension prevalence of six European countries (England, Finland, Germany, Italy, Spain, and Sweden) is 44.2% for the age group of 35 to 64 years old. Among these countries as well as Canada and the United States, Germany has the highest hypertension prevalence for the same age group (55%) [14]. In contrast, however, the percentage of population having hypertension in Japan is lower (a study in 1983 showed less than 20% for age group 40 to 64 years old [15]); the Japanese government has led health campaigns aimed at reducing hypertension in its population [16]. Some believe that the relatively low incidence of hypertension in Japan is culture-related. For example, popular traditional Japanese food such as Natto (made from soybeans) and fish (containing fatty acid) have been shown to help reduce high blood pressure and/or relieve hypertension symptoms [17][18][19].

Given the above evidence, one may hypothesize that assuming 1) the same percentage of prevalence in the overall population and 2) every hypertensive person is treated, the overall per-capita demand for hypertensive medications in Germany is much greater (roughly $\frac{(55\% - 20\%)}{20\%} = 175\%$ more) than that in Japan. However, the data in this work shows that the per-capita sales levels of antihypertensives in Germany and Japan have a smaller gap (per-capita sales in Germany is only 29% more than that in Japan). This phenomenon and its possible underlying causes are illustrated and discussed in greater detail in section 3.3.

3.2 Types of antihypertensives

As mentioned at the beginning of section 3.1, hypertension refers to an elevation of the blood pressure in the human body. With hypertension, the blood force against the arterial walls is abnormally high, which results in overworking of both the heart and the blood vessels. The mechanisms of antihypertensives are then to lower blood pressure by one of

or combination of: (1) opening and widening the blood vessels, (2) preventing the blood vessels from closing and tightening, or (3) reducing the workload of the heart [20]. Currently, there are ten types of antihypertensives categorized by their mechanisms of action [21]: diuretics, alpha-blockers, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), central adrenergic inhibitors, peripheral adrenergic inhibitors and blood vessel dialators.

In the data and the analysis of this chapter, the most commonly used categories of medications are included: beta-blockers, calcium channel blockers, ACE inhibitors and ARBs. Further, the ARBs are categorized as the "new" generation of antihypertensives, ACE inhibitors are categorized as the "middle" generation, and the remainder (beta blockers and calcium channel blockers) are the "old" generation of antihypertensives. Table 3.1 summarizes the different types of antihypertensives categorized by their mechanisms of action as well as their generation [21]. (Appendix 1 gives a complete list of the compounds included in this study.)

Table 3. 1   Categories of antihypertensives by mechanisms of action in this study

Categories	Mechanism of action	Generation
Beta blockers	Reduce the workload of the heart by blocking nervous system to release certain chemicals that bind with beta receptors in the heart, which could trigger a rapid heartbeat.	Old
ARBs	Inhibit the action of angiotensin II by blocking it from entering angiotensin II receptors in the body.	New
ACE inhibitors	Block the production of angiotensin II, which causes blood vessels to tighten.	Middle
Calcium channel blockers	Block calcium ions from signaling the blood vessels to constrict or tighten.	Old

Source: American Heart Association, http://www.americanheart.org/

Although positive effects of pharmacological treatment of hypertension are well established, the outcome depends on the patient's conditions and the specific antihypertensive medication used. Adverse outcomes were reported for short-acting nifedipine in 1995 [22]. In 1996 an increased cancer incidence was observed in users of calcium channel blockers (including verapamil, diltiazem and nifedipine) [23]. A recent meta-analysis of randomized clinical trials found a significantly lower preventive effectiveness against myocardial infarction and congestive heart failure among patients allocated to intermediate- and long-acting calcium channel blockers than among those on other antihypertensives [24]. Generally, the newer medications have fewer and/or less severe side effects, which are a strong factor that boosts the sales of such medications. Table 3.2 illustrates the generally recognized side effects of antihypertensives [21].

Despite the different side effects, there is no current agreement on which class of drug should be initially prescribed to treat high blood pressure. Physicians prescribe antihypertensive based on each patient's past medical history and current symptoms and conditions, as well as their own experience. In addition, if the use of a single antihypertensive does not lower blood pressure sufficiently, then physicians may prescribe two or more types of antihypertensives to work in combination. Independent of the prescription, patients are always recommended to change their lifestyle to help control their condition.

Table 3. 2   Side effects of antihypertensives by mechanisms of action in this study

Categories	Side effects	Generation
Beta blockers	insomnia, cold hands and feet, tiredness or depression, a slow heartbeat or symptoms of asthma	Old
ARBs	occasional dizziness; relatively expensive prices	New
ACE inhibitors	skin rash; loss of taste; a chronic dry, hacking cough; and in rare instances, kidney damage	Middle
Calcium channel blockers	palpitations, swollen ankles, constipation, headache or dizziness	Old

Source: American Heart Association, http://www.americanheart.org

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3.3 Descriptive analysis of the sales and promotion of antihypertensives

3.3.1 The sales of antihypertensives

Firstly, the overall antihypertensive markets in number of patient days in Germany and Japan are plotted and compared. As shown in Figure 3.1, the sales of antihypertensives increased steadily in both countries (0.67 to 1.83 million patient days for Germany and 0.80 to 2.05 million patient days for Japan, from first quarter of 1992 to the fourth quarter of 2003). Between 1992 and 1999, the total sales of antihypertensives grew faster in Japan than in Germany. (The average annual growth rates are 7.6% and 6.4% respectively.) However, in years 2000-2003 the sales have increased more quickly in Germany than in Japan. (The average annual growth rates of total patient days of antihypertensives are 13.4% for Germany and 7.1% for Japan.) At the end of 2003, Germany had a similar level of antihypertensives sales as Japan, despite the fact that it has only about two-thirds of Japan's population.
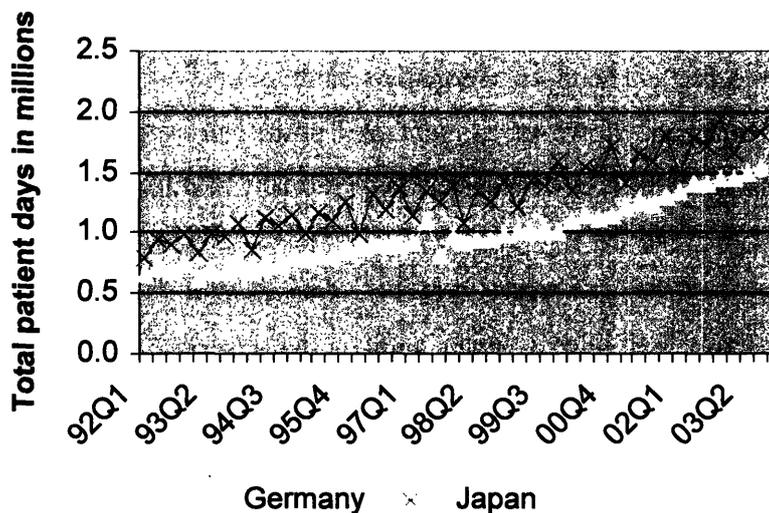
Figure 3. 1   Total patient days for antihypertensives in Germany and Japan
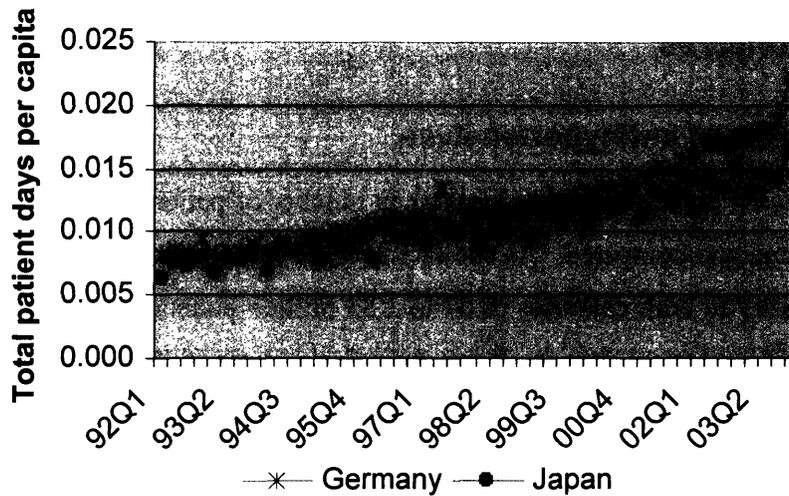
Figure 3. 2   Total patient days per capita for antihypertensives in Germany and Japan

The different acceleration rates of the sales in antihypertensives between Germany and Japan can be further illustrated under the patient-days-per-capita (total patient days divided by total population) scale in Figure 3.2. At the beginning of 1992, one German consumed 28.9% more antihypertensives than did a Japanese (0.008 v. 0.006 patient days per capita), and by the end of 2003, this number increased to 37.8% (0.022 v. 0.016 patient days per capita). Therefore, Germany's antihypertensive sales have been growing faster than that of Japan. However, as mentioned at the end of section 3.1, the difference of antihypertensives sales (per capita) between Germany and Japan remains smaller than expected.

Despite the relatively high sales in Japan, antihypertensives seem to be more expensive in Japan than in Germany. Figures 3.3 and 3.4 indicate the total sales per capita and the price per patient day (derived by dividing total sales by total patient days of each year) in purchasing power parity (PPP)-adjusted US dollars[3]. Figure 3.3 shows that the surplus of total per-capita spending in antihypertensives for Japan relative to Germany started to increase since late 1990. The per-patient-day price in Germany has been steadily

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[3] Local currencies were converted into PPP-adjusted US dollars in this study.

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decreasing, while remaining relatively steady in Japan since the late 90's. At the end of year 2003, the price of antihypertensives is $0.73 in Japan, about 2.5 times of the price in Germany at that time ($0.29).
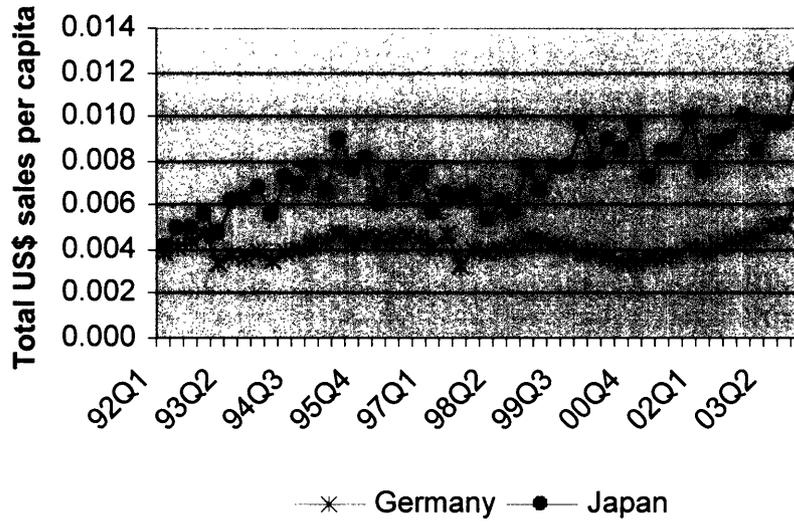
Figure 3. 3   Total sales (in PPP-adjusted US$) per capita for antihypertensives
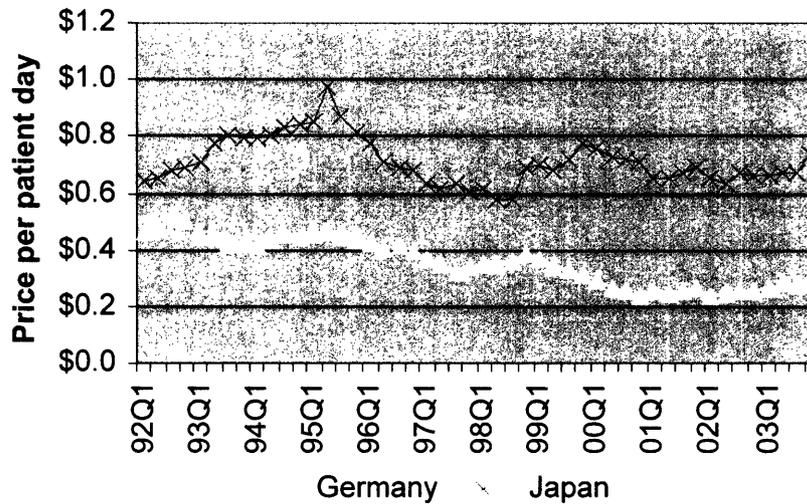
Figure 3. 4   Price per patient day (in PPP-adjusted US$) for antihypertensives

The differences in per-patient-day price between Germany and Japan can be explained by looking into the patient-day market share of each generation and the price difference by generation of therapies. Figures 3.5 and 3.6 illustrate the change in market share of antihypertensives over time in each country; Figures 3.7 and 3.8 are the average per-patient-day prices of the new generation defined in section 3.2 (i.e., the ARBs).
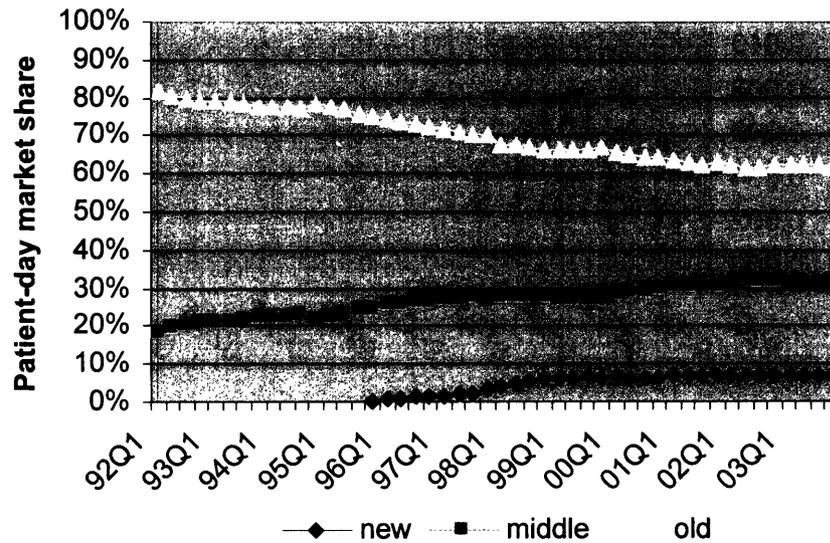
Figure 3. 5   Market share (in patient days) of antihypertensives in Germany
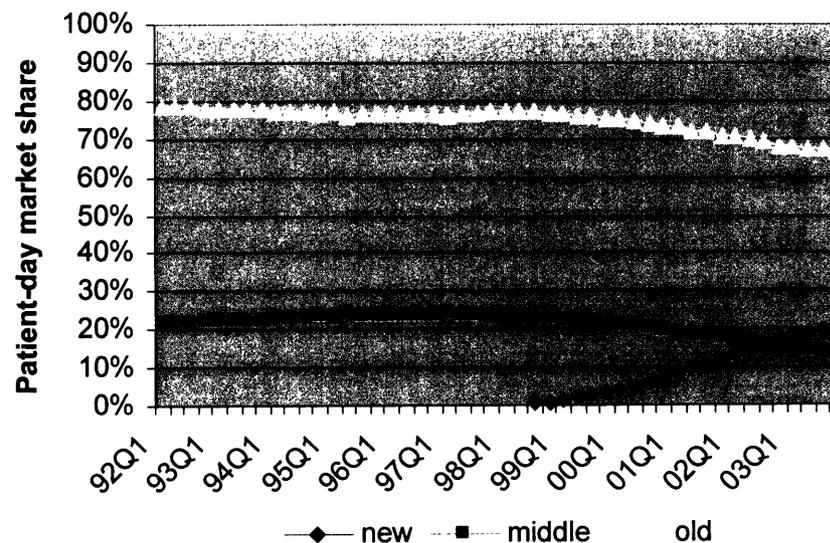
Figure 3. 6   Market share (in patient days) of antihypertensives in Japan

As seen in Figures 3.5 and 3.6, the share of new drugs increased over time in both countries but this new share in Japan is higher than that in Germany (21% and 7% respectively in the 4th quarter of 2003). The price of the new drugs, which is the highest of all three generations, is much higher in Japan than in Germany (about $1.30 vs. $0.70 respectively at the end of 2003, as shown in Figures 3.7 and 3.8). Therefore, the combination of higher prices and larger share of new drugs contributes to a higher average price per patient day for all generations in Japan than that in Germany. In addition, it is worth noting that the prices of all new compounds tend to converge in both countries. This is likely to be a result of centralized pricing control from the governments.
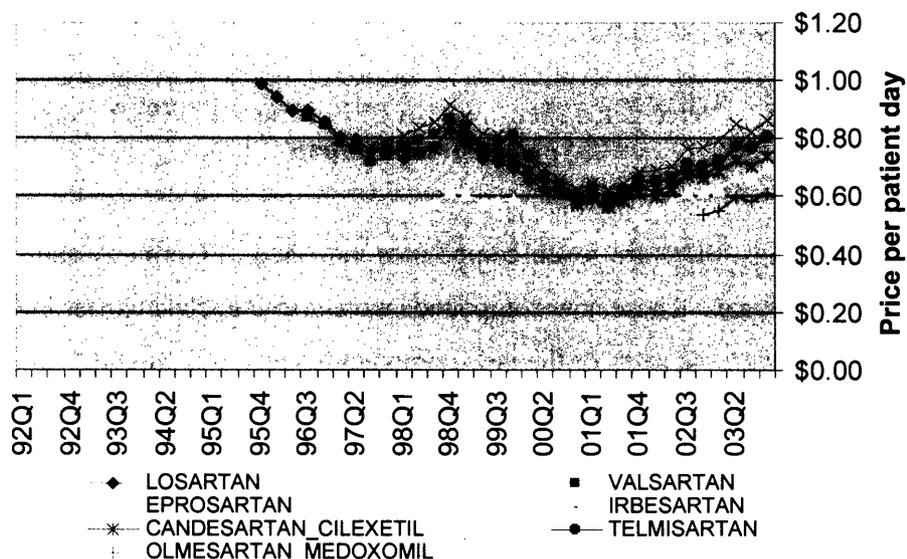
Figure 3. 7   Price per patient day (in PPP-adjusted US$) for new antihypertensives in Germany
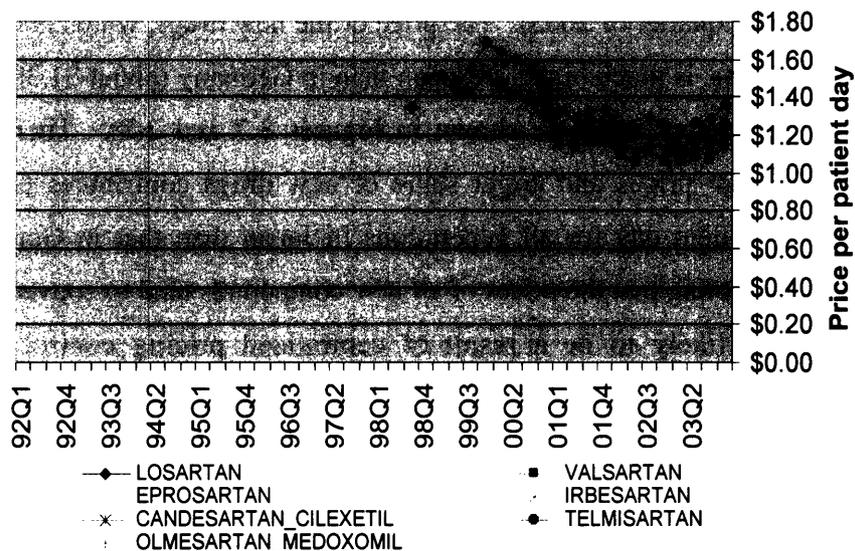
Figure 3. 8   Price per patient day (in PPP-adjusted US$) for new antihypertensives in Japan

Among the new drugs, there are seven compounds launched in Germany and only four compounds sold in Japan. These new compounds were also launched earlier in Germany than in Japan; however, the sales of the new compounds grew and gained their shares in the overall antihypertensive market much quicker in the Japanese market than in the German market. These all suggest that the German antihypertensive market is more mature than Japan. However, in both markets, certain compounds showed similar performance in sales. As shown in Figures 3.9 and 3.10, candesartan cilexetil and valsartan had the top and second-to-top sales volumes in both countries at the end of the time period.
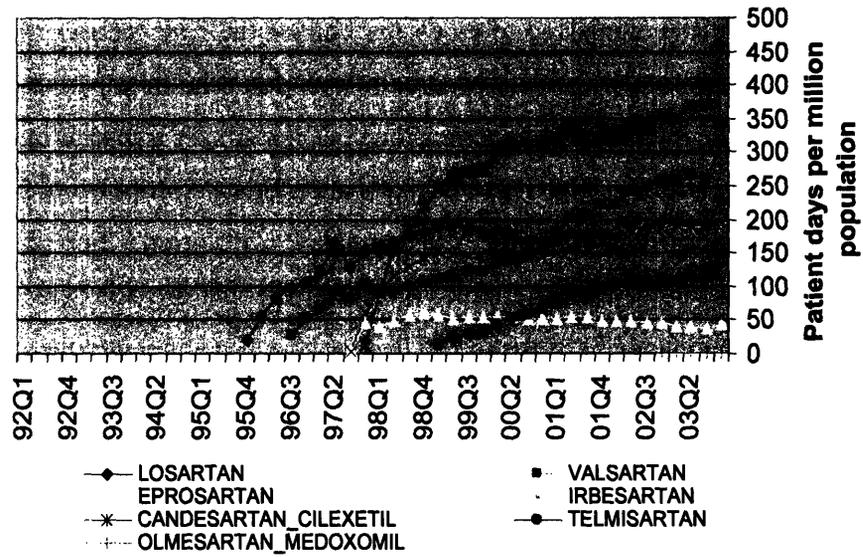
Figure 3. 9   Patient days per million population for new antihypertensives in Germany
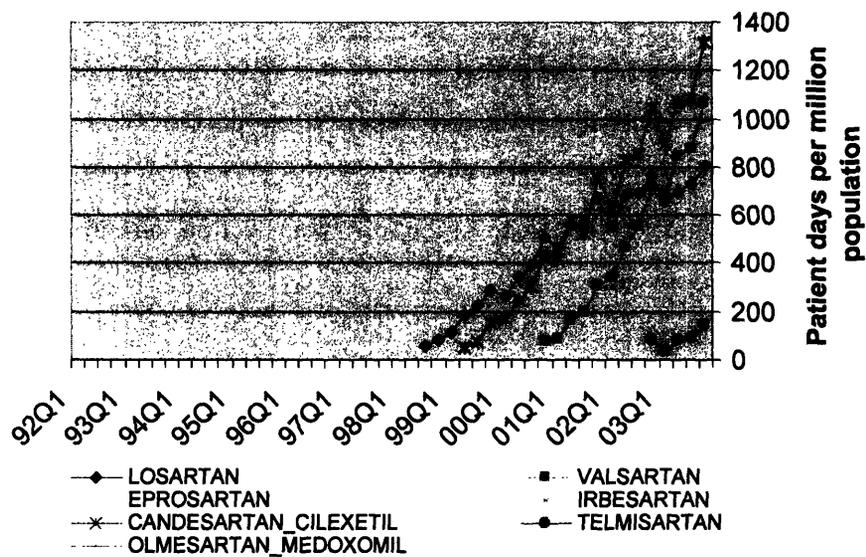
Figure 3. 10   Patient days per million population for new antihypertensives in Japan

Although Germany has much higher per-capita (the figures show per-million-population values) sales of antihypertensives towards the end of the time period, the difference between Germany and Japan is relatively small throughout the time period of our study. This suggests that the incidence of hypertension does not simply translate into the sales of hypertensive medications. The reasons that cause this disproportional relationship between the "potential demand" and "real demand" are varied. For example, since hypertension usually does not have strong symptoms, some are not detected (they are called "masked hypertension") or treated. The Japanese government's health campaigns have increased not only the prevention of hypertension (long-term effect on antihypertensive sales), but also the awareness of hypertension diagnoses and treatment (short-term effect on antihypertensive sales). Since both Germany and Japan have social insurance systems, which offer almost full coverage of prescriptions, the disparity of drug sales is less likely to be due to affordability of individuals. However, in such systems there are situations that some prescribed drugs are never consumed. Thirdly, the studies mentioned in section 3.1 were constrained to specific age groups, and the differences among age groups in Germany and Japan are unknown. In all these cases, the projected demand will not be reflected by the actual sales of the hypertension medications. The actual percentage of treated hypertension depends on public awareness, medical examination, medication options and very often direct and/or indirect economic behaviors of pharmaceutical companies. In the following section, promotional efforts of antihypertensives are discussed.

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3.3.2 The promotion of antihypertensives

Since direct-to-consumer advertising (for prescription drugs) is prohibited in both countries, the decision-making on drug prescription resides primarily in the physicians. Among all types of promotional activities to physicians, detailing is the most important promotional practice in the pharmaceutical industry. Hence the intensity of detailing is a good indicator of overall promotional efforts. In this section, detailing activities for antihypertensives in Germany and Japan are compared and discussed. (I note that the detailing information in Japan is only available between 1998 and 2003.)

Antihypertensives are much more heavily promoted in Japan than in Germany through detailing to physicians. Figures 3.11 and 3.12 show the total detailing counts per capita and per physician. On the class level, the number of detailing visits in Japan is about six times that in Germany in both cases (per capita and per physician). One possible explanation of the high detailing counts in Japan is that physicians are allowed to dispense medicines in Japan. However in Germany this is not the case.
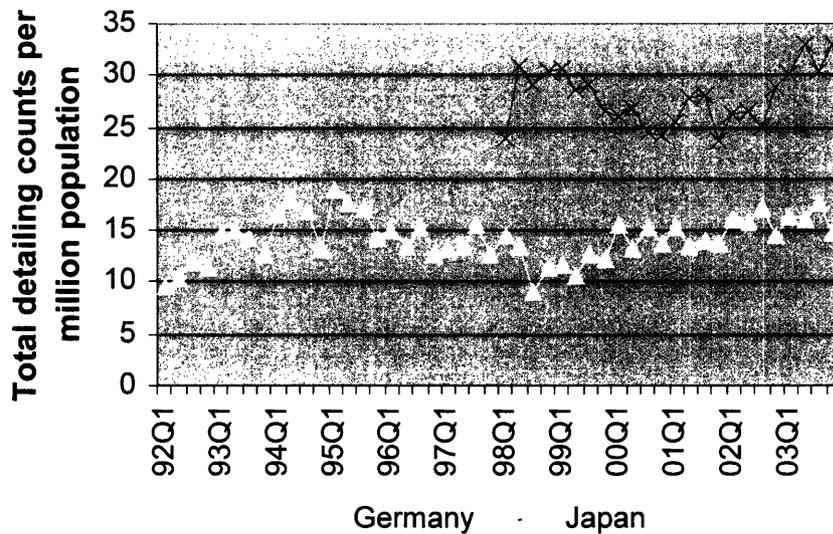
Figure 3. 11   Total detailing counts per million population for antihypertensives
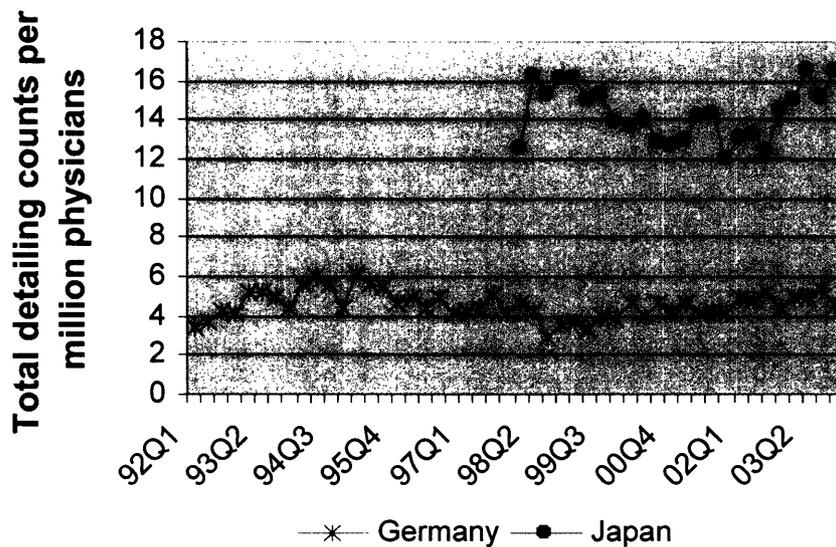
Figure 3. 12   Total detailing counts per million physicians for antihypertensives

Figures 3.13 and 3.14 illustrate the share of detailing counts by generation of drugs. In both countries the new drugs reached and exceeded the detailing level of old drugs, which dominated the early and mid stages of the market (50% for Japan and 44% for Germany at the beginning of 1992). Comparing Figures 3.5 and 3.13 vs. 3.6 and 3.14, the sales-to-detailing ratio of new drugs in Germany is much lower than in Japan, implying that the Japanese market is more prone to new drugs' penetration.
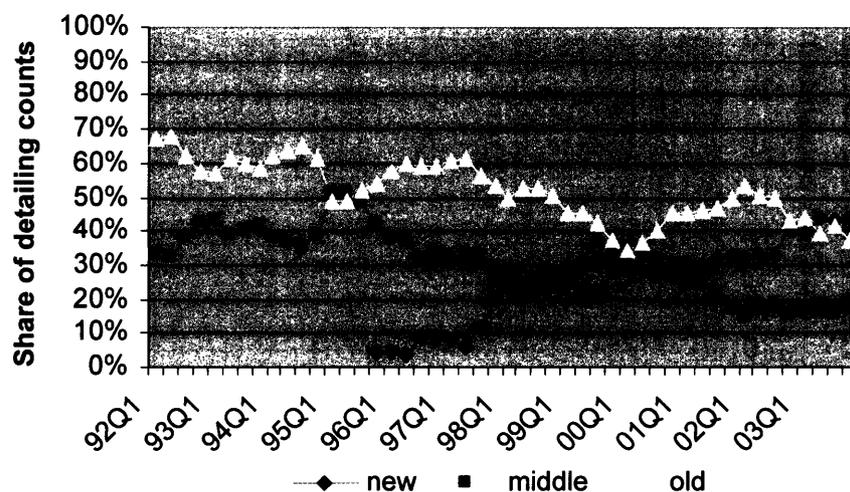
Figure 3. 13   Share of detailing counts by generation for antihypertensives in Germany
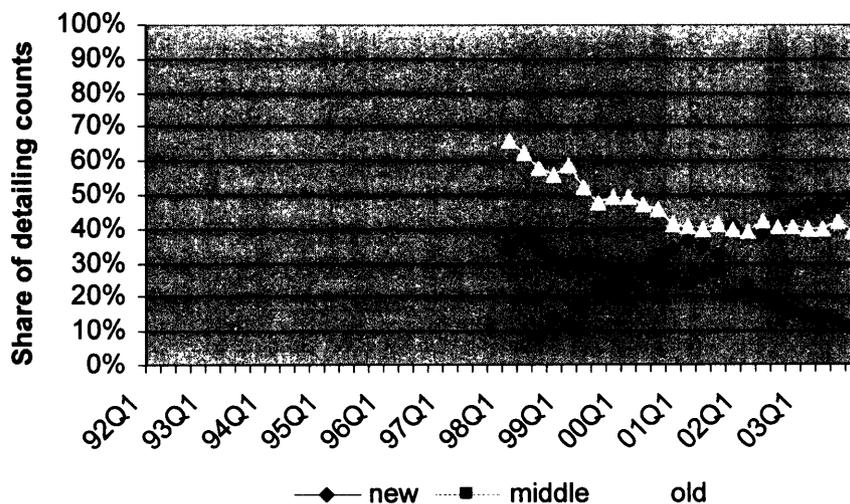
Figure 3. 14   Share of detailing counts by generation for antihypertensives in Japan

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The descriptive analysis has shown the co-existence of relatively high sales and rigorous promotion at both market- and generation-level in Japan. Many previous studies, primarily of the U.S. market, have shown that the pharmaceutical market and sales can be positively influenced by promotion efforts and pricing strategies. Does this relation exist in the German and the Japanese market? If yes, to what extent is the influence of promotion on sales in this particular case? It (among other factors) will be numerically evaluated through econometrics models in section 3.4.

3.4 Econometric analysis

In this section, the regression models at the class, generation, and product levels discussed in chapter 2 are estimated. The models are aimed to quantitatively examine the relationship between diffusion of medicines (sales volume and market share) and economic, demographic and policy factors. These factors include the overall wealth of the society (GDP per capita), availability of medical care (represented by number of physicians per capita), promotion intensity (lagged detailing counts), regulated prices, and age structure of the population. The right-hand-side (RHS) variables tot_detail_capita_lag1 and tot_detail_capita_lag4 are regressed in separate models because of their high pair-wise correlation (> 0.9).

3.4.1 Therapeutic-class-level analysis

Table 3.3 shows the regression results of the log-form Equation 1 in chapter 2: log_tot_pd_capita is the dependent variable; price, number of compounds, and detailing information are correspondingly calculated at the class level. As seen from Table 3.3, at the therapeutic-class-level regressions, only the time trend variable has a positive significant parameter estimate for both countries. The percentage of people who are older than 65 years old has a negative significant parameter estimate in Japan. All of the other parameters are insignificant. (Detailed SAS outputs are included in Appendix 2.)

Table 3. 3   Regression results of Equation 1 (dependent variable: log_tot_pd_capita)

Variable	Parameter estimate	
	Germany	Japan
Intercept	9.75	13.67
	(0.41)	(0.41)
log_income_1Kcapita	0.85	-4.14
	(0.27)	(-1.20)
log_phys_1Mpop	-2.13	-2.11
	(-0.77)	(-0.69)
pct0_14	14.56	1.31
	(0.26)	(0.29)
pct65p	6.62	**-7.28**
	(0.17)	**(-3.03)**
time	**0.03**	**0.08**
	(3.07)	**(5.64)**
log_price_class	0.13	-0.48
	(0.64)	(-1.02)
log_price_ratio	-0.10	-0.59
	(-0.24)	(-0.51)
log_num_compound	-0.61	-0.04
	(-1.10)	(-0.03)
log_tot_detail_capita_lag4	0.13	0.18
	(0.76)	(0.88)
log_tot_detail_capita_lag1*	0.13	-0.08
	(1.31)	(-0.32)
Number of observations	32	22
Adjusted R-square	0.93	0.86

t-values are shown in the parenthesis below the parameter estimates.
model is run with log_tot_detail_capita_lag4 replaced by log_tot_detail_capita_lag1

Hence the class-level regression model has shown us that the total patient days including new, middle and old generations have increased over time in both countries, which is consistent with the descriptive analysis in section 3.3. On the other hand, the changes of the average price and the aggregated promotion efforts were not able to explain the expansion of the antihypertensive markets. One possible reason to explain why most parameters are insignificant at the class-level is that much of the effects of the factors such as detailing, competition, and prices are dampened due to the aggregation of

information. This calls for a need for generation- and product-level analyses of these medications, which are discussed in the following sections.

3.4.2 Generation-level analysis

In this section, the sales of antihypertensives in number of patient days are regressed at the generation level (Equation 2). Then the number of patient days for new drugs is used as the dependent variable (Equation 3). The RHS variables such as price, detailing information, and the number of compounds are adjusted accordingly to be at the generation level. As described in Equations 2 in chapter 2, dummy variables differentiating the generations of antihypertensives are also used. The omitted dummy variable is the old generation.

Regression results of the linear form of Equation 2 indicate highly significant differences among the new, middle and old generations in both countries – the negative signs of the parameters indicate that the sales of the new-generation and the middle-generation antihypertensives are less than that of the old generation. The values of these estimates are listed in Table 3.4. (The detailed SAS outputs are shown in Appendix 2.) The estimated parameters show that the absolute difference of drug saless between the new-/middle-generation and the old-generation is smaller in Germany (-4.74 for new and –2.36 for the middle generation) than in Japan (-9.28 for new and –3.94 for the middle generation). It might seem contradicting to the findings in Figures 3.5 and 3.6, in which the percentage of new generation was higher in Japan than in Germany. However, since Germany had a larger per-capita patient-day level, the regression results reflected this absolute value difference rather than the difference in percentage. In addition, the interaction variable timenew and timemiddle all have significant and positive parameters. This indicates that as time went by the new and the middle generations have increased sales and the gap between the new and the old generation shrank, consistent with the observation from the descriptive analysis.

Table 3. 4   Regression results of Equation 2 (dependent variable: log_gen_pd_capita)

Variable	Parameter estimate	
	Germany	Japan
Intercept	-43.55	28.60
	(-0.81)	(0.69)
log_income_1Kcapita	-3.51	6.82
	(-0.43)	(1.43)
log_phys_1Mpop	3.75	-5.89
	(0.58)	(-1.13)
pct0_14	44.21	-68.29
	(0.35)	(-1.45)
pct65p	42.02	**-45.56**
	(0.47)	**(-2.36)**
time	-0.0016	-0.016
	(-0.53)	(-0.65)
log_price_ratio	-1.17	-1.59
	(-0.95)	(-0.88)
log_price_gen	-0.78	0.44
	(-1.80)	(0.84)
log_num_new_compound	**0.32**	**0.43**
	(2.24)	**(2.91)**
new	**-4.74**	**-9.28**
	(-12.62)	**(-14.92)**
middle	**-2.36**	**-3.94**
	(-5.67)	**(-5.72)**
timenew	**0.093**	**0.19**
	(11.24)	**(21.25)**
timemiddle	**0.048**	**0.071**
	(3.90)	**(3.79)**
log_gen_detail_capita_lag1	**-0.46**	**-0.78**
	(-4.18)	**(-5.22)**
log_gen_detail_capita_lag4*	**-0.81**	-0.86
	(-2.86)	(-1.65)
Number of observations	99	66
Adjusted R-square	0.960	0.984

t-values are shown in the parenthesis below the parameter estimates.
model is run with rel_detail_lag1 replaced by rel_detail_lag4
Omitted generation variable: old

The number of new compounds has a significant and positive parameter estimates in both countries. This might suggest that increasing the variety of the new drugs has helped to expand the market for the new and other generations. Secondly, three out of four of the

detailing variables have significant negative parameters. The negative sign for the promotion variables is a result of the co-existence of the heavily detailed low-sales-level new generation and the lightly detailed high-sales-level middle and old generations. To be more specific, the newly launched medicines were heavily promoted (about the same level as the old generation at the end of the time period for both Germany and Japan), however, the sales were not able to catch up with the long-existing older generations that are less heavily promoted. The regression results for the new generation showed a significant positive correlation to the sales volume, which will be shown and discussed in Table 3.5 and paragraphs that follow. Lastly, the parameter for the time variable in this regression indicates the time trend of the old generation. It is insignificant for Germany and Japan, which indicates that the old antihypertensives did not show a clear upward or downward trend in the two countries.

Since one of the key goals in this work is to examine how the new generation of medications is diffused, a regression model with number of new patient days being the dependent variable (logarithm form of Equation 3 in chapter 2) was run to identify the factors that contribute to the sales of the new medications. Table 3.5 shows a summary of the regression results with the LHS variable being the share of the patient days of the new medications (in logarithm form).

In this set of regressions, the parameter estimates of the time trend variable, population age variables, number of new compounds and both detailing variables are significant for Germany and Japan. Again, the positive time parameter indicates significant growth of the new generation; the negative age parameters suggest that people aged between 15 and 65 contributed to the increase of the sales of the new drugs; the positive parameter of the number of new compounds indicates the expansion of the new generation sales is accompanied by the increased options for treatment within the generation. The positive detailing parameters suggest that the more the promotional efforts, the more sales of medicines. In addition, the lagged cumulative four quarters detailing has a stronger effect than the lagged one quarter detailing in Germany (0.45 vs. 0.24).

Table 3. 5   Regression results of Equation 3 (dependent variable: log_share_new_pd)

Variable	Parameter estimate	
	Germany	Japan
Intercept	99.74	-17.51
	(2.29)	(-0.36)
log_income_1Kcapita	-10.15	27.07
	(-1.52)	(3.14)
log_phys_1Mpop	3.85	-5.03
	(0.64)	(0.74)
pct0_14	-376.92	-168.14
	(-3.09)	(-2.20)
pct65p	-274.45	-79.59
	(3.33)	(-3.04)
Time	0.05	0.09
	(2.24)	(2.60)
log_price_ratio	0.0009	3.23
	(0.00)	(-0.76)
log_share_num_newcmpnd	9.87	13.96
	(4.04)	(2.19)
log_rel_detail_lag1	0.24	0.62
	(2.08)	(3.12)
log_rel_detail_lag4*	0.45	0.58
	(7.73)	(9.69)
Number of observations	32	21
Adjusted R-square	0.967	0.997

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_rel_detail_lag1 replaced by log_rel_detail_lag4

One may have noted that none of the price/price-related variables in the above three sets of regressions (shown in Tables 3.3 – 3.5) has a significant parameter estimate (except for a barely significant price ratio variable for Japan in Table 3.4). This probably reflects the fact that both Germany and Japan have social-based health care systems, which have 1) centralized price controls and 2) wide coverage for pharmaceutical expenses of their citizens. As a result, the actual sales are relatively close to the real demand/need and are independent from the price of the drugs. Since direct-to-consumer advertising (for prescription drugs) is prohibited in both countries, the sales of drugs is more dependent on the doctors' awareness and knowledge of certain medicines, which is delivered via the means of detailing and other communications within the national health care systems.

3.4.3 Product-level analysis

However, it is presumptuous to rush into the conclusion that these two markets are completely price inelastic. The governments on the one hand take price control, and on the other hand encourage using less expensive medications by policies such as co-payment and positive/negative lists of drugs. More disaggregated product-level analyses have shown that the pricing policy and the social-based health care systems did provide a mechanism to realize (to some extent) price-based product selection. Table 3.6 shows the product-level regression results, which support the above argument. (The detailed SAS outputs are shown in Appendix 2.)

At the product level, most of the estimated parameters are significant in Germany and more than half of the parameter estimates are significant in Japan. The negative parameter for the product price suggests the textbook-market characteristic: the lower the price, the higher the sales of the products. Although the demands in both countries are relatively price inelastic ($-1<$ price elasticity <0), Germany appears to be more price-elastic than Japan (-0.60 vs. -0.15). This is consistent with the fact that Germany has more competing antihypertensive medications, less control of the pricing of innovative drugs and less-universal coverage of pharmaceutical expenses by the government [25].

In this set of regression, the dummy variables 'new' and 'middle' have positive signs in Germany and Japan (except for middle in Japan). This is not consistent with the results shown in Table 3.4, where all dummies have negative signs. This may be a result of high product-level variance of the sales of new and middle generation medications. Thus at aggregated level the variance is cancelled.

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Table 3. 6   Regression results of Equation 4 (dependent variable: log_prod_pd_capita)

Variable	Parameter estimate	
	Germany	Japan
Intercept	**49.65**	82.91
	(3.18)	(1.14)
log_income_1Kcapita	-5.85	**-30.96**
	(-1.42)	**(-2.88)**
log_phys_1Mpop	1.67	-0.52
	(0.62)	(-0.06)
pct0_14	**-227.45**	35.71
	(-4.66)	(0.36)
pct65p	**-135.22**	19.10
	(-4.02)	(0.41)
time	-0.007	-0.06
	(-0.57)	(-1.21)
log_price_prod	**-0.60**	**-0.15**
	(-16.54)	**(-2.63)**
log_num_new_compound	0.011	0.027
	(0.74)	(0.53)
generic	**-0.71**	**-2.50**
	(-6.49)	**(-7.08)**
new	**1.87**	**4.37**
	(10.86)	**(11.10)**
middle	**1.04**	**-0.47**
	(16.48)	**(-3.98)**
oldgen	**0.39**	-0.39
	(3.21)	(-0.93)
log_prod_detail_capita_lag1	**-0.07**	**-0.04**
	(-4.07)	**(-4.53)**
log_prod_detail_capita_lag4*	**-0.062**	0.0038
	(-12.82)	(0.36)
Number of observations	12389	3217
Adjusted R-square	0.06	0.14

t-values are shown in the parenthesis below the parameter estimates.
model is run with log_rel_detail_lag14 replaced by log_rel_detail_lag4
Omitted generation variable: old

In this regression model, some dummy variables are also added in addition to the new- and old-generation dummies. The generic dummy variable differentiates generics drugs (products labeled as "G" or "NA" in the IMS database) from the branded drugs. The branded drugs are defined as products labeled with "O" (originator), "B" (other branded), or "L" (licensee) in the IMS database. The branded drug dummy variable is omitted in the regression. The results show that the generic drugs have fewer sales than the branded drugs in Germany and Japan. However, Germany uses more generics than Japan (-0.71 and -2.50 respectively). This is partially because that under the social-based health care system, since the demand price elasticity is low (as shown in the regression), the generics substitute branded drugs more slowly than the market with greater price competition. Japan's low price elasticity may have further slowed down the adoption of generics. Other factors may include the patent expiration dates of each drug (drugs are launched later in Japan than in Germany), the market share of the drugs with patent protection, and physicians' traditional perceptions of generic drugs. The variable "oldgen" has opposite signs in the two countries (0.39 for Germany and -0.39 for Japan, but not significant). The positive sign indicates that the old generics have more sales than newer generics and old branded drugs in Germany. This result is consistent with the previous studies [1] and the findings for the generics dummy earlier in the same regression that generics are more common in Germany than in Japan.

Three out of four promotion variables have significant negative signs in the regression results shown in Table 3.6, contrary to the results shown in the generation-level regressions (shown in Table 3.5). This may be a result of the heavy promotion of certain very new products, whose sales volume has not picked up and a result of the opposite situation for some old products. (At the aggregated generation level, this is not differentiated.) The insignificant parameters for the time variable may result from the same reason.

3.5 Summary for the antihypertensive markets

In sum, the German and the Japanese antihypertensive markets have exhibited both the effects of competitive markets and government interventions. Firstly, at the aggregated class-level, the markets expanded over time in terms of volume (patient days) and revenue (US$). Secondly, there is a clear difference in antihypertensive sales volume among the three generations. In Germany the new generation had penetrated the antihypertensive market more slowly than that in Japan, because the Germany market is more mature and competitive. The fast increase in the share of the new generation in Japan has resulted in a higher average price than that in Germany. In both countries, the price controls and competition have led the prices of the various new-generation antihypertensives to converge over time. Thirdly, detailing activities have significant positive impact on the sales of new drugs in Germany. Finally, at the product-level the price variable shows a low demand price elasticity of the antihypertensives. In both countries the branded antihypertensives were used more than the generics, with Japan being the stronger case. However, the generics were clearly used more in the old generation than in the new and middle generation in the German market; this is not the case for Japan, where none of the generations had dominant generic sales.

Chapter 4 Antidepressants in Germany and Japan

In chapter 3 the market, sales patterns of antihypertensives and the factors that contribute to them were analyzed for Germany and Japan. This chapter follows a similar structure as in chapter 3 but instead for the case of antidepressants. Firstly, a background discussion on depression and antidepressant medications is introduced. Following that, descriptive analyses of the antidepressants at the class, generation and compound level are presented. Then econometric models are used to quantify and compare the factors that contributed to the sales and diffusion of antidepressants during 1992-2003 in Germany and Japan. Finally, a summary based on the descriptive and econometric analyses is presented at the end of this chapter.

4.1 Symptoms and causes of depressive disorders

Depression is a serious medical illness. Typical symptoms of depression are a persistent sad, anxious, or "empty" mood, feelings of hopelessness, guilt, worthlessness, helplessness, pessimism, loss of interest or pleasure in hobbies and activities that were once enjoyed [26]. There are three most common types of depression: (1) Major depression: It can disable one's ability to work, study, sleep, eat, and enjoy once pleasurable activities. Major depression can occur once or several times in a lifetime. (2) Dysthymia: It is less severe than the major depression. It involves chronic symptoms that keep one from functioning well or from feeling good. (3) Bipolar disorder: Bipolar disorder is also called manic-depressive illness. It is characterized by cycling mood changes: severe highs (mania) and lows (depression) [26].

Untreated depression has many negative effects. They include: reduced ability to fight infection; resistance to seek for or comply with treatment of illnesses; sleep deprivation; alcohol and drug abuse; reduced ability in work life, family life, and social life; and suicidal behaviors [27].

The biological causation of depression remains unclear, albeit it is widely recognized by scientists that people suffering from depressive disorder have smaller hippocampus (a small part of brain) than people who do not suffer from depression. A smaller hippocampus has fewer serotonin receptors, which is a chemical messenger that allows communication between nerves in the brain and the body (also called neurotransmitter) [27]. Hence the medications for depression are aimed to increase either the amount of serotonin or the neurotransmitters in the patients' brain.

Although scientists have not found out why depressed people have a smaller hippocampus, they do realize some of genetic the factors that can lead to depression. Firstly, some onsets of depression can be 'inherited'. Some types of depression (such as bipolar disorder) are passed from parents to children, suggesting a biological vulnerability that is transferred genetically [26]. Studies have also shown that depression can be gender-related: women experience depression about twice as often as men, related to hormonal variation [28].

However, there are many people with depression whose families do not have a history of depression. Thus non-genetic factors such as major changes in life patterns, financial burdens, serious illnesses (such as stroke, Parkinson's disease), and other stresses at home, work, or school may contribute to the onset of depression. Usually the onset of depression is due to a combination of several of the factors mentioned above.

4.2 Cultural factors of the prevalence and treatment of depression

Similar to hypertension and many other diseases or conditions, the prevalence of depression and percentage of treated patients are closely related to regional culture and tradition. In particular, Japan has distinct differences in diagnosis and treatment of depression from Germany, other parts of Europe, and the U.S. due to cultural origins. These reasons are briefly discussed in this section.

Mental illness has long been stigmatized and inadequately addressed in Japan [29]. The suicide rate was one of the highest among developed countries (24.1 per 100,000 population in 2000) [30]. In an epidemiological study 29.9% of a population randomly selected from 300 communities in Japan had depression [31]. The prevalent ignorance of depression and other mental illnesses by the Japanese public comes from deep cultural roots. Traditionally, Japanese people consider depressive symptoms as natural or just a sign of an individual's weaknesses, instead of a medical condition. As a Japanese psychiatrist Tooru Takahashi described, "Melancholia, sensitivity, fragility – theses are not negative things in a Japanese context... It never occurred to us that we should try to remove them." [29] The word for "depression" traditionally referred only to major or manic depressive disorders and was seldom heard outside psychiatric circles. The mentally ill are seen to bring shame to one's family name [32]. Even the medical professionals' awareness of depression was extremely insufficient. Naoki Watanabe, an expert in suicide and depression said in an interview with the BBC News, "Doctors and nurses in Japan are not trained to recognize depression." [33] As a result, the sales of antidepressants were very low before the late 1990's. Eli Lily, the manufacturer of Prozac (the U.S. product name of fluoxetine) found virtually no demand for antidepressants in Japan when it intended to introduce Prozac to the Japanese market in the 1980's [29].

Only beginning in 1999, a Japanese company (Meiji Seika Kaisha) started to promote depromel (product name of fluvoxamine in Japan), a more than 10 years' delay from the same drug being marketed in Europe and the United States [34]. One year later, GlaxoSmithKline entered the Japanese market with its product Paxil (product name of paroxetine). Both companies marketed their antidepressants with a nation-wide education campaign for depression [29]. At the same time, the Japanese government conducted health campaign as well. These campaigns have successfully increased much awareness of depression in the public and among medical professionals. As a result, the antidepressant market in Japan started to expand quickly.

Among the developed countries other than Japan, Germany has relatively high prevalence of depression (about 9.2% in West Germany in 1996 [35]) and low percentage of treated patients (35% [36] of those, i.e. about 3% of the total population). In addition, Germany has slightly higher percentage of females during the time period (shown in Figure 1.5), who are more susceptible to depression than men. However, as compared to Japan, the prevalence of depression in Germany is lower. In addition, the awareness and treatment of depression has a much longer history than in Japan; therefore the percentage of treated patients is much higher. As will be shown in section 4.3, Germany also has a more varied selection of antidepressant medications than does Japan.

Given the above facts, one may hypothesize that although both markets for antidepressants have grown due to the increased awareness and diagnostics, the Japanese market would be smaller than the German market (on a per-capita scale); and the sales of antidepressants in the Japanese market would show a more dramatic take-off starting from the late 90's. The results of the data analysis in this work are consistent with these hypotheses. For example, the per-capita sales levels of antidepressants in Germany and Japan have a large gap (per-capita sales in Germany is 1.5 time of that in Japan in 2003). This, together with other findings, is illustrated and discussed in greater detail in section 4.3.

4.3 Types of antidepressants

Despite the heterogeneous prevalence and recognition, depression has drawn more and more attention from doctors, researchers, governments, and the public in many countries. Research and development of treatments for depressive disorders have been conducted by government- and industry-funded projects. Currently, there are four common types of antidepressants categorized by their mechanisms of action: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) [27]. The newer generation of antidepressants (such as SSRIs) generally has fewer side effects than the older generation (such as the TCAs) [26].

In the analysis of this work, two generations of medications are defined by mechanisms of action and the time they have been in the market. The SSRIs, the SNRIs and a few other newer antidepressants (bupropion and mirtazapine) are categorized as the "new" generation; TCAs, MAOIs, mood stabilizers and psycho stimulants are classified as the "old" generation. There is no "middle" generation for antidepressants in this chapter. Table 4.1 summarizes the different types and side effects of antidepressants sorted by their mechanisms of action as well as their generations [27]. Appendix 3 gives a complete list of the compounds included in this study.

Although in general the new generation of antidepressants has fewer side effects than the old generation, the efficacy and reaction to medication depend on individual patients. Usually the physicians will try a variety of antidepressants (and dosages) before finding the most effective medication or combination of medications [26].

Table 4. 1   Categories and side effects of antidepressants by mechanisms of action in this study

Categories	Mechanism of action	Side effects	Generation
TCAs	Increase the amount of serotonin and/or norepinephrine in the brain	Dry mouth, blurred vision, increased fatigue and sleepiness, weight gain, muscle twitching (tremors), constipation, bladder problems such as urine retention, dizziness, daytime drowsiness, increased heart rate, sexual problems.	Old
MOAIs	Increase the amount of norepinephrine and serotonin in the brain	Must avoid certain foods and medications to avoid dangerous interactions, serious side effects may include: headache, heart racing, chest pain, neck stiffness, nausea and vomiting.	Old
SSRIs	Increase the amount of serotonin in the brain	Reversible sexual problems, dizziness, headaches, nausea right after a dose, insomnia, feeling jittery	New
SNRIs	Increase the amounts of neurotransmitters, norepinephrine and dopamine in the brain.	Weight loss, decreased appetite, restlessness, insomnia, anxiety, constipation, dry mouth, diarrhea, dizziness, drowsiness, blurred vision, lightheadedness	New

Source: www.WebMD.com

Besides the above-mentioned medications, there are other treatments for depressions such as electroconvulsive therapy (ECT), psychotherapies and herbal medicines. Herbal medications (such as St. John's Wort) for treating depression are used in Europe and some Asian countries. However, the actual sales of such medication are relatively small and difficult to estimate (as they are usually sold as diet supplements). Due to the constraints of data availability, they are not included in this study.

4.4 Descriptive analysis of the sales and promotion of antidepressants

4.4.1 The sales of antidepressants

Firstly, the overall antidepressant markets in number of patient days in Germany and Japan are plotted and compared (during 1992-2003). As shown in Figure 4.1, the total sales of antidepressant tripled in Germany (from 0.11 to 0.30 million patient days) and Japan (from 0.06 to 0.18 million patient days) during the time period. In Japan, two stages with distinct sales growth rates of antidepressants can be observed: The first stage is from 1992 to 1998 (7 years), in which the yearly sales grew by 0.08 million patient days (from 0.28 to 0.36 million patient days); the second stage is between 1999 and 2003 (5 years), in which the yearly sales increased by 0.23 million patient days (from 0.41 to nearly 0.65 thousand patient days). This is consistent with the hypothesis made at the end of section 4.1 that the Japanese antidepressant market experienced a large expansion after the introduction of fluvoxamine and paroxetine in the late 1990's, accompanied by massive educational and promotional campaigns. In contrast, the growth in Germany is more evenly distributed over the time period than that in Japan.
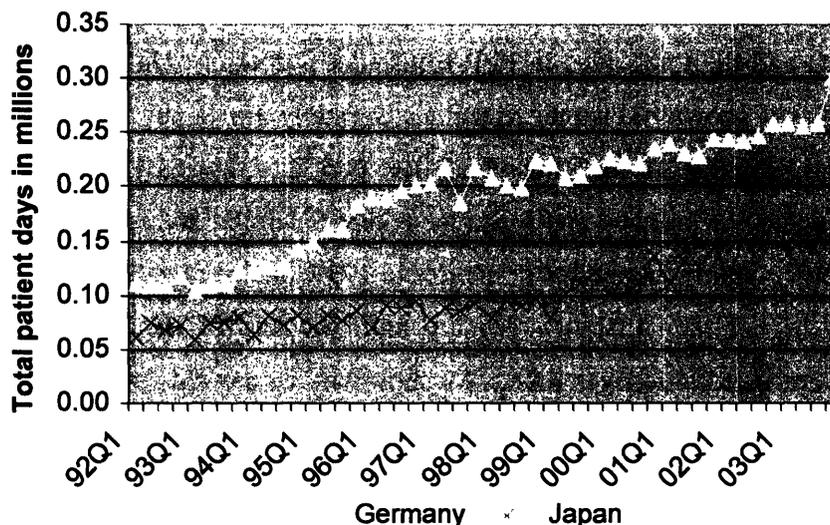
Figure 4. 1   Total patient days for antidepressants in Germany and Japan
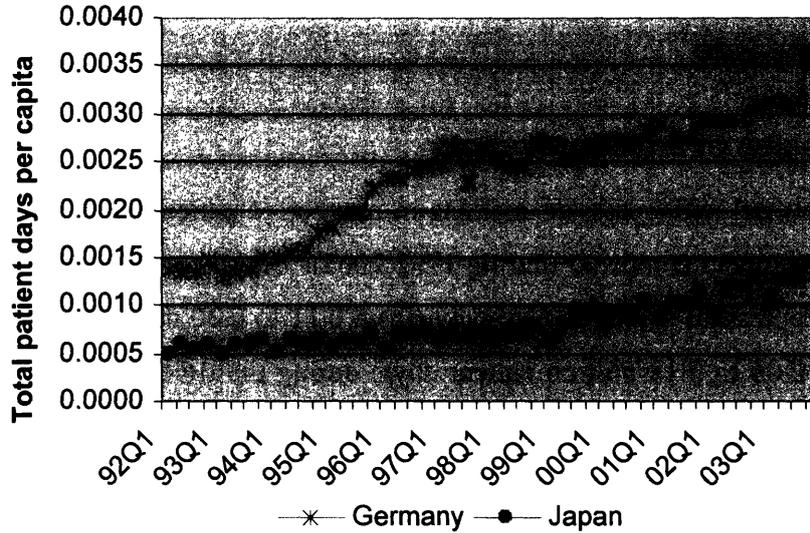
Figure 4. 2   Total patient days per capita for antidepressants in Germany and Japan

The characteristics of the antidepressant markets in Germany and Japan are further illustrated under the patient-days-per-capita scale in Figure 4.2. The German market shows a steeper growth on a per-capita scale and the two stages in the Japanese market appear to have a clearer distinction in sales volumes at the beginning of year 1999.

Figures 4.3 and 4.4 are the price per patient day (total sales divided by total patient days of each year) and the total sales in PPP-adjusted US dollars. Unlike the price for the antihypertensives shown in chapter 3, neither Germany nor Japan had consistent higher prices for antidepressants during the whole time period of the study. The average prices of antidepressants in Germany and Japan were kept to similar levels from 1992 to the 2nd quarter of 1999. Starting from the 3rd quarter in 1999, the average price in Japan became consistently higher than that in Germany until the end of the data, and this price difference kept increasing over time. As shown in Figure 4.4, the total US$ sales in Japan almost reached the same level as that in Germany in 2003, despite the fact that Germany had about 40% more sales volume (patient days) than Japan (shown in Figure 4.1).
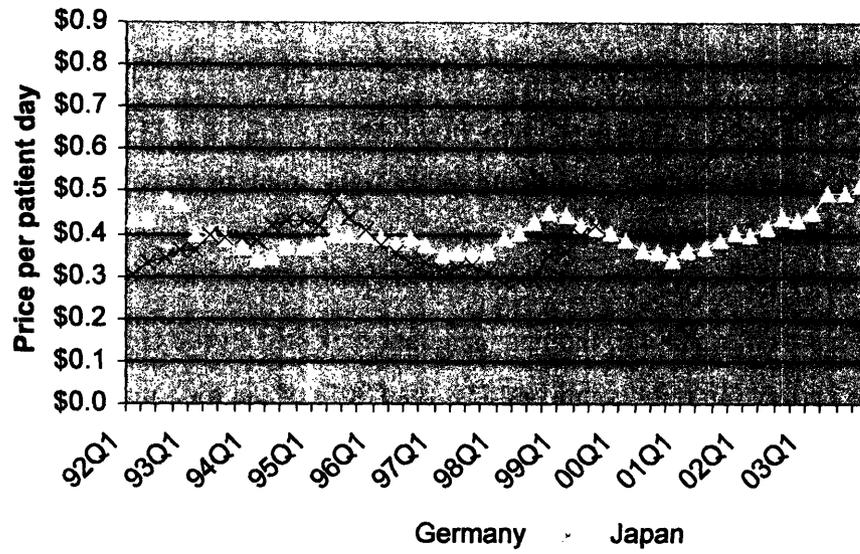
Figure 4. 3   Price per patient day (in PPP-adjusted US$) for antidepressants
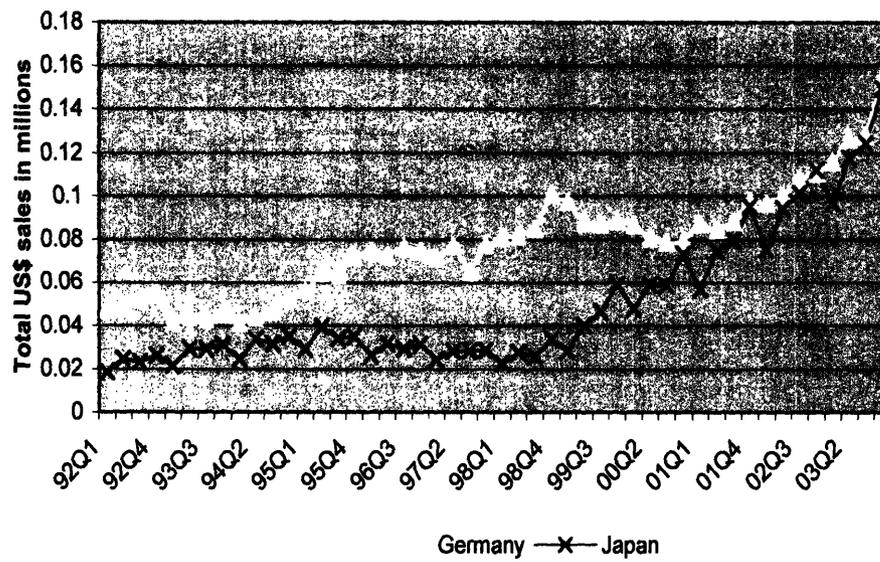
Figure 4. 4   Total sales (in PPP-adjusted US$) for antidepressants

The difference in per-patient-day price between Germany and Japan partially results from the same reason as in the antihypertensives case: The expensive new drugs had a higher share in Japan than that in Germany in the last 4-5 years of the time period and lower share in the first 7-8 years. Figures 4.5 and 4.6 illustrate the change of the market share of new and old generations of antidepressants over time in each country. (The generations are defined in section 3.2.)

As shown in Figures 4.5 and 4.6, the new generation existed in the German market for the whole time period, but only comprised less than 30% of the total market share at the end of 2003. In Japan although the new generation was introduced much later (in 1999), the market share of the new generation was able to grow quickly and reached almost 40% of the total market sales by 2003.
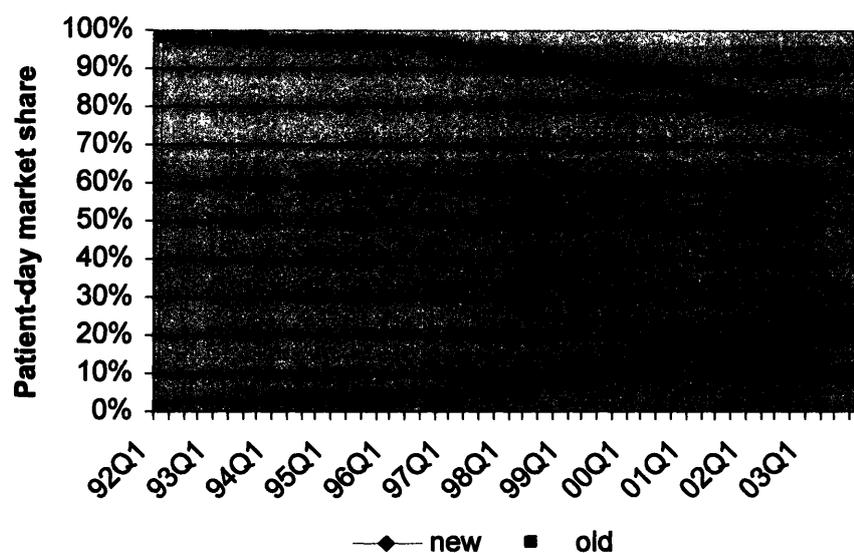
Figure 4. 5   Market share (in patient days) of antidepressants in Germany
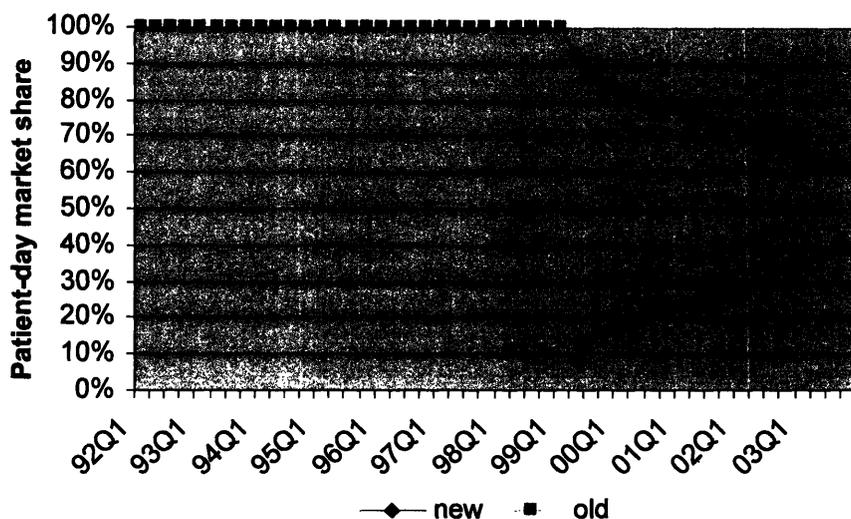
Figure 4. 6   Market share (in patient days) of antidepressants in Japan

Figures 4.7 and 4.8 are the average per-patient-day prices of the new compounds. The prices of new compounds in Germany experienced a converging trend and diverged again in the last three years in the time period, ranging from $0.45 to $1.80. This is different from what is observed in the antihypertensives case, where the prices converged but did not diverge again. The reason for this phenomenon is that among the new drugs, the ones that were launched relatively late (such as venlafaxine and sertraline) remained at their price levels since launch until 2003; however, the ones that were launched relatively early (such as paroxetine and fluoxetine) had price decrease because generic versions started to enter the market, which are cheaper than the branded version. Since the prices shown in Figure 4.7 are averaged branded and generic drug prices, they decrease as generics entered the market. In Japan, there were only 2 new compounds launched in the market, and the prices were $1.04 and $1.84 at the end of the time period respectively. In both countries, the prices generally had a downward trend.
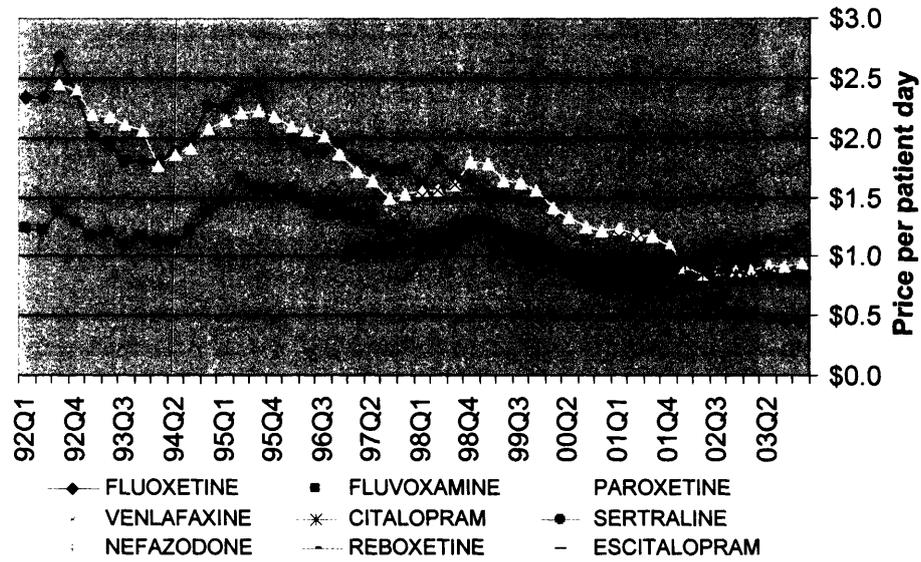
Figure 4.7   Price per patient day (in PPP-adjusted US$) for new antidepressants in Germany
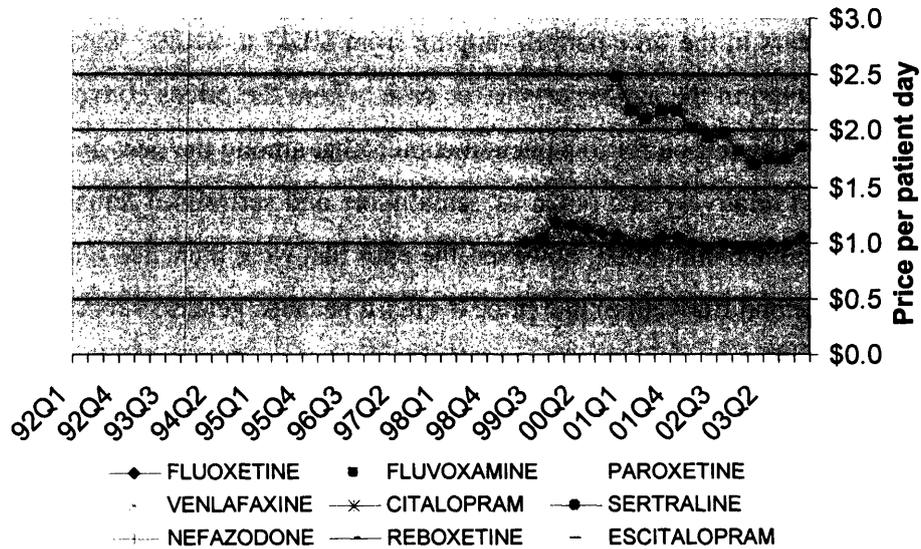
Figure 4.8   Price per patient day (in PPP-adjusted US$) for new antidepressants in Japan

As seen in the above figures, nine new compounds were launched in Germany and only two compounds were sold in Japan. Figures 4.9 and 4.10 illustrate the patient days per million population for each of these compounds in both countries. In Germany, citalopram turned out to be the biggest player in the market, reaching over 0.00035 patient days per capita in the fourth quarter of 2003. However, fluvoxamine and paroxetine, the two compounds that were successfully marketed in Japan did not do as well in the German market. This may be due to the more intensive competition in the market and from the new entrants that might be more technologically advanced (such as citalopram and sertraline).

Patient days per million population

400
350
300
250
200
150
100
50
0

92Q1 92Q4 93Q3 94Q2 95Q1 95Q4 96Q3 97Q2 98Q1 98Q4 99Q3 00Q2 01Q1 01Q4 02Q3 03Q2

—◆— FLUOXETINE   ■ FLUVOXAMINE   PAROXETINE
VENLAFAXINE   —✳— CITALOPRAM   —●— SERTRALINE
+ NEFAZODONE   —— REBOXETINE   – ESCITALOPRAM
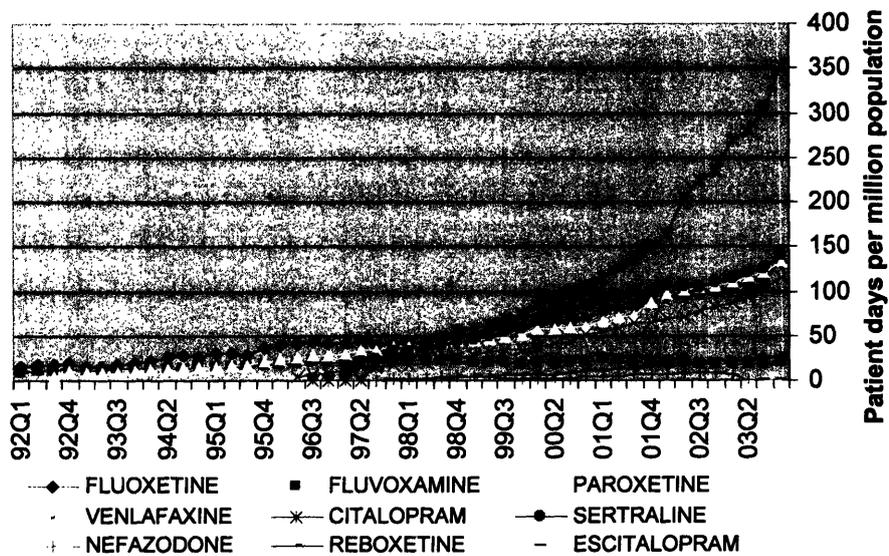
Figure 4.9   Patient days per million population for new antidepressants in Germany

65
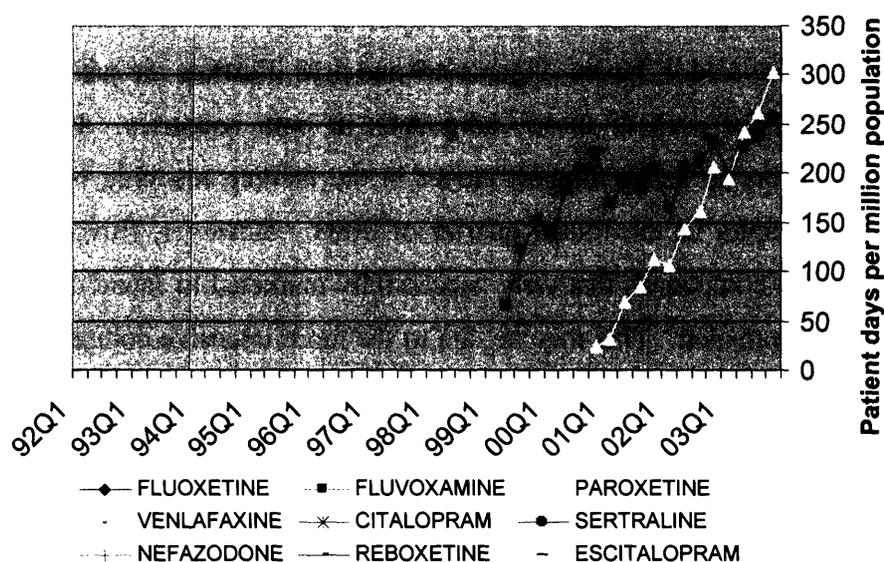
Figure 4.10   Patient days per million population for new antidepressants in Japan

In sum, both the Germany and Japanese markets showed a growing trend for the sales of antidepressants in patient-day and US$ units. As a more mature market, Germany shows the following characteristics as compared to Japan: (1) Germany has a larger total sales and per capita sales than Japan; (2) The growth in Germany is more modest and steady than that in Japan; (3) The German market adopted the new drugs earlier and has more competing compounds within the new generation. The large difference in the average prices in the two markets at the second half of time period does not necessarily suggest that the drugs are overpriced in Japan. This is because many drugs were launched in Japan later than in Germany, and the prices of drugs are usually negatively correlated with time in both countries, i.e., a downward trend over time due to the decrease of branded drug prices and the launching of cheaper generics after patent expiration. If we compare the first-year-after-launch prices of the 2 new compounds existing in both markets, the prices are very similar in both countries. (The price for fluvoxamine was even higher in Germany.) Hence the seemingly high price in Japan is partially a result of delayed launches of certain compounds. The fast growth of the new generation (in share volume) in Japan may have been a result of less competition and the government health campaign as well as promotions by pharmaceutical companies.

4.4.2 The promotion of antidepressants

In this section, detailing activities for the promotion of antidepressants in Germany and Japan are compared and discussed (again, note that the detailing information in Japan is only available between 1998 and 2003).

Similar to the case of antihypertensives, antidepressants are more heavily promoted in Japan at the end of the time period than in Germany through detailing to physicians because of the launches of the new compounds. Figures 4.11 and 4.12 show the promotional efforts in total detailing counts per-million-population and per-million-physicians scales. There is a sharp increase for detailing counts in Japan in 1999, due to the heavy promotion by Meiji Seika Kaisha and GlaxoSmithKline, manufacturers of fluvoxamine and paroxetine.
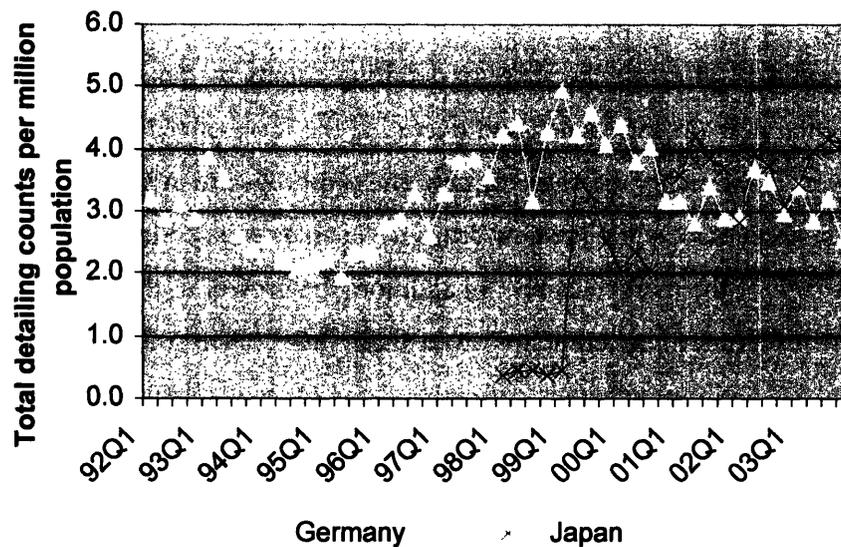
Figure 4.11   Total detailing counts per million population for antidepressants
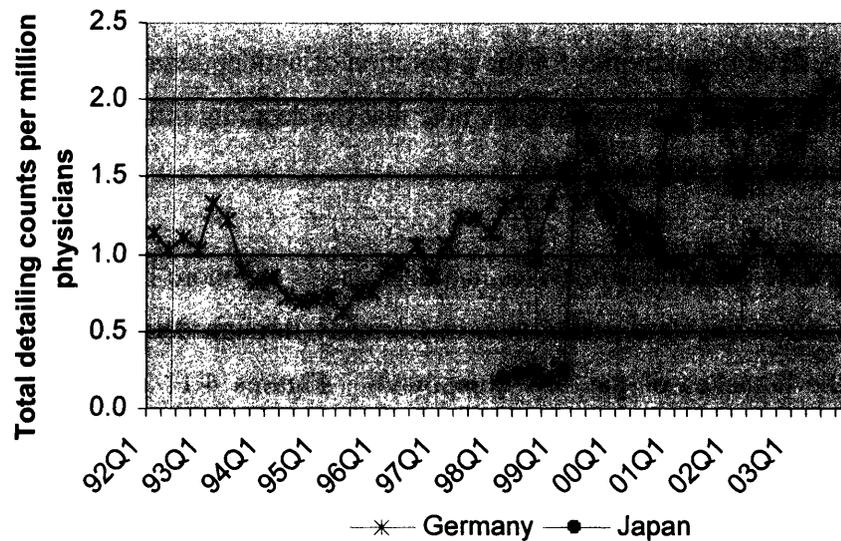
Figure 4.12 Total detailing counts per million physicians for antidepressants

Figures 4.13 and 4.14 illustrate the share of detailing counts by generation of drugs. In both countries the new drugs reached and exceeded the level of old drugs at the end of 2003. However, in Germany the share of new and old drugs are at similar levels (about 50% for both generations); while the new drugs in Japan dominated in sales volume since launch (about 80% of the market share). In addition, the growth of the new generation is more gradual in Germany, as compared to a high share level since launch in Japan. Recall that in the antihypertensives case, the share of new medication had a steady growth in Japan and in Germany.

In conclusion, the descriptive analysis has shown distinct patterns of sales and promotion activities in Germany and Japan. In Germany, the antidepressant market is relatively mature, and the data shows more competition and less abrupt changes. In Japan, the new generation of antidepressants shows a successful growth since launch and has expanded the overall market as well. Similar to the Japanese antihypertensive market, the relatively high sales of new antidepressants come with vigorous promotional efforts. In the next

section, the relationship of sales and promotion as well as other factors will be examined quantitatively using regression models.
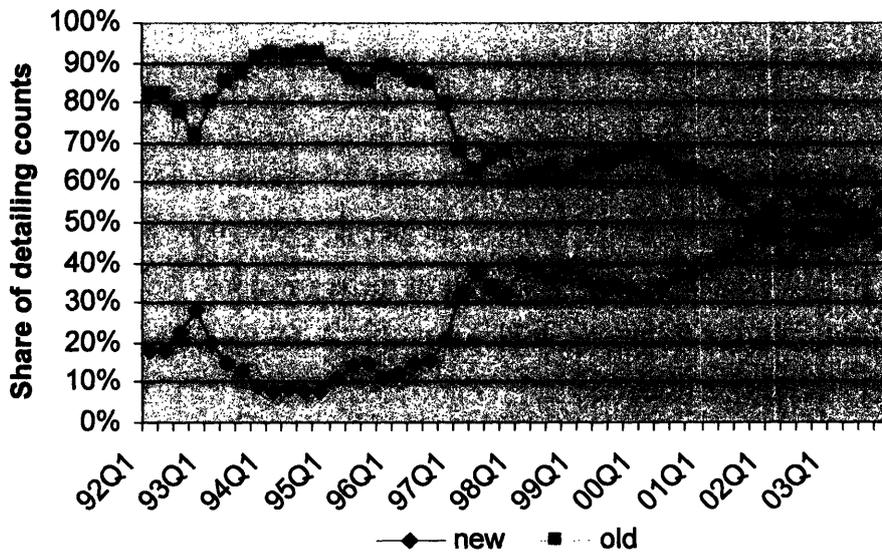
Figure 4.13   Share of detailing counts by generation for antidepressants in Germany
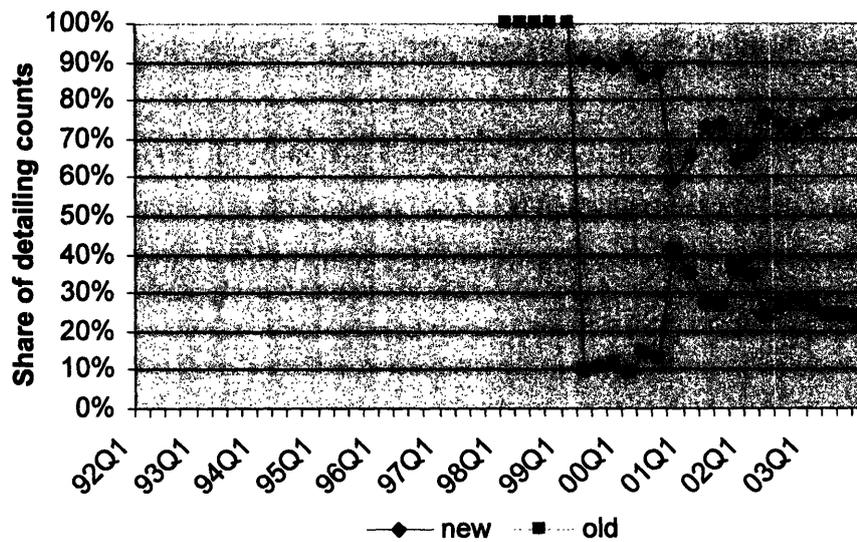
Figure 4.14   Share of detailing counts by generation for antidepressants in Japan

4.5 Econometric analysis

In this section, the same regression models (Equations 1-4) introduced in chapter 2 and used in chapter 3 are adopted to examine quantitatively the relationship between the diffusion of antidepressants and economic, demographic and policy factors. To recap, these factors are: 1) the overall wealth of the society (GDP per capita), 2) availability of medical care (represented by number of physicians per capita), 3) promotion intensity (lagged detailing counts), 4) regulated prices, and 5) age structure of the population. Again, the right-hand-side (RHS) variable tot_detail_capita_lag1 appears in separate regressions from tot_detail_capita_lag4 in all of the regressions due to their high pair-wise correlation. In the following sections 4.4.1 – 4.4.3 the class-, generation- and product-level analyses are discussed.

4.5.1 Therapeutic-class-level analysis

The regression outputs of the logarithmic form of Equation 1 in chapter 2 for the antidepressant medications in Germany and Japan are shown in Table 4.2. (Detailed SAS outputs are included in Appendix 4.) The dependent variable is the total patient days per capita at therapeutic class level (log_tot_pd_capita); the RHS variables (price, number of compounds, and detailing information) were also calculated at the therapeutic class level.

As seen from Table 4.2, the time trend variable has significant parameter estimates for both countries (0.03 for Germany and 0.15 for Japan). This is similar to the findings for the antihypertensives in chapter 3, in which the parameters are positive and significant (0.03 for Germany and 0.08 for Japan).

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Table 4. 2   Regression results of Equation 1 (dependent variable: log_tot_pd_capita)

Variable	Parameter estimate	
	Germany	**Japan**
Intercept	**30.98**	82.55
	(2.14)	(1.75)
log_income_1Kcapita	0.59	-10.16
	(0.36)	(-1.81)
log_phys_1Mpop	-1.83	-9.16
	(-1.59)	(-1.67)
pct0_14	**8.45**	2.76
	(2.44)	(0.37)
pct65p	**6.15**	**-6.23**
	(2.36)	**(-2.06)**
time	**0.026**	**0.15**
	(3.24)	**(4.64)**
log_price_class	**0.29**	**-1.14**
	(2.01)	**(-2.09)**
log_price_ratio	**0.71**	1.37
	(3.85)	(1.91)
log_num_compound	0.66	-0.84
	(1.70)	(-1.13)
log_tot_detail_capita_lag1	0.086	-0.053
	(1.13)	(-1.27)
log_tot_detail_capita_lag4*	0.069	0.0021
	(1.54)	(0.03)
Number of observations	46	19
Adjusted R-square	0.955	0.924

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_tot_detail_capita_lag1 replaced by log_tot_detail_capita_lag4

The age structure variable pct65p (percentage of people who are 65 or older) are significant for both countries but with opposite signs (6.15 for Germany and -6.23 for Japan). This is consistent with the studies that the Japanese senior people tend not to treat their depression [32]. Hence the decrease of pct65p over time did not drive down the sales of the antidepressants in Japan.

The price variable log_price_class also have significant parameter estimates in Germany and Japan. This seems to be different from the case for the antihypertensives, where the class-level price variables are insignificant. However, the absolute values of the t-statistics for these variables in Table 4.2 are low (only about 2). As was explained in chapter 3, the price elasticity at aggregated levels could be less representative than that at the disaggregated level. The price elasticities at generation and product levels are illustrated and analyzed in sections 4.4.2 and 4.4.3.

4.5.2 Generation-level analysis

In this section, the sales of antidepressants in number of patient days are regressed at the generation level (Equation 2). Following that, Equation 3 with the number of patient days for new drugs only being the dependent variable is applied to the data. Similar to chapter 3, the RHS variables such as price, detailing information, and the number of compounds are adjusted accordingly to be at the generation level. As described in Equation 2 in chapter 2, dummy variables differentiating the generations of antihypertensives are used (with the old generation as omitted variable). The omitted dummy variable is the old generation. The regression results of Equation 2 (in logarithmic form) and Equation 3 (in linear form) are shown in Tables 4.3 and 4.4 (The detailed SAS outputs are shown in Appendix 4.).

The results illustrated in Table 4.3 for antidepressants are somewhat similar to the results for the antihypertensives (in Table 3.4). Firstly, the difference between the new generation and the old generation is highly significant. In both countries, the new generation has negative parameters, indicating a dominance of the old generation in sales volume. The absolute difference of drug sales between the new generation and the old generation is smaller in Germany (-3.35) than in Japan (-4.07).

Table 4. 3   Regression results of Equation 2 (dependent variable: log_gen_pd_capita)

Variable	Parameter estimate	
	Germany	Japan
Intercept	**-30.65**	-53.40
	(-3.50)	(-1.53)
log_income_1Kcapita	**-5.00**	-8.77
	(-2.04)	(-1.46)
log_phys_1Mpop	**4.88**	8.62
	(2.52)	(1.84)
pct0_14	-6.28	**124.24**
	(-0.27)	**(2.22)**
pct65p	5.74	-27.40
	(0.37)	(-1.50)
time	0.0068	**0.046**
	(0.94)	**(3.03)**
log_price_ratio	**0.33**	-0.84
	(2.47)	(-1.49)
log_price_gen	**-0.44**	-0.11
	(-3.88)	(-0.39)
log_num_new_compound	**0.24**	**0.24**
	(3.91)	**(2.00)**
new	**-3.35**	**-4.07**
	(-15.26)	**(-13.68)**
timenew	**0.059**	**0.081**
	(26.19)	**(12.98)**
log_gen_detail_capita_lag4	0.063	**0.47**
	(1.20)	**(5.30)**
log_gen_detail_capita_lag1*	-0.053	0.0056
	(-1.47)	(0.06)
Number of observations	88	38
Adjusted R-square	0.997	0.987

t-values are shown in the parenthesis below the parameter estimates.
model is run with rel_detail_lag4 replaced by rel_detail_lag1
Omitted generation variable: old

Secondly, the number of new compounds has significant and positive parameter estimates in both countries. This again suggests that the increasing variety of the new drugs has been coupled with the expansion of the market for the new and the old generations. However, in Japan the parameter estimate has a very low significant t-statistic. This is

because there are only two new compounds launched during the time period (shown in sections 4.1 and 4.3), hence the effect of the change of new compounds is not as clear as that in Germany, where there are nine new compounds in the market.

Finally, the interactive variable timenew have significant and positive parameters in both countries. This indicates that as time went by the new generations had faster increasing in sales than the old generation.

Table 4.3 also showed some results that are different from those in Table 3.4 in chapter 3. First, in Table 3.4 three out of four of the detailing variables have significant negative parameters. However, in Table 4.3 there is only one (log_gen_detail_capita_lag4 for Japan) that is positive and significant. A possible explanation for the insignificant promotion variables is that they are a result of the co-existence of the heavily detailed low-sales-level new generation and the lightly detailed high-sales-level middle and old generations. Secondly, the parameter for the time variable in Table 4.3 is significant for Japan, as compared to the insignificant parameters for the antihypertensives in chapter 3. These indicate that in Japan the overall trend for both new and old generations is to increase over time. However, in Germany the old generation experienced decreasing sales over certain period of time, accompanied by the increasing sales of the new generation. Thirdly, two of the demographic and economic variables are significant in Germany: log_income_1Kcapita (-5.00) and log_phys_1Mpop (4.88). This may suggest that the generation-level sales of the antidepressants are related to the number of physicians in Germany. However, the decrease of GDP does not decrease the sales of antidepressants.

The new generation was then separated from the old generation; Table 4.4 shows a summary of the regression result with the LHS variable being the share of the patient days of the new medications (the linear form of Equation 3).

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Table 4. 4   Regression results of Equation 3 (dependent variable: share_new_pd)

Variable	Parameter estimate	
	Germany	Japan
Intercept	**2.00**	-1.20
	(2.39)	(-1.27)
income_1Kcapita	0.005	-0.030
	(0.57)	(-0.73)
phys_1Mpop	**-0.00010**	-0.00010
	(-2.18)	(-0.45)
pct0_14	**-6.33**	9.54
	(-2.11)	(1.15)
pct65p	**-4.14**	2.29
	(-2.02)	(0.98)
time	**0.0071**	**0.016**
	(7.57)	**(10.43)**
price_ratio	**-0.019**	-0.0043
	(-4.31)	(-0.26)
share_num_newcmpnd	**-0.61**	-0.14
	(-10.46)	(-0.74)
rel_detail_lag1	**0.019**	-0.0034
	(2.17)	(-1.68)
rel_detail_lag4*	0.0079	-0.00018
	(1.96)	(-0.29)
Number of observations	46	18
Adjusted R-square	0.989	0.994

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_rel_detail_lag1 replaced by log_rel_detail_lag4

In this set of regression, the parameter estimates for the time trend variable are positive and significant at the 95% confidence level for both countries. This result is consistent with the regression for the new antihypertensives, where in both Germany and Japan the new generation gained its sales volume with time. In Germany, the age variables have negative parameters, which suggest that people aged between 15 and 65 contributed to the increase of the sales of the new drugs.

The price ratio variable and the share of the number of new compounds variable both are negative and significant in Germany. The price ratio variable indicates a relationship

between demand and the relative price of the available products: the higher the new drugs' prices as compared to the old drugs' prices, the less the sales of the new drug as compared to the old drugs. The negative sign for the share of number of new compounds may suggest that the number of old drugs increased over time at a faster speed than the new drugs.

The regression results in Table 4.4 do not display a clear relationship of the lagged relative detailing and sales of new drugs. In Table 3.5 all of the relative detailing variables are significant, however, in Table 4.4 only the lagged cumulative 4-quarter relative detailing is significant in Germany (0.019). The insignificance of the detailing variable is probably caused by the increase in the level of detailing for the old generation in response of the promotion of the new generation. Significant parameter estimates are found when the relative detailing variable is substituted by the level of detailing counts of the new drugs (not shown in Table 4.4).

4.5.3 Product-level analysis

In chapter 3 the product-level analyses for the antihypertensives have shown that the pricing policy and the social-based health care systems could provide a mechanism to realize certain price-based product selection. Table 4.5 shows the product-level regression results for the antidepressants, which supports the above argument for the German market. (SAS outputs of the regression in Table 4.5 are shown in Appendix 4.)

Table 4. 5   Regression results of Equation 4 (dependent variable: log_prod_pd_capita)

Variable	Parameter estimate	
	Germany	Japan
Intercept	27.14	46.19
	(1.25)	(0.48)
log_income_1Kcapita	-6.23	-2.54
	(-1.05)	(-0.17)
log_phys_1Mpop	4.81	-4.19
	(1.17)	(-0.35)
pct0_14	**-254.90**	-62.83
	(-3.19)	(-0.56)
pct65p	**-122.06**	-62.37
	(-2.27)	(-1.00)
time	-0.033	0.08
	(-1.72)	(1.21)
log_price_prod	**-0.24**	**0.27**
	(-4.07)	**(2.12)**
log_num_new_compound	0.26	-0.073
	(1.27)	(-1.21)
generic	**0.32**	**-1.12**
	(4.39)	**(-2.72)**
new	0.20	**2.03**
	(1.67)	**(6.08)**
log_prod_detail_capita_lag1	**-0.040**	**0.066**
	(-7.41)	**(5.28)**
log_prod_detail_capita_lag4*	**-0.016**	-0.034
	(-2.50)	(-1.51)
Number of observations	5739	670
Adjusted R-square	0.034	0.148

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_rel_detail_lag14 replaced by log_rel_detail_lag4
Omitted generation variable: old

At the product level, the parameter for the product price in Germany is negative (-0.24), which suggests the competitive market characteristic: the lower the price, the higher the sales of the products. But the demand is relatively inelastic. However, in Japan this parameter is positive and significant (0.27). This is a result of the special situation for antidepressants' diffusion in Japan: the government (as well as the industry) has jointly promoted the adoption of the new generation of antidepressants, which are more

expensive than the old generation. Because of the high health care insurance coverage, the drugs that have more advanced efficacy are used regardless of the higher prices. The higher sales of the more expensive medications has driven the price variable to appear positive. (In contrast, in Germany the more competing antidepressant medications, more space for price-setting and possibly because of the less health care coverage [25] have resulted in a more competitive demand elasticity.)

As a reminder, the 'generic' dummy variable differentiates generics drugs (products labeled as "G" or "NA" in the IMS database) from the branded drugs. The branded (omitted) drugs are defined as products labeled with "O" (originator), "B" (branded), or "L" (licensee) in the IMS database. The results show that the generic drugs are more widely used in Germany (0.32) than in Japan (-1.12). This finding is consistent with that in chapter 3 (Table 3.6). However, for the antidepressant case, generics are used more than the branded drugs, as compared to the antihypertensive case where generics are used less in Germany. This is partially because many of the new branded antidepressant drugs have lost their patent protection in Germany.

Both of the promotion variables have significant negative signs in Germany (shown in Table 4.5), a same non-intuitive result as that in Table 3.6. Again, this may be a result of the heavy promotion of certain very new products, whose sales volume has not picked up and a result of the opposite situation for some old products. However in Japan, there were only two compounds available in the market, which are more homogenous in terms of their launch time and promotional patterns.

4.6 Summary for the antidepressant markets

In summary, the German and the Japanese antihypertensive markets have shown evidence of the effects of competitive markets and government interventions. However, as compared to the antihypertensive market, the non-economic factors (such as culture and government intervention) played a more important role in the sales of antidepressant in Japan.

At the therapeutic-class-level, the markets expanded significantly over time in terms of volume (patient days) and revenue (US$) in both countries. In Japan there is a clear distinction of two stages in terms of the sales of the antidepressants. This is a result of tradition and educational campaigns conducted by the pharmaceutical industry and the government.

Similar to the antihypertensive markets, there is a clear difference in antidepressants sales volume between the new and the old generations (new < old). In Germany the new generation included a greater number of compounds and was launched earlier than that in Japan, but penetrated the antihypertensive market more slowly than that in Japan, because the Germany market is more mature and competitive. Although in Japan there were only two new compounds in the market, the number of new compounds showed positive and significant correlation with the generation-level patient day sales in both markets.

The averaged price level of antidepressants is higher in the Japanese market since the later launch of the more expensive new medications. Before that, the prices of antidepressants were at similar levels in the two countries. In both countries, the price level exhibited an approximately downward trend. In contrast to the antihypertensive prices, the new antidepressant prices diverged at the end of the time period in Germany due to the launches of several new compounds.

The price variables do not have very significant parameters at the aggregated class and generation levels. At the product level, Germany and Japan had opposite signs for their

price elasticities. (Remember for the antihypertensives both elasticities are negative.) This demonstrates that in Germany the demand is relatively inelastic to prices and that antidepressant sales in Japan has been heavily influenced by cultural and health care policy factors than the price factor. This pattern of the sales of the new-generation medications in the Japanese market can also be shown in the regression of share_new_pd (in Table 4.4).

Between the two therapeutic classes, the detailing activities for antidepressants have less significant impact on the sales of new drugs in Germany and Japan than for the antihypertensives. In contrast to the antihypertensives case, the detailing effects of the antidepressants are not very clear at all levels (class, generation, and product) for the two countries.

Finally, in Germany the generic antidepressants are used more than the branded drugs, with Japan being the opposite case. Overall, Germany appears to be a more competition-driven market than Japan, in terms of the variety of products in the market, the price elasticity, the effects of detailing, and the adoption of generic drugs.

Chapter 5 Cross-country and cross-therapeutic-class comparison and conclusion

Using regression models, in this chapter I examine the cross-country and cross-therapeutic-class differences in factors that affect the diffusion of antihypertensives and antidepressants in Germany and Japan. Instead of separating the data by country and therapeutic classes (as in chapters 3 and 4), I pool the regression data and add country and class dummy variables into the regression models. The regressions in the following sections are at therapeutic class, generation and product levels respectively. For each set of regression, I conduct Chow tests to check whether there are differences in the parameter estimates between the two countries and the two therapeutic classes.

5.1 Cross-country and cross-therapeutic-class comparison

5.1.1 Therapeutic-class-level regression

The regression outputs of the linear form of Equation 5 in chapter 2 for the antihypertensive and antidepressant medications in Germany and Japan are presented in Table 5.1. (Detailed SAS outputs are included in Appendix 5.) The dependent variable is the total patient days per capita at therapeutic class level (log_tot_pd_capita); the RHS variables include price, number of compounds, detailing information, demographic information, country dummy and therapeutic class dummy variable. (Japan and antidepressants are the omitted reference groups.)

As seen from Table 5.1, the country dummy variable "Germany" has a positive and significant parameter estimate (0.021). This means that the per-capita sales of the two

medications are higher in Germany than in Japan. Similarly, the therapeutic class dummy variable "antihypertensives" is positive and significant (0.011), which implies that the antihypertensives are utilized more than the antidepressants in the two countries. The parameters of the two dummy variables suggest that assuming all of the other variables fixed, the sales of antidepressants in Germany has 0.021 patient days per capita more than in Japan; and the sales of antihypertensives in Germany is (0.021+0.011) = 0.032 patient days per capita than the sales of antidepressants in Japan.

Equation 5 only allows the intercepts of the two countries and the two therapeutic classes to be different. In order to further examine if the parameter estimates are statistically significantly different across country and therapeutic class, a Chow test is performed: the H_0 hypothesis is that there is no cross-country or cross therapeutic-class difference in the parameter estimates (the details of how the Chow-statistic is calculated was discussed in chapter 2). At the class level, the unrestricted sum of squared residuals (SSR_u) of the logarithm model is 0.241, and the semi-restricted sum of squared residuals $SSR_{sr} = 0.838$. With N = 120, k = 40, and q = 28, the Chow-statistic = 7.055 ~ $F_{28, 80}$. The critical value at 5%-significance level is 1.617, which is smaller than the Chow-statistic. Hence the null hypothesis is rejected. Therefore, the Chow test has shown that the there are significant cross-country and/or cross-therapeutic-class differences in the sales of antihypertensives and antidepressants at the therapeutic-class level. Comparing Tables 3.3 and 4.2, the cross-country difference is small for the antihypertensives but relatively large for the antidepressants. (For example, the parameter estimates for log_price_class as well as pct65p have opposite signs for the two countries.)

Table 5. 1   Regression results of Equation 5 (dependent variable: tot_pd_capita)

Variable	Parameter estimate
Intercept	0.029 (1.49)
income_1Kcapita	-0.00013 (-0.26)
phys_1Mpop	**-0.000015** **(-6.50)**
pct0_14	-0.031 (-0.46)
pct65p	-0.020 (-0.47)
time	**0.00030** **(6.60)**
price_class	**-0.0074** **(-5.45)**
price_ratio	**0.0012** **(8.21)**
num_compound	-0.000014 (-0.48)
Germany	**0.021** **(6.74)**
antihypertensives	**0.011** **(18.15)**
tot_detail_capita_lag1	**158.12** **(3.33)**
tot_detail_capita_lag4*	**41.92** **(4.03)**
Number of observations	120
Adjusted R-square	0.982

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_tot_detail_capita_lag1 replaced by log_tot_detail_capita_lag4
omitted variables: Japan, antidepressants

5.1.2 Generation-level regression

In this section results are presented for two regressions. Firstly, the sales of antihypertensives and antidepressants are regressed at the generation level (Equation 6 in chapter 2). Secondly, the new generation is regressed as described in Equation 7. Again, country and therapeutic class dummy variables are added into the RHS variables in addition to price, detailing information, and the number of compounds, demographic variables, dummy variables differentiating the generations of medications. The corresponding reference cases are the old generation, Japan, and antidepressants. The regression results of Equation 6 (in linear form) and Equation 7 (in linear form) are shown in Tables 5.2 and 5.3. (The detailed SAS outputs are shown in Appendix 5.)

The results of the generation-level regression in Table 5.2 indicate positive and significant parameter estimate for the "antihypertensive" dummy variable (0.0069). This result is consistent with that shown in Table 5.1, but has a smaller magnitude here. However, the parameter estimate for "Germany" is insignificant at 95% confidence level. This implies that the sales have a clear cross-class difference, but not a cross-country difference at the generation level, assuming the other parameters are the same.

Similar to the generation-level regression, the parameter estimate for the country dummy "Germany" in the new-generation share equation is insignificant (shown in Table 5.3). However, the new-generation share regression showed a different result from the class- and the generation-level regression for the therapeutic class dummy variable. As shown in Table 5.3, the "antihypertensives" variable has a negative and significant parameter estimate (equals to -0.24). This indicates that, for the new-generation medications, the share of new antihypertensives sales has a 24% difference with that of antidepressants, when all other variables have the same values.

Chow tests are also performed to examine if the parameter estimates are significantly different across country and therapeutic class for Equations 6 and 7. At the generation level, the unrestricted sum of squared residuals $SSR_u = 8.251$, and the semi-restricted sum

of squared residuals $SSR_{sr} = 27.219$. With $N = 296$, $k = 52$, and $q = 36$, the Chow-statistic $= 15.582$, greater than the critical value of $F_{36, 244}$ at 5%-significance level (equals to 1.484). Hence the null hypothesis is rejected – the Chow test shows that the there are significant cross-country and/or cross-therapeutic-class differences in the sales of antihypertensives and antidepressants at the generation level. A further investigation of the regression results reveals that Japan tends to have larger absolute values for the significant parameters for both therapeutic classes; moreover, the antihypertensive class tends to have larger absolute values of the estimated parameters than those for the antidepressants (comparing Tables 3.4 and 4.3).

Similarly for the share of new medication regressions, the unrestricted sum of squared residuals $SSR_u = 0.705$, and the semi-restricted sum of squared residuals $SSR_{sr} = 7.409$, $N = 117$, $k = 36$, and $q = 25$; thus the Chow-statistic $= 30.821 > 1.615$, the critical value of $F_{25, 81}$ at 5%-significance level. Again, the null hypothesis is rejected. Hence there are significant cross-country and/or cross-therapeutic-class differences in the sales of new antihypertensives and new antidepressants at generation level. In this case, most of the significant parameter estimates are quite different for the two countries for both therapeutic classes.

Table 5. 2   Regression results of Equation 6 (dependent variable: gen_pd_capita)

Variable	Parameter estimate
Intercept	**0.043** **(2.87)**
log_income_1Kcapita	**-0.0013** **(-3.27)**
log_phys_1Mpop	0.0000014 (0.74)
pct0_14	-0.022 (-0.40)
pct65p	**-0.098** **(-3.13)**
time	**0.00016** **(4.34)**
price_ratio	**-0.00028** **(-2.23)**
price_gen	**0.0052** **(14.22)**
num_new_compound	**0.00013** **(1.97)**
new	**-0.0090** **(-13.81)**
middle	**-0.011** **(-13.98)**
timenew	**0.000043** **(3.23)**
timemiddle	**0.00019** **(8.24)**
Germany	-0.0014 (-0.55)
antihypertensives	**0.0069** **(23.37)**
gen_detail_capita_lag1	**-518.52** **(-15.56)**
gen_detail_capita_lag4*	**-142.42** **(-7.52)**
Number of observations	296
Adjusted R-square	0.898

t-values are shown in the parenthesis below the parameter estimates.
*model is run with rel_detail_lag1 replaced by rel_detail_lag4
Omitted generation variables: old, Japan, antidepressants

Table 5. 3   Regression results of Equation 7 (dependent variable: share_new_pd)

Variable	Parameter estimate
Intercept	**-2.82** **(-4.57)**
income_1Kcapita	0.0085 (0.57)
phys_1Mpop	-0.000025 (-0.34)
pct0_14	**10.19** **(4.52)**
pct65p	**8.35** **(6.29)**
time	**0.0047** **(3.35)**
price_ratio	**-0.037** **(-7.61)**
share_num_newcmpnd	**-0.67** **(-5.13)**
Germany	0.021 (0.22)
antihypertensives	**-0.24** **(-12.43)**
rel_detail_lag1	**-0.0057** **(-2.58)**
rel_detail_lag4*	-0.000090 (-0.14)
Number of observations	117
Adjusted R-square	0.930

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_rel_detail_lag1 replaced by log_rel_detail_lag4

5.1.3 Product-level regression

The regression results in Tables 5.1-5.3 have all shown significant cross-therapeutic-class difference. However, the cross-country difference is significant at the aggregated level (the therapeutic class level) and insignificant at the disaggregated level (the generation level). This is true for a finer disaggregated level – the product level. Table 5.4 presents the product-level regression results (based on the logarithm form of Equation 8 in chapter 2) for the two classes of medications in the German and Japanese markets. (Detailed SAS outputs are listed in Appendix 5.)

The parameter estimate for the antihypertensive therapeutic class dummy variable is 0.71 and significant. This value means that given other things equal, the antihypertensives are utilized (in logarithm per-capita form) 0.71 more than the antidepressants. The country dummy "Germany" is still insignificant, indicating an unclear cross-country difference of the sales of the two medications, with all other parameters being the same.

Finally, a Chow test is used to check if there are statistically significant differences in the parameter estimates across country and across therapeutic class at the product level. In this case the unrestricted sum of squared residuals SSR_u = 141718.47, and the semi-restricted sum of squared residuals SSR_{sr} = 149019.00. With N = 22017, k = 48, and q = 33, the Chow-statistic = 34.294. The Chow-statistic follows an F-distribution with degrees of freedom 33 and 21969, with critical value at 5%-significance level equal to 1.390. Since the calculated Chow-statistic is greater than the critical value of $F_{33, 21969}$, the null hypothesis is rejected. This means that the there are significant cross-country and/or cross-therapeutic-class differences in the sales of antihypertensives and antidepressants at the product level. Tables 3.6 and 4.5 show that the rejection of the Chow-test could be a result of both cross-country and cross-class differences. For example, the log_price_prod variable has estimated parameters with opposite signs for the antidepressants in Germany and Japan, and also for the two therapeutic classes in Japan.

Table 5. 4   **Regression results of Equation 8 (dependent variable: log_prod_pd_capita)**

Variable	Parameter estimate
Intercept	**34.98**
	(3.23)
log_income_1Kcapita	-2.59
	(-1.00)
log_phys_1Mpop	1.21
	(0.77)
pct0_14	**-201.76**
	(-10.94)
pct65p	**-110.69**
	(-9.33)
time	-0.015
	(-1.56)
log_price_prod	**-0.41**
	(-15.50)
log_num_new_compound	**-0.026**
	(-2.42)
generic	**-0.55**
	(-6.16)
new	**0.98**
	(11.21)
middle	**0.59**
	(10.98)
oldgen	**0.25**
	(2.52)
Germany	-0.18
	(-0.23)
antihypertensives	**0.71**
	(16.17)
log_prod_detail_capita_lag1	**-0.026**
	(-8.40)
log_prod_detail_capita_lag4*	**10.48**
	(9.52)
Number of observations	22017
Adjusted R-square	0.057

t-values are shown in the parenthesis below the parameter estimates.
*model is run with log_rel_detail_lag14 replaced by log_rel_detail_lag4
Omitted generation variable: old

5.2 Conclusion

As stated in chapter 1, the purpose of this study has been to examine the diffusion of antihypertensive and antidepressant medications in Germany and Japan between the first quarter of 1992 and the last quarter of 2003. Particularly, the questions of interest are: How do demographic, economic, cultural and health care system factors affect diffusion? What is the role of promotion? Do pharmaceuticals diffuse differently within and across countries and therapeutic classes? What are the health care policy implications? These questions have been qualitatively and quantitatively addressed in chapters 3, 4 and the first half of this chapter. In this final section, I summarize the findings regarding the above issues.

Overall markets

Firstly, the overall German and the Japanese antihypertensive and antidepressant markets have exhibited both the effects of government interventions and a competitive market. Specially, Germany appears to be a more competition-driven market than Japan, in terms of the variety of products in the market, the price elasticity, the effects of detailing, and the adoption of generic drugs. At the aggregated class-level, the markets expanded over time in terms of volume (patient days) and revenue (US$) for both medication classes. However, as compared to the antihypertensive market, the non-economic factors (such as culture and government intervention) appeared to have played a more important role in the sales of antidepressant in Japan. This is represented by the two stages of the sales of antidepressants in Japan, as a result of traditions and educational campaigns conducted by the pharmaceutical industry and the government.

Secondly, there is a significant difference in the volume of sales among the three generations (new < old). For both the antihypertensives and antidepressants, in Germany the new generation has consisted of a greater number of compounds and was launched earlier than that in Japan, but penetrated the antihypertensive market more slowly than that in Japan. This reflects a German market that is more mature and competitive. In addition, the rapid increase in and higher share of the new generation in Japan have

resulted in a higher average price than that in Germany. Although Japan had fewer compounds in the market (only two new antidepressant compounds), the number of new compounds showed a positive and significant correlation with the generation-level patient day sales in both markets.

Lastly, there is a difference in the use of branded drugs versus the generic drugs. In general, generic drugs are used more in Germany than in Japan. The branded antihypertensives are used more than the generics, particularly in Japan. (Remember that the old-generation generics are used more than the new- and middle-generation generics in the German market.) This is also true for the antidepressants in Japan. However, in Germany the generic antihypertensives are used more than the branded drugs.

Demographic, economic and cultural factors

The age structure of the population reveals different patterns for the two countries. Two variables that represent the age composition of the population (pct0_14 and pct65p) are used in the econometric analysis. These variables have negative and significant parameters in the product-level regressions for both the antihypertensives and the antidepressants in Germany. This suggests that the middle-aged population (between 15 and 65 years old) in Germany consume more antihypertensives and antidepressants, despite the fact that the prevalence of some condition such as hypertension is age-related – older people are more likely to have hypertension. However, this is not the same for Japan. The parameter estimates are not significant for the Japanese market for both medications in the product-level regression.

The economic factor annual GDP per thousand-population (income_1Kcapita) is insignificant in most of the regressions, or has inconsistent signs of parameters in the other regressions. This may suggest that under the health care systems of Germany and Japan, the sales of the medications are not (or not closely) related to national income.

Cultural factors were analyzed in chapters 3 and 4 qualitatively. As mentioned earlier in this section and in chapters 3 and 4, not only the prevalence of hypertension and

depression but also the relative sales of the medications is closely related to the cultures of the countries. The main cultural factors are: the composition of food intake, life styles, as well as the public's and medical professionals' understanding of the condition and treatments. In this study, the antidepressant market in Japan appeared to be most affected by cultural factors.

Role of promotion

Across the two therapeutic classes, the detailing activities for antidepressants have less significant impact on the sales of new drugs in Germany and Japan than on antihypertensives. In some regressions such as the new antihypertensives, the promotion variables (new-to-old relative counts of detailing) have positive and significant parameter estimates. However, the role of the detailing activities is not consistent across country and therapeutic classes. The detailing variables were insignificant in the regression of the sales of the new antidepressants in Japan. In addition, the detailing effects are not very clear for mixed new, middle and old generations at all levels (class, generation, and product) for the two countries. The reason for the insignificant parameters in the new-generation regressions is probably the low number of available observations as compared to the number of explanatory variables. The reason for the unclear results of mixed-generation regressions is that some of the older drugs were able to maintain relatively high levels of sales volume but had low detailing efforts. (In Germany free samples, which is part of the detailing, are not allowed to be distributed to physicians after one year following launch, according to the pharmaceutical industry practice code [37].) On the other hand, some new drugs are heavily promoted but have not reached a high market share.

Cross-country and cross-therapeutic-class difference

The regressions with country dummies (Equations 5 - 8) have shown that at the therapeutic class level, Germany has more sales of both medications (in number of patient days per capita). However at more disaggregated levels (generation and product level) the cross-country difference in the intercepts of the regression is not significant.

The cross-therapeutic-class analyses have consistent regression results at all levels. Antihypertensives were sold more than antidepressant medications when all generations are included in one equation, while the new-generation antidepressants were sold in greater amounts than the new-generation antihypertensives.

The Chow tests show that at all levels the parameter estimates in the regression models have significant cross-country/class differences, as was discussed in section 5.1. This means that at least some of the demand elasticities of the demographic, economic and health care system factors are different in Germany and Japan, or different for antihypertensive and antidepressants medications, or both.

Health care system factors

As discussed in chapter 1 where the two health care systems were compared, there are stringent price controls in Germany and Japan. In both countries, price controls and competition have led the prices of medications that have existed in the market for a certain time to decrease and converge over time (illustrated by the new-generation antihypertensives and antidepressants). However, the total expenditures on antihypertensives and antidepressants per patient day (i.e., average price levels) are different between the two countries. In general, Japan tended to have higher average prices than Germany, since the shares of the more expensive new drugs and branded drugs were higher. This case is especially illustrated by the antidepressant market. In the first eight years (1992-1999) the prices of antidepressants are at similar levels in the two countries. Since the launch of the two new compounds, the average price level in Japan has rapidly exceeded that in Germany.

In the logarithmic form regressions, the price variables did not have very significant parameters at the aggregated class and generation levels. At the product level, the price variables were significant for both therapeutic classes and countries. However, for antihypertensives the price elasticities are small and negative for Germany and Japan; while for the antidepressants the price elasticity estimate is positive for Japan. The negative price elasticities tell us that although the price is regulated the health care

systems in these countries have also provided mechanisms that to some extent allow competition. The low price elasticity demonstrates that under the social-based health care systems, where the out-of-pocket payment is low, the demand for pharmaceuticals is relatively price inelastic. The positive sign of the price elasticity for the antidepressant market in Japan reflects an influential effect of the cultural and non-price health care policy factors. As stated in chapter 4, industry and the Japanese government both launched education campaigns, which have enhanced the awareness and thus sales of antidepressants.

The number-of-physicians variable in the regression either was insignificant or had negative signs. This tells us that the sales of pharmaceuticals (at least antihypertensives and antidepressants) do not have a clear relationship with the density of the physicians who prescribe them. The possible reasons are: firstly, both countries are developed and the supply of the physicians is sufficient; secondly, although in Germany the physicians have financial incentives to have as many patients as possible, they have much less incentive to prescribe as much medications as possible, because of the way their compensation is calculated. (For example, although the compensation is fee-for-service based, German physicians are limited by health care policies to expand the number of their patients [1].) Thirdly, although there are certain amounts of untreated patients who have hypertension and depression, the causation of the lack of treatment is more likely to be cultural reasons rather than the (in)sufficiency of physicians. Thus the fluctuations of the number of physicians did not influence much of the actual sales of the medications.

Appendix 1: List of antihypertensive compounds

Table A1. 1   List of antihypertensive compounds

New generation	Middle generation	Old generation	
CANDESARTAN	ALACEPRIL	ACEBUTOLOL	DILTIAZEM
CILEXETIL	BENAZEPRIL	ALPRENOLOL	EFONIDIPINE
EPROSARTAN	CAPTOPRIL	AMLODIPINE	ESMOLOL
IRBESARTAN	CILAZAPRIL	AMOSULALOL	FELODIPINE
LOSARTAN	DELAPRIL	ARANIDIPINE	FENDILINE
OLMESARTAN	ENALAPRIL	AROTINOLOL	GALLOPAMIL
MEDOXOMIL	FOSINOPRIL	ATENOLOL	INDENOLOL
TELMISARTAN	IMIDAPRIL	AZELNIDIPINE	ISRADIPINE
VALSARTAN	LISINOPRIL	BARNIDIPINE	LABETALOL
	MOEXIPRIL	BENIDIPINE	LACIDIPINE
	PERINDOPRIL	BEPRIDIL	LANDIOLOL
	QUINAPRIL	BETAXOLOL	LERCANIDIPINE
	RAMIPRIL	BEVANTOLOL	MANIDIPINE
	SPIRAPRIL	BISOPROLOL	MEPINDOLOL
	TEMOCAPRIL	BOPINDOLOL	METOPROLOL
	TRANDOLAPRIL	BUFETOLOL	MIBEFRADIL
		BUNITROLOL	NADOLOL
		BUPRANOLOL	NEBIVOLOL
		CARTEOLOL	NICARDIPINE
		CARVEDILOL	NIFEDIPINE
		CELIPROLOL	NILVADIPINE
		CILNIDIPINE	NIPRADILOL

Appendix 2: SAS outputs of the regression results in chapter 3

Table A2. 1   SAS output of Table 3.3

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Germany
The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	1.20580	0.13398	49.38	<.0001
Error	23	0.06240	0.00271		
Corrected Total	32	1.26820			

Root MSE	0.05209	R-Square	0.9508
Dependent Mean	-4.30568	Adj R-Sq	0.9315
Coeff Var	-1.20977		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	6.58809	20.46892	0.32	0.7505
log_income_1Kcapita		1	0.66758	2.95160	0.23	0.8231
log_phys_1Mpop		1	-1.47400	2.36512	-0.62	0.5393
pct0_14	pct0_14	1	10.12708	54.15775	0.19	0.8533
pct65p	pct65p	1	5.30924	36.99520	0.14	0.8871
time	Q1 1992 = 1	1	0.02996	0.00972	3.08	0.0053
log_price_class		1	0.13197	0.19345	0.68	0.5019
log_price_ratio		1	-0.17280	0.41633	-0.42	0.6820
log_num_compound		1	-0.70807	0.51965	-1.36	0.1862
log_tot_detail_capita_lag1		1	0.12739	0.09732	1.31	0.2035

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	1.20277	0.13364	46.98	<.0001
Error	23	0.06543	0.00284		
Corrected Total	32	1.26820			

Root MSE	0.05334	R-Square	0.9484
Dependent Mean	-4.30568	Adj R-Sq	0.9282
Coeff Var	-1.23874		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	9.75084	23.94184	0.41	0.6876
log_income_1Kcapita		1	0.85256	3.20582	0.27	0.7927
log_phys_1Mpop		1	-2.13039	2.77119	-0.77	0.4499
pct0_14	pct0_14	1	14.55507	56.06354	0.26	0.7975
pct65p	pct65p	1	6.61866	38.82520	0.17	0.8661
time	Q1 1992 = 1	1	0.03049	0.00994	3.07	0.0055
log_price_class		1	0.13317	0.20860	0.64	0.5295
log_price_ratio		1	-0.10366	0.43630	-0.24	0.8143
log_num_compound		1	-0.61101	0.55442	-1.10	0.2818
log_tot_detail_capita_lag4		1	0.12609	0.16686	0.76	0.4575

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	0.37664	0.04185	14.84	<.0001
Error	12	0.03383	0.00282		
Corrected Total	21	0.41048			

Root MSE	0.05310	R-Square	0.9176
Dependent Mean	-4.38710	Adj R-Sq	0.8558
Coeff Var	-1.21032		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	25.32019	43.60516	0.58	0.5722
log_income_1Kcapita		1	-4.72632	5.49197	-0.86	0.4063
log_phys_1Mpop		1	-3.72809	3.05330	-1.22	0.2455
log_pct0_14		1	-0.15322	4.42297	-0.03	0.9729
log_pct65p		1	-6.19609	2.81478	-2.20	0.0480
time	Q1 1992 = 1	1	0.07468	0.01437	5.20	0.0002
log_price_class		1	-0.20342	0.34021	-0.60	0.5610
log_price_ratio		1	-0.81198	1.17741	-0.69	0.5035
log_num_compound		1	-0.19040	1.16475	-0.16	0.8729
log_tot_detail_capita_lag1		1	-0.08274	0.25772	-0.32	0.7537

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	0.37844	0.04205	15.75	<.0001
Error	12	0.03204	0.00267		
Corrected Total	21	0.41048			

Root MSE	0.05167	R-Square	0.9220	
Dependent Mean	-4.38710	Adj R-Sq	0.8634	
Coeff Var	-1.17776			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	13.66519	33.26574	0.41	0.6885
log_income_1Kcapita		1	-4.14490	3.46030	-1.20	0.2541
log_phys_1Mpop		1	-2.10836	3.05083	-0.69	0.5027
log_pct0_14		1	1.31480	4.55082	0.29	0.7776
log_pct65p		1	-7.28005	2.40129	-3.03	0.0104
time	Q1 1992 = 1	1	0.07766	0.01376	5.64	0.0001
log_price_class		1	-0.47690	0.46659	-1.02	0.3269
log_price_ratio		1	-0.59411	1.17450	-0.51	0.6221
log_num_compound		1	-0.03511	1.09283	-0.03	0.9749
log_tot_detail_capita_lag4		1	0.18229	0.20617	0.88	0.3940

Table A2. 2   SAS output of Table 3.4

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Germany
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	170.12330	13.08641	182.46	<.0001
Error	85	6.09631	0.07172		
Corrected Total	98	176.21961			

Root MSE	0.26781	R-Square	0.9654
Dependent Mean	-5.94041	Adj R-Sq	0.9601
Coeff Var	-4.50825		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-43.55080	54.07925	-0.81	0.4229
log_income_1Kcapita		1	-3.50578	8.14663	-0.43	0.6680
log_phys_1Mpop		1	3.75293	6.48608	0.58	0.5644
pct0_14	pct0_14	1	44.20788	127.56665	0.35	0.7298
pct65p	pct65p	1	42.02033	90.35808	0.47	0.6431
time	Q1 1992 = 1	1	-0.01600	0.03040	-0.53	0.6000
log_price_ratio		1	-1.17295	1.24101	-0.95	0.3473
log_price_gen		1	-0.78032	0.43386	-1.80	0.0756
log_num_new_compound		1	0.31764	0.14186	2.24	0.0278
log_gen_detail_capita_lag1		1	-0.46143	0.11041	-4.18	<.0001
new		1	-4.73896	0.37562	-12.62	<.0001
middle		1	-2.36035	0.41603	-5.67	<.0001
timenew		1	0.09309	0.00828	11.24	<.0001
timemiddle		1	0.04771	0.01224	3.90	0.0002

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Germany
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	169.51387	13.03953	165.29	<.0001
Error	85	6.70575	0.07889		
Corrected Total	98	176.21961			

Root MSE	0.28088	R-Square	0.9619
Dependent Mean	-5.94041	Adj R-Sq	0.9561
Coeff Var	-4.72822		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-40.75342	57.28322	-0.71	0.4788
log_income_1Kcapita		1	-7.06680	8.65372	-0.82	0.4164
log_phys_1Mpop		1	4.74759	6.85184	0.69	0.4903
pct0_14	pct0_14	1	36.74112	134.57944	0.27	0.7855
pct65p	pct65p	1	28.27575	94.89868	0.30	0.7665
time	Q1 1992 = 1	1	0.01242	0.03096	0.40	0.6893
log_price_ratio		1	-0.72086	1.31860	-0.55	0.5860
log_price_gen		1	-0.55169	0.44834	-1.23	0.2219
log_num_new_compound		1	0.14939	0.14664	1.02	0.3112
log_gen_detail_capita_lag4		1	-0.80924	0.28339	-2.86	0.0054
new		1	-4.84192	0.39358	-12.30	<.0001
middle		1	-1.37119	0.31641	-4.33	<.0001
timenew		1	0.08389	0.00833	10.07	<.0001
timemiddle		1	0.01815	0.00905	2.01	0.0481

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Japan
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	95.14661	7.31897	316.70	<.0001
Error	52	1.20173	0.02311		
Corrected Total	65	96.34835			

Root MSE	0.15202	R-Square	0.9875	
Dependent Mean	-5.98423	Adj R-Sq	0.9844	
Coeff Var	-2.54036			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	28.59710	41.38113	0.69	0.4926
log_income_1Kcapita		1	6.81952	4.77000	1.43	0.1588
log_phys_1Mpop		1	-5.89238	5.19685	-1.13	0.2621
pct0_14	pct0_14	1	-68.29084	47.11902	-1.45	0.1533
pct65p	pct65p	1	-45.56261	19.31144	-2.36	0.0221
time	Q1 1992 = 1	1	-0.01599	0.02459	-0.65	0.5182
log_price_ratio		1	-1.59180	1.81708	-0.88	0.3850
log_price_gen		1	0.44094	0.52538	0.84	0.4052
log_num_new_compound		1	0.42955	0.14748	2.91	0.0053
log_gen_detail_capita_lag1		1	-0.78006	0.14947	-5.22	<.0001
new		1	-9.27632	0.62160	-14.92	<.0001
middle		1	-3.94499	0.68945	-5.72	<.0001
timenew		1	0.18828	0.00886	21.25	<.0001
timemiddle		1	0.07158	0.01888	3.79	0.0004

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Japan
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	94.60874	7.27760	217.54	<.0001
Error	52	1.73961	0.03345		
Corrected Total	65	96.34835			

Root MSE	0.18290	R-Square	0.9819
Dependent Mean	-5.98423	Adj R-Sq	0.9774
Coeff Var	-3.05644		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	63.91913	57.69288	1.11	0.2730
log_income_1Kcapita		1	-0.60861	9.02063	-0.07	0.9465
log_phys_1Mpop		1	-8.29021	6.67860	-1.24	0.2201
pct0_14	pct0_14	1	-52.20628	59.38093	-0.88	0.3834
pct65p	pct65p	1	-43.54128	25.08703	-1.74	0.0886
time	Q1 1992 = 1	1	0.05137	0.03082	1.67	0.1016
log_price_ratio		1	0.43284	2.31354	0.19	0.8523
log_price_gen		1	-0.14112	0.69886	-0.20	0.8408
log_num_new_compound		1	0.25056	0.18715	1.34	0.1865
log_gen_detail_capita_lag4		1	-0.85610	0.51756	-1.65	0.1041
new		1	-8.32644	0.86366	-9.64	<.0001
middle		1	-1.11468	0.43928	-2.54	0.0142
timenew		1	0.16403	0.01012	16.20	<.0001
timemiddle		1	-0.00468	0.01247	-0.38	0.7090

Table A2. 3   SAS output of Table 3.5

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: log_share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	16.08525	2.01066	114.18	<.0001
Error	23	0.40503	0.01761		
Corrected Total	31	16.49028			

Root MSE	0.13270	R-Square	0.9754
Dependent Mean	-3.14615	Adj R-Sq	0.9669
Coeff Var	-4.21792		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	99.73688	43.62016	2.29	0.0318
log_income_1Kcapita		1	-10.14717	6.65668	-1.52	0.1411
log_phys_1Mpop		1	3.85131	6.05325	0.64	0.5309
pct0_14	pct0_14	1	-376.91743	121.81338	-3.09	0.0051
pct65p	pct65p	1	-274.45458	82.36994	-3.33	0.0029
time	Q1 1992 = 1	1	0.05240	0.02341	2.24	0.0352
log_price_ratio		1	0.00089835	1.18877	0.00	0.9994
share_num_newcmpnd		1	9.87276	2.44535	4.04	0.0005
log_rel_detail_lag1		1	0.23975	0.11528	2.08	0.0489

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: log_share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	16.35644	2.04456	351.36	<.0001
Error	23	0.13383	0.00582		
Corrected Total	31	16.49028			

Root MSE	0.07628	R-Square	0.9919
Dependent Mean	-3.14615	Adj R-Sq	0.9891
Coeff Var	-2.42461		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	21.98112	26.40635	0.83	0.4137
log_income_1Kcapita		1	-6.78810	3.83658	-1.77	0.0901
log_phys_1Mpop		1	6.14784	3.09993	1.98	0.0594
pct0_14	pct0_14	1	-200.60574	72.56170	-2.76	0.0110
pct65p	pct65p	1	-136.50871	50.83992	-2.69	0.0132
time	Q1 1992 = 1	1	0.01848	0.01417	1.30	0.2050
log_price_ratio		1	-0.67686	0.68694	-0.99	0.3347
share_num_newcmpnd		1	6.26350	1.47913	4.23	0.0003
log_rel_detail_lag4		1	0.45274	0.05860	7.73	<.0001

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: log_share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	18.49516	2.31189	161.85	<.0001
Error	12	0.17141	0.01428		
Corrected Total	20	18.66657			

Root MSE	0.11952	R-Square	0.9908
Dependent Mean	-2.63746	Adj R-Sq	0.9847
Coeff Var	-4.53151		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-17.50589	49.05177	-0.36	0.7274
log_income_1Kcapita		1	27.06616	8.61271	3.14	0.0085
log_phys_1Mpop		1	-5.02998	6.78552	-0.74	0.4728
pct0_14	pct0_14	1	-168.13973	76.28644	-2.20	0.0478
pct65p	pct65p	1	-79.58810	26.20509	-3.04	0.0103
time	Q1 1992 = 1	1	0.08899	0.03423	2.60	0.0232
log_price_ratio		1	3.23475	4.28385	0.76	0.4647
share_num_newcmpnd		1	13.95853	6.36812	2.19	0.0488
log_rel_detail_lag1		1	0.62016	0.19902	3.12	0.0089

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: log_share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	18.63141	2.32893	795.00	<.0001
Error	12	0.03515	0.00293		
Corrected Total	20	18.66657			

Root MSE	0.05412	R-Square	0.9981
Dependent Mean	-2.63746	Adj R-Sq	0.9969
Coeff Var	-2.05215		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-65.58020	22.91945	-2.86	0.0143
log_income_1Kcapita		1	11.59543	4.50149	2.58	0.0243
log_phys_1Mpop		1	4.80391	3.37144	1.42	0.1797
pct0_14	pct0_14	1	-38.39929	39.41107	-0.97	0.3491
pct65p	pct65p	1	-37.69159	13.14405	-2.87	0.0142
time	Q1 1992 = 1	1	0.04189	0.01694	2.47	0.0294
log_price_ratio		1	-0.20622	2.00398	-0.10	0.9197
share_num_newcmpnd		1	10.63009	2.92488	3.63	0.0034
log_rel_detail_lag4		1	0.58132	0.06000	9.69	<.0001

Table A2. 4   SAS output of Table 3.6

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Germany
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	4766.10527	397.17544	63.68	<.0001
Error	12377	77202	6.23752		
Corrected Total	12389	81968			

Root MSE	2.49750	R-Square	0.0581
Dependent Mean	-12.09900	Adj R-Sq	0.0572
Coeff Var	-20.64223		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	49.65332	15.61195	3.18	0.0015
log_income_1Kcapita		1	-5.85408	4.11692	-1.42	0.1551
log_phys_1Mpop		1	1.67296	2.69596	0.62	0.5349
pct0_14	pct0_14	1	-227.45407	48.84605	-4.66	<.0001
pct65p	pct65p	1	-135.22230	33.64257	-4.02	<.0001
time	Q1 1992 = 1	1	-0.00740	0.01297	-0.57	0.5681
log_price_prod		1	-0.60180	0.03639	-16.54	<.0001
log_num_new_compound		1	-0.01079	0.01461	-0.74	0.4603
log_prod_detail_capita_lag1		1	-0.01606	0.00395	-4.07	<.0001
generic		1	-0.71455	0.11010	-6.49	<.0001
new		1	1.86797	0.17194	10.86	<.0001
middle		1	1.03528	0.06281	16.48	<.0001
oldgen		1	0.39332	0.12239	3.21	0.0013

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Germany
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	8009.32653	667.44388	100.45	<.0001
Error	15959	106039	6.64449		
Corrected Total	15971	114049			

Root MSE	2.57769	R-Square	0.0702
Dependent Mean	-12.43637	Adj R-Sq	0.0695
Coeff Var	-20.72703		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	35.79596	18.67339	1.92	0.0553
log_income_1Kcapita		1	-6.15665	5.92927	-1.04	0.2991
log_phys_1Mpop		1	2.02929	4.76739	0.43	0.6704
pct0_14	pct0_14	1	-186.48696	51.21838	-3.64	0.0003
pct65p	pct65p	1	-108.41577	35.46508	-3.06	0.0022
time	Q1 1992 = 1	1	-0.01226	0.01296	-0.95	0.3440
log_price_prod		1	-0.76312	0.03362	-22.70	<.0001
log_num_new_compound		1	-0.01008	0.01360	-0.74	0.4584
log_prod_detail_capita_lag4		1	-0.06242	0.00487	-12.82	<.0001
generic		1	-0.50843	0.10909	-4.66	<.0001
new		1	1.13680	0.13319	8.54	<.0001
middle		1	1.00358	0.05816	17.26	<.0001
oldgen		1	0.22363	0.11986	1.87	0.0621

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives in Japan
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	4677.81948	389.81829	45.23	<.0001
Error	3205	27620	8.61764		
Corrected Total	3217	32297			

Root MSE	2.93558	R-Square	0.1448	
Dependent Mean	-12.36091	Adj R-Sq	0.1416	
Coeff Var	-23.74890			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	82.91347	72.67320	1.14	0.2540
log_income_1Kcapita		1	-30.96404	10.75405	-2.88	0.0040
log_phys_1Mpop		1	-0.52221	8.72172	-0.06	0.9523
pct0_14	pct0_14	1	35.70880	98.67018	0.36	0.7175
pct65p	pct65p	1	19.10362	46.68294	0.41	0.6824
time	Q1 1992 = 1	1	-0.06080	0.05012	-1.21	0.2252
log_price_prod		1	-0.15112	0.05749	-2.63	0.0086
log_num_new_compound		1	0.02678	0.05047	0.53	0.5957
log_prod_detail_capita_lag1		1	-0.04318	0.00953	-4.53	<.0001
generic		1	-2.50215	0.35346	-7.08	<.0001
new		1	4.36729	0.39351	11.10	<.0001
middle		1	-0.47101	0.11821	-3.98	<.0001
oldgen		1	-0.39031	0.41829	-0.93	0.3508

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives in Japan
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	5561.89499	463.49125	56.47	<.0001
Error	4047	33214	8.20704		
Corrected Total	4059	38776			

Root MSE	2.86479	R-Square	0.1434
Dependent Mean	-12.56644	Adj R-Sq	0.1409
Coeff Var	-22.79718		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	97.20588	62.92745	1.54	0.1225
log_income_1Kcapita		1	-26.66384	9.05578	-2.94	0.0033
log_phys_1Mpop		1	-3.06886	7.48012	-0.41	0.6816
pct0_14	pct0_14	1	-5.39162	82.00528	-0.07	0.9476
pct65p	pct65p	1	4.32520	39.98995	0.11	0.9139
time	Q1 1992 = 1	1	-0.04971	0.04344	-1.14	0.2525
log_price_prod		1	-0.10812	0.04964	-2.18	0.0295
log_num_new_compound		1	0.01556	0.04416	0.35	0.7245
log_prod_detail_capita_lag4		1	0.00379	0.01048	0.36	0.7172
generic		1	-2.47631	0.28181	-8.79	<.0001
new		1	4.57784	0.38203	11.98	<.0001
middle		1	-0.26069	0.10612	-2.46	0.0141
oldgen		1	-0.30798	0.33131	-0.93	0.3526

Appendix 3: List of antidepressant compounds

Table A3. 1   List of antihypertensive compounds

New generation	Old generation	
CITALOPRAM	AMFETAMINIL	METHYLPHENIDATE
ESCITALOPRAM	AMITRIPTYLINE	MIANSERIN
FLUOXETINE	AMITRIPTYLINOXIDE	MILNACIPRAN
FLUVOXAMINE	AMOXAPINE	MIRTAZAPINE
NEFAZODONE	CLOMIPRAMINE	MOCLOBEMIDE
PAROXETINE	DESIPRAMINE	NORTRIPTYLINE
REBOXETINE	DIBENZEPIN	OPIPRAMOL
SERTRALINE	DOSULEPIN	OXITRIPTAN
VENLAFAXINE	DOXEPIN	PEMOLINE
	FENETYLLINE	PIPRADROL
	HYPERICUM PERFORATUM	SETIPTILINE
	IMIPRAMINE	TRANYLCYPROMINE
	LITHIUM	TRAZODONE
	LOFEPRAMINE	TRIMIPRAMINE
	MAPROTILINE	VILOXAZINE

Appendix 4: SAS outputs of the regression results in chapter 4

Table A4. 1   SAS output of Table 4.2

With detailing variable lagged 1 quarter

Log-log regression for antidepressants in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	3.34468	0.37163	107.85	<.0001
Error	36	0.12405	0.00345		
Corrected Total	45	3.46873			

Root MSE	0.05870	R-Square	0.9642
Dependent Mean	-6.07228	Adj R-Sq	0.9553
Coeff Var	-0.96671		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	30.97769	14.47857	2.14	0.0392
log_income_1Kcapita		1	0.58767	1.64238	0.36	0.7226
log_phys_1Mpop		1	-1.82943	1.15170	-1.59	0.1209
log_pct0_14		1	8.44702	3.46390	2.44	0.0198
log_pct65p		1	6.15444	2.60951	2.36	0.0239
time	Q1 1992 = 1	1	0.02583	0.00798	3.24	0.0026
log_price_class		1	0.29182	0.14483	2.01	0.0514
log_price_ratio		1	0.71095	0.18466	3.85	0.0005
log_num_compound		1	0.65769	0.38758	1.70	0.0983
log_tot_detail_capita_lag1		1	0.08646	0.07641	1.13	0.2653

With detailing variable lagged 4 quarters

Log-log regression for antidepressants in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	2.83874	0.31542	102.75	<.0001
Error	34	0.10437	0.00307		
Corrected Total	43	2.94310			

Root MSE	0.05540	R-Square	0.9645
Dependent Mean	-6.04959	Adj R-Sq	0.9552
Coeff Var	-0.91583		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	16.75868	21.45099	0.78	0.4401
log_income_1Kcapita		1	-2.67790	2.66937	-1.00	0.3229
log_phys_1Mpop		1	0.95360	2.21860	0.43	0.6700
log_pct0_14		1	7.94840	4.14831	1.92	0.0638
log_pct65p		1	5.88796	2.94452	2.00	0.0536
time	Q1 1992 = 1	1	0.02434	0.00762	3.20	0.0030
log_price_class		1	0.15948	0.18240	0.87	0.3881
log_price_ratio		1	0.50209	0.16886	2.97	0.0054
log_num_compound		1	0.80785	0.23843	3.39	0.0018
log_tot_detail_capita_lag4		1	0.06939	0.04518	1.54	0.1338

With detailing variable lagged 1 quarter

Log-log regression for antidepressants in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	0.53713	0.05968	25.32	<.0001
Error	9	0.02121	0.00236		
Corrected Total	18	0.55834			

Root MSE	0.04855	R-Square	0.9620
Dependent Mean	-6.86870	Adj R-Sq	0.9240
Coeff Var	-0.70678		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	82.54803	47.30015	1.75	0.1149
log_income_1Kcapita		1	-10.16187	5.62924	-1.81	0.1045
log_phys_1Mpop		1	-9.16014	5.47161	-1.67	0.1284
log_pct0_14		1	2.75599	7.39928	0.37	0.7182
log_pct65p		1	-6.22885	3.03098	-2.06	0.0700
time	Q1 1992 = 1	1	0.15369	0.03311	4.64	0.0012
log_price_class		1	-1.14223	0.54704	-2.09	0.0664
log_price_ratio		1	1.36992	0.71554	1.91	0.0878
log_num_compound		1	-0.84344	0.74409	-1.13	0.2863
log_tot_detail_capita_lag1		1	-0.05337	0.04186	-1.27	0.2343

With detailing variable lagged 4 quarters

Log-log regression for antidepressants in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: log_tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	0.53330	0.05926	21.30	<.0001
Error	9	0.02504	0.00278		
Corrected Total	18	0.55834			

Root MSE	0.05275	R-Square	0.9552
Dependent Mean	-6.86870	Adj R-Sq	0.9103
Coeff Var	-0.76792		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	54.46485	47.64773	1.14	0.2825
log_income_1Kcapita		1	-9.85995	6.19669	-1.59	0.1460
log_phys_1Mpop		1	-5.22298	5.32685	-0.98	0.3525
log_pct0_14		1	3.95844	7.99845	0.49	0.6325
log_pct65p		1	-6.44926	3.33789	-1.93	0.0854
time	Q1 1992 = 1	1	0.13611	0.03340	4.08	0.0028
log_price_class		1	-0.93364	0.56741	-1.65	0.1343
log_price_ratio		1	0.79003	0.77491	1.02	0.3346
log_num_compound		1	-0.32799	0.83940	-0.39	0.7051
log_tot_detail_capita_lag4		1	0.00212	0.08246	0.03	0.9800

Table A4. 2   SAS output of Table 4.3

With detailing variable lagged 1 quarter

Log-log regression for antidepressants in Germany
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	193.18472	17.56225	2295.14	<.0001
Error	81	0.61981	0.00765		
Corrected Total	92	193.80453			

Root MSE	0.08748	R-Square	0.9968
Dependent Mean	-7.41323	Adj R-Sq	0.9964
Coeff Var	-1.17999		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-16.26336	9.05423	-1.80	0.0762
log_income_1Kcapita		1	4.19641	1.53343	2.74	0.0076
log_phys_1Mpop		1	-2.42840	1.10993	-2.19	0.0316
pct0_14	pct0_14	1	49.51385	23.68285	2.09	0.0397
pct65p	pct65p	1	41.90877	16.36340	2.56	0.0123
time	Q1 1992 = 1	1	-0.00644	0.00797	-0.81	0.4216
log_price_ratio		1	0.21953	0.16466	1.33	0.1862
log_price_gen		1	-0.24272	0.11309	-2.15	0.0348
log_num_new_compound		1	0.39902	0.07650	5.22	<.0001
log_gen_detail_capita_lag1		1	-0.05339	0.03635	-1.47	0.1458
new		1	-3.55628	0.20476	-17.37	<.0001
timenew		1	0.05836	0.00253	23.05	<.0001

With detailing variable lagged 4 quarters

Log-log regression for antidepressants in Germany
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	175.62936	15.96631	2870.10	<.0001
Error	76	0.42279	0.00556		
Corrected Total	87	176.05215			

Root MSE	0.07459	R-Square	0.9976
Dependent Mean	-7.37718	Adj R-Sq	0.9973
Coeff Var	-1.01103		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-30.64686	8.76646	-3.50	0.0008
log_income_1Kcapita		1	-5.00225	2.44612	-2.04	0.0443
log_phys_1Mpop		1	4.87841	1.93260	2.52	0.0137
pct0_14	pct0_14	1	-6.27766	22.87770	-0.27	0.7845
pct65p	pct65p	1	5.74161	15.70655	0.37	0.7157
time	Q1 1992 = 1	1	0.00681	0.00723	0.94	0.3493
log_price_ratio		1	0.33221	0.13443	2.47	0.0157
log_price_gen		1	-0.43680	0.11244	-3.88	0.0002
log_num_new_compound		1	0.24302	0.06210	3.91	0.0002
log_gen_detail_capita_lag4		1	0.06281	0.05238	1.20	0.2343
new		1	-3.35247	0.21969	-15.26	<.0001
timenew		1	0.05936	0.00227	26.19	<.0001

With detailing variable lagged 1 quarter

Log-log regression for antidepressants in Japan
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	16.75815	1.52347	119.04	<.0001
Error	26	0.33275	0.01280		
Corrected Total	37	17.09090			

Root MSE	0.11313	R-Square	0.9805
Dependent Mean	-7.72701	Adj R-Sq	0.9723
Coeff Var	-1.46406		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	40.18373	43.69777	0.92	0.3662
log_income_1Kcapita		1	-7.59246	9.99922	-0.76	0.4545
log_phys_1Mpop		1	-3.96417	5.83409	-0.68	0.5028
pct0_14	pct0_14	1	51.81126	94.87634	0.55	0.5897
pct65p	pct65p	1	-26.80679	27.80115	-0.96	0.3438
time	Q1 1992 = 1	1	0.06972	0.02371	2.94	0.0068
log_price_ratio		1	0.95324	0.71375	1.34	0.1933
log_price_gen		1	0.00580	0.50994	0.01	0.9910
log_num_new_compound		1	-0.04526	0.16027	-0.28	0.7799
log_gen_detail_capita_lag1		1	0.00564	0.09514	0.06	0.9532
new		1	-4.46290	0.71755	-6.22	<.0001
timenew		1	0.08630	0.00917	9.41	<.0001

With detailing variable lagged 4 quarters

Log-log regression for antidepressants in Japan
Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	16.93079	1.53916	249.95	<.0001
Error	26	0.16010	0.00616		
Corrected Total	37	17.09090			

Root MSE	0.07847	R-Square	0.9906
Dependent Mean	-7.72701	Adj R-Sq	0.9867
Coeff Var	-1.01556		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-53.39801	34.87106	-1.53	0.1378
log_income_1Kcapita		1	-8.76972	6.00797	-1.46	0.1564
log_phys_1Mpop		1	8.62075	4.69250	1.84	0.0776
pct0_14	pct0_14	1	124.23758	55.96355	2.22	0.0353
pct65p	pct65p	1	-27.39800	18.25052	-1.50	0.1453
time	Q1 1992 = 1	1	0.04590	0.01517	3.03	0.0055
log_price_ratio		1	-0.83754	0.56180	-1.49	0.1480
log_price_gen		1	-0.11405	0.29437	-0.39	0.7016
log_num_new_compound		1	0.23803	0.11930	2.00	0.0566
log_gen_detail_capita_lag4		1	0.47230	0.08919	5.30	<.0001
new		1	-4.07193	0.29776	-13.68	<.0001
timenew		1	0.08091	0.00623	12.98	<.0001

Table A4. 3   SAS output of Table 4.4

With detailing variable lagged 1 quarter

Linear regression for antidepressants in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	0.25288	0.03161	503.16	<.0001
Error	37	0.00232	0.00006282		
Corrected Total	45	0.25520			

Root MSE	0.00793	R-Square	0.9909	
Dependent Mean	0.10110	Adj R-Sq	0.9889	
Coeff Var	7.83982			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	1.99739	0.83570	2.39	0.0221
income_1Kcapita		1	0.00500	0.00876	0.57	0.5717
phys_1Mpop		1	-0.00010397	0.00004766	-2.18	0.0356
pct0_14	pct0_14	1	-6.33465	3.00655	-2.11	0.0420
pct65p	pct65p	1	-4.14127	2.04727	-2.02	0.0504
time	Q1 1992 = 1	1	0.00709	0.0009371	7.57	<.0001
price_ratio		1	-0.01930	0.00447	-4.31	0.0001
share_num_newcmpnd		1	-0.61066	0.05836	-10.46	<.0001
rel_detail_lag1		1	0.01944	0.00896	2.17	0.0366

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With detailing variable lagged 4 quarters

Linear regression for antidepressants in Germany

The REG Procedure
Model: MODEL1
Dependent Variable: share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	0.24120	0.03015	449.10	<.0001
Error	35	0.00235	0.00006713		
Corrected Total	43	0.24355			

Root MSE	0.00819	R-Square	0.9904
Dependent Mean	0.10449	Adj R-Sq	0.9881
Coeff Var	7.84151		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	1.47346	1.04898	1.40	0.1689
income_1Kcapita		1	0.01128	0.01654	0.68	0.4997
phys_1Mpop		1	-0.0001444	0.00009226	-1.57	0.1266
pct0_14	pct0_14	1	-4.24068	3.68672	-1.15	0.2578
pct65p	pct65p	1	-3.12527	2.47112	-1.26	0.2143
time	Q1 1992 = 1	1	0.00672	0.00114	5.88	<.0001
price_ratio		1	-0.01713	0.00521	-3.29	0.0023
share_num_newcmpnd		1	-0.57026	0.06658	-8.56	<.0001
rel_detail_lag4		1	0.00794	0.00405	1.96	0.0578

With detailing variable lagged 1 quarter

Linear regression for antidepressants in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	0.10074	0.01259	344.37	<.0001
Error	9	0.0003291	0.00003657		
Corrected Total	17	0.10107			

Root MSE	0.00605	R-Square	0.9967	
Dependent Mean	0.27157	Adj R-Sq	0.9938	
Coeff Var	2.22667			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-1.19890	0.94259	-1.27	0.2353
income_1Kcapita		1	-0.02990	0.04101	-0.73	0.4846
phys_1Mpop		1	-0.00010466	0.00023441	-0.45	0.6658
pct0_14	pct0_14	1	9.54166	8.33259	1.15	0.2817
pct65p	pct65p	1	2.28590	2.33404	0.98	0.3530
time	Q1 1992 = 1	1	0.01590	0.00152	10.43	<.0001
price_ratio		1	-0.00428	0.01642	-0.26	0.8001
share_num_newcmpnd		1	-0.13707	0.18591	-0.74	0.4797
rel_detail_lag1		1	-0.00342	0.00203	-1.68	0.1268

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With detailing variable lagged 4 quarters

Linear regression for antidepressants in Japan

The REG Procedure
Model: MODEL1
Dependent Variable: share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	0.10064	0.01258	264.18	<.0001
Error	9	0.00042858	0.00004762		
Corrected Total	17	0.10107			

Root MSE	0.00690	R-Square	0.9958	
Dependent Mean	0.27157	Adj R-Sq	0.9920	
Coeff Var	2.54101			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-0.55885	1.03798	-0.54	0.6034
income_1Kcapita		1	0.02623	0.03772	0.70	0.5044
phys_1Mpop		1	-0.00020007	0.00026122	-0.77	0.4633
pct0_14	pct0_14	1	-0.23213	6.78603	-0.03	0.9735
pct65p	pct65p	1	0.51539	2.45607	0.21	0.8385
time	Q1 1992 = 1	1	0.01496	0.00171	8.75	<.0001
price_ratio		1	-0.01298	0.02392	-0.54	0.6007
share_num_newcmpnd		1	0.00799	0.20786	0.04	0.9702
rel_detail_lag4		1	-0.00017646	0.00060880	-0.29	0.7785

Table A4. 4   SAS output of Table 4.5

With detailing variable lagged 1 quarter

Log-log regression for Antidepressants in Germany
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	10	1293.44365	129.34436	21.40	<.0001
Error	5728	34620	6.04404		
Corrected Total	5738	35914			

Root MSE	2.45846	R-Square	0.0360
Dependent Mean	-13.18949	Adj R-Sq	0.0343
Coeff Var	-18.63957		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	27.13772	21.62814	1.25	0.2096
log_income_1Kcapita		1	-6.22941	5.90824	-1.05	0.2918
log_phys_1Mpop		1	4.81227	4.11386	1.17	0.2421
pct0_14	pct0_14	1	-254.89713	79.97294	-3.19	0.0014
pct65p	pct65p	1	-122.05771	53.86337	-2.27	0.0235
time	Q1 1992 = 1	1	-0.03263	0.01900	-1.72	0.0859
log_price_prod		1	-0.23616	0.05796	-4.07	<.0001
log_num_new_compound		1	0.25835	0.20300	1.27	0.2032
log_prod_detail_capita_lag1		1	-0.04042	0.00546	-7.41	<.0001
generic		1	0.31902	0.07273	4.39	<.0001
new		1	0.19530	0.11683	1.67	0.0946

With detailing variable lagged 4 quarters

Log-log regression for Antidepressants in Germany
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	10	1635.99703	163.59970	26.24	<.0001
Error	8257	51480	6.23469		
Corrected Total	8267	53116			

Root MSE	2.49694	R-Square	0.0308
Dependent Mean	-13.39929	Adj R-Sq	0.0296
Coeff Var	-18.63484		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-21.70602	23.79342	-0.91	0.3617
log_income_1Kcapita		1	-18.78735	8.14979	-2.31	0.0212
log_phys_1Mpop		1	17.34228	6.58389	2.63	0.0085
pct0_14	pct0_14	1	-303.36185	75.73472	-4.01	<.0001
pct65p	pct65p	1	-156.97820	51.65706	-3.04	0.0024
time	Q1 1992 = 1	1	-0.02132	0.01773	-1.20	0.2291
log_price_prod		1	-0.49767	0.04646	-10.71	<.0001
log_num_new_compound		1	0.24033	0.17085	1.41	0.1596
log_prod_detail_capita_lag4		1	-0.01571	0.00627	-2.50	0.0123
generic		1	0.30784	0.06306	4.88	<.0001
new		1	0.46261	0.09611	4.81	<.0001

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With detailing variable lagged 1 quarter

Log-log regression for Antidepressants in Japan
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	10	436.00581	43.60058	12.62	<.0001
Error	659	2276.47085	3.45443		
Corrected Total	669	2712.47666			

Root MSE	1.85861	R-Square	0.1607
Dependent Mean	-11.52305	Adj R-Sq	0.1480
Coeff Var	-16.12949		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	46.19082	95.63923	0.48	0.6293
log_income_1Kcapita		1	-2.54268	14.58026	-0.17	0.8616
log_phys_1Mpop		1	-4.18688	12.03726	-0.35	0.7281
pct0_14	pct0_14	1	-62.82561	111.51595	-0.56	0.5734
pct65p	pct65p	1	-62.37477	62.66362	-1.00	0.3199
time	Q1 1992 = 1	1	0.08235	0.06794	1.21	0.2259
log_price_prod		1	0.27416	0.12949	2.12	0.0346
log_num_new_compound		1	-0.07332	0.06080	-1.21	0.2282
log_prod_detail_capita_lag1		1	0.06567	0.01244	5.28	<.0001
generic		1	-1.12249	0.41273	-2.72	0.0067
new		1	2.03498	0.33475	6.08	<.0001

With detailing variable lagged 4 quarters

Log-log regression for Antidepressants in Japan
Omitted drug type: branded; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: log_prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	10	443.74905	44.37490	10.04	<.0001
Error	751	3318.01168	4.41812		
Corrected Total	761	3761.76073			

Root MSE	2.10193	R-Square	0.1180	
Dependent Mean	-11.69398	Adj R-Sq	0.1062	
Coeff Var	-17.97450			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	32.61102	98.38110	0.33	0.7404
log_income_1Kcapita		1	-8.70892	13.69017	-0.64	0.5249
log_phys_1Mpop		1	-1.23863	11.85028	-0.10	0.9168
pct0_14	pct0_14	1	-8.70359	97.53709	-0.09	0.9289
pct65p	pct65p	1	-56.87060	65.23434	-0.87	0.3836
time	Q1 1992 = 1	1	0.10011	0.07208	1.39	0.1653
log_price_prod		1	0.46164	0.12195	3.79	0.0002
log_num_new_compound		1	-0.07201	0.05948	-1.21	0.2264
log_prod_detail_capita_lag4		1	-0.03381	0.02241	-1.51	0.1317
generic		1	-0.98358	0.46210	-2.13	0.0336
new		1	1.90762	0.36046	5.29	<.0001

Appendix 5: SAS outputs of the regression results in chapter 5

Table A5. 1   SAS output of Table 5.1

With detailing variable lagged 1 quarter

Linear regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants

The REG Procedure
Model: MODEL1
Dependent Variable: tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	0.00412	0.00037415	592.98	<.0001
Error	108	0.00006814	6.309715E-7		
Corrected Total	119	0.00418			

Root MSE	0.00079434	R-Square	0.9837
Dependent Mean	0.00717	Adj R-Sq	0.9821
Coeff Var	11.08097		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.02904	0.01948	1.49	0.1389
income_1Kcapita		1	-0.00013132	0.00049715	-0.26	0.7922
phys_1Mpop		1	-0.00001478	0.00000227	-6.50	<.0001
pct0_14	pct0_14	1	-0.03090	0.06754	-0.46	0.6482
pct65p	pct65p	1	-0.02017	0.04333	-0.47	0.6426
time	Q1 1992 = 1	1	0.00030254	0.00004586	6.60	<.0001
price_class		1	-0.00737	0.00135	-5.45	<.0001
price_ratio		1	0.00122	0.00014870	8.21	<.0001
num_compound		1	-0.00001386	0.00002914	-0.48	0.6352
germany		1	0.02062	0.00306	6.74	<.0001
antihypertensives		1	0.01092	0.00060154	18.15	<.0001
tot_detail_capita_lag1		1	158.11705	47.54147	3.33	0.0012

With detailing variable lagged 4 quarters

Linear regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants

The REG Procedure
Model: MODEL1
Dependent Variable: tot_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	0.00405	0.00036833	605.18	<.0001
Error	106	0.00006451	6.086311E-7		
Corrected Total	117	0.00412			

Root MSE	0.00078015	R-Square	0.9843	
Dependent Mean	0.00727	Adj R-Sq	0.9827	
Coeff Var	10.73663			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.05418	0.01859	2.91	0.0044
income_1Kcapita		1	-0.00092052	0.00049951	-1.84	0.0681
phys_1Mpop		1	-0.00001129	0.00000296	-3.82	0.0002
pct0_14	pct0_14	1	-0.06916	0.06706	-1.03	0.3047
pct65p	pct65p	1	-0.06760	0.04141	-1.63	0.1055
time	Q1 1992 = 1	1	0.00033842	0.00004309	7.85	<.0001
price_class		1	-0.00867	0.00142	-6.09	<.0001
price_ratio		1	0.00122	0.00014701	8.27	<.0001
num_compound		1	-0.00000416	0.00002414	-0.17	0.8636
germany		1	0.01556	0.00395	3.94	0.0001
antihypertensives		1	0.01052	0.00061140	17.21	<.0001
tot_detail_capita_lag4		1	41.92037	10.40070	4.03	0.0001

Table A5. 2   SAS output of Table 5.2

With detailing variable lagged 1 quarter

Linear regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.00275	0.00018347	173.92	<.0001
Error	280	0.00029539	0.00000105		
Corrected Total	295	0.00305			

Root MSE	0.00103	R-Square	0.9031
Dependent Mean	0.00291	Adj R-Sq	0.8979
Coeff Var	35.28839		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.04326	0.01505	2.87	0.0044
income_1Kcapita		1	-0.00127	0.00038784	-3.27	0.0012
phys_1Mpop		1	0.00000142	0.00000193	0.74	0.4616
pct0_14	pct0_14	1	-0.02176	0.05415	-0.40	0.6880
pct65p	pct65p	1	-0.09808	0.03133	-3.13	0.0019
time	Q1 1992 = 1	1	0.00015969	0.00003681	4.34	<.0001
price_ratio		1	-0.00028275	0.00012657	-2.23	0.0263
price_gen		1	0.00515	0.00036235	14.22	<.0001
num_new_compound		1	0.00013077	0.00006633	1.97	0.0496
gen_detail_capita_lag1		1	-518.51748	33.33287	-15.56	<.0001
new		1	-0.00895	0.00064812	-13.81	<.0001
middle		1	-0.01146	0.00081936	-13.98	<.0001
timenew		1	0.00004293	0.00001329	3.23	0.0014
timemiddle		1	0.00018872	0.00002291	8.24	<.0001
germany		1	-0.00141	0.00256	-0.55	0.5826
antihypertensives		1	0.00690	0.00029524	23.37	<.0001

With detailing variable lagged 4 quarters

Linear regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants; Omitted generation: old

The REG Procedure
Model: MODEL1
Dependent Variable: gen_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.00257	0.00017127	103.66	<.0001
Error	275	0.00045433	0.00000165		
Corrected Total	290	0.00302			

Root MSE	0.00129	R-Square	0.8497	
Dependent Mean	0.00295	Adj R-Sq	0.8415	
Coeff Var	43.62366			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.04959	0.01936	2.56	0.0110
income_1Kcapita		1	-0.00132	0.00056118	-2.35	0.0195
phys_1Mpop		1	-0.00000116	0.00000316	-0.37	0.7143
pct0_14	pct0_14	1	-0.01508	0.06795	-0.22	0.8245
pct65p	pct65p	1	-0.11830	0.03987	-2.97	0.0033
time	Q1 1992 = 1	1	0.00020722	0.00004657	4.45	<.0001
price_ratio		1	-0.00009245	0.00015738	-0.59	0.5574
price_gen		1	0.00593	0.00047632	12.46	<.0001
num_new_compound		1	0.00018566	0.00009292	2.00	0.0467
gen_detail_capita_lag4		1	-142.41556	18.94664	-7.52	<.0001
new		1	-0.01111	0.00083679	-13.27	<.0001
middle		1	-0.00742	0.00094245	-7.87	<.0001
timenew		1	0.00006270	0.00001748	3.59	0.0004
timemiddle		1	0.00006674	0.00002599	2.57	0.0108
germany		1	0.00165	0.00427	0.39	0.7003
antihypertensives		1	0.00747	0.00051063	14.63	<.0001

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Table A5. 3 SAS output of Table 5.3

With detailing variable lagged 1 quarter

Linear regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants

The REG Procedure
Model: MODEL1
Dependent Variable: share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	10	0.97374	0.09737	154.24	<.0001
Error	106	0.06692	0.00063133		
Corrected Total	116	1.04066			

Root MSE	0.02513	R-Square	0.9357
Dependent Mean	0.11340	Adj R-Sq	0.9296
Coeff Var	22.15708		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-2.82432	0.61782	-4.57	<.0001
income_1Kcapita		1	0.00850	0.01485	0.57	0.5681
phys_1Mpop		1	-0.00002504	0.00007373	-0.34	0.7348
pct0_14	pct0_14	1	10.18805	2.25636	4.52	<.0001
pct65p	pct65p	1	8.35483	1.32883	6.29	<.0001
time	Q1 1992 = 1	1	0.00465	0.00139	3.35	0.0011
price_ratio		1	-0.03677	0.00483	-7.61	<.0001
share_num_newcmpnd		1	-0.66775	0.13027	-5.13	<.0001
germany		1	0.02085	0.09658	0.22	0.8295
antihypertensives		1	-0.23859	0.01919	-12.43	<.0001
rel_detail_lag1		1	-0.00568	0.00220	-2.58	0.0112

With detailing variable lagged 4 quarters

Linear regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants

The REG Procedure
Model: MODEL1
Dependent Variable: share_new_pd

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	10	0.96001	0.09600	152.96	<.0001
Error	104	0.06527	0.00062761		
Corrected Total	114	1.02528			

Root MSE	0.02505	R-Square	0.9363
Dependent Mean	0.11491	Adj R-Sq	0.9302
Coeff Var	21.80122		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-2.80119	0.63109	-4.44	<.0001
income_1Kcapita		1	-0.01661	0.01798	-0.92	0.3579
phys_1Mpop		1	0.00016500	0.00010137	1.63	0.1066
pct0_14	pct0_14	1	10.92493	2.20471	4.96	<.0001
pct65p	pct65p	1	8.66036	1.31232	6.60	<.0001
time	Q1 1992 = 1	1	0.00431	0.00138	3.12	0.0024
price_ratio		1	-0.03278	0.00474	-6.91	<.0001
share_num_newcmpnd		1	-0.48693	0.12662	-3.85	0.0002
germany		1	-0.24349	0.13383	-1.82	0.0717
antihypertensives		1	-0.20768	0.01882	-11.03	<.0001
rel_detail_lag4		1	-0.00008993	0.00066035	-0.14	0.8919

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Table A5. 4 SAS output of Table 5.4

With detailing variable lagged 1 quarter

Log-log regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants;
Omitted generation: old; Omitted drug type: branded

The REG Procedure
Model: MODEL1
Dependent Variable: prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	14	0.00001727	0.00000123	93.26	<.0001
Error	22002	0.00029094	1.322323E-8		
Corrected Total	22016	0.00030820			

Root MSE	0.00011499	R-Square	0.0560	
Dependent Mean	0.00003875	Adj R-Sq	0.0554	
Coeff Var	296.75168			

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.00034144	0.00023118	1.48	0.1397
income_1Kcapita		1	-0.00000749	0.00000523	-1.43	0.1521
phys_1Mpop		1	-4.1024E-8	2.328532E-8	-1.76	0.0781
pct0_14	pct0_14	1	-0.00001795	0.00077898	-0.02	0.9816
pct65p	pct65p	1	-0.00035030	0.00049078	-0.71	0.4754
time	Q1 1992 = 1	1	5.119305E-7	4.457607E-7	1.15	0.2508
price_prod		1	-1.52738E-7	5.508128E-8	-2.77	0.0056
num_new_compound		1	0.00000110	8.265382E-7	1.34	0.1817
prod_detail_capita_lag1		1	55.74573	3.35645	16.61	<.0001
generic		1	-0.00001623	0.00000393	-4.13	<.0001
new		1	0.00001416	0.00000358	3.95	<.0001
middle		1	2.091006E-7	0.00000236	0.09	0.9293
oldgen		1	9.489773E-7	0.00000439	0.22	0.8289
germany		1	0.00001332	0.00003015	0.44	0.6587
antihypertensives		1	0.00003071	0.00000237	12.97	<.0001

With detailing variable lagged 4 quarters

Log-log regression for antihypertensives and antidepressants in Germany and Japan
Omitted country: Japan; Omitted therapeutic class: antidepressants;
Omitted generation: old; Omitted drug type: branded

The REG Procedure
Model: MODEL1
Dependent Variable: prod_pd_capita

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	14	0.00001307	9.335789E-7	87.46	<.0001
Error	29047	0.00031007	1.067481E-8		
Corrected Total	29061	0.00032314			

Root MSE	0.00010332	R-Square	0.0404
Dependent Mean	0.00003227	Adj R-Sq	0.0400
Coeff Var	320.17025		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.00049214	0.00019249	2.56	0.0106
income_1Kcapita		1	-0.00001143	0.00000502	-2.28	0.0227
phys_1Mpop		1	2.452702E-9	2.839996E-8	0.09	0.9312
pct0_14	pct0_14	1	-0.00067395	0.00062828	-1.07	0.2834
pct65p	pct65p	1	-0.00061946	0.00040202	-1.54	0.1234
time	Q1 1992 = 1	1	5.2317E-7	3.488127E-7	1.50	0.1337
price_prod		1	-1.25321E-7	4.458483E-8	-2.81	0.0049
num_new_compound		1	5.029669E-7	6.542198E-7	0.77	0.4420
prod_detail_capita_lag4		1	10.48063	1.10081	9.52	<.0001
generic		1	-0.00001668	0.00000326	-5.11	<.0001
new		1	0.00001287	0.00000258	4.98	<.0001
middle		1	0.00000567	0.00000192	2.95	0.0031
oldgen		1	0.00000393	0.00000363	1.08	0.2787
germany		1	-0.00003507	0.00003682	-0.95	0.3409
antihypertensives		1	0.00002366	0.00000186	12.69	<.0001

References

[1] Ullrich K. Hoffmeyer, Thomas R. McCarthy, *Financing Health Care*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1994

[2] Ramarao Desiraju, Harikesh Nair, Pradeep Chintagunta, "Diffusion of New Pharmaceutical Drugs In Developing and Developed Nations", *International Journal of Research in Marketing*, May 24 2004

[3] John Vernon, "Concentration, Promotion, and Market Share Stability in the Pharmaceutical Industry", *The Journal of Industrial Economics*, vol.19 (3): 246-266, 1971

[4] Ernst R. Berndt, Linda T. Bui, et al., "The Roles of Marketing, Product Quality, and Price Competition in the Growth and Composition of the U.S. Antiulcer Drug Industry," in T. F. Bresnahan and R. J. Gordon, eds., *The Economics of New Goods*, 58, NBER Studies in Income and Wealth. Chicago: University of Chicago Press, pp. 277-322, 1997

[5] Ernst R. Berndt, Stanley N. Finkelstein, "Price Indexes for Anti-Hypertensive Drugs That Incorporate Quality Change: A Progress Report on a Feasibility Study," *Working Paper,* MIT, 1992

[6] Ernst R. Berndt, Iain M. Cockburn, Zvi Griliches, "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Antidepressant Drugs", *Brookings Paper on Economic Activity: Microeconomics,* pp. 133-188, 1996

[7] Todd Clark, *Pharma Handbook*, New Orleans, LA: Voi Consulting, International Pharmaceutical Publishing Group, 2004

[8] PubMed, a database a service by the National Library of Medicine, retrieved in February 2005, from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

[9] Professor Ernst R. Berndt, Sloan School of Management, Massachusetts Institute of Technology, Cambridge, MA; Dr. Dirk M. Hentschel, M.D., Brigham and Women's Hospital, Boston, MA

[10] O. Carretero, S. Oparil, "Essential Hypertension Part I: Definition and Etiology", *Circulation 101*: 329–335, 2000

[11] WebMD health guide, retrieved in March 2005 from http://my.webmd.com/hw/ hypertension/aa26786.asp

[12] J. A. Staessen, et al. "Hypertension Prevalence and Stroke Mortality Across Populations", *JAMA* 289: pp 2363-2369, 2003

[13] S. Oparil, "Arterial hypertension", in M. Goldman, J. Bennett, eds., *Cecil Textbook of Medicine*, 21st ed., vol. 1, pp. 258–273, 2000 Philadelphia, PA: W.B. Saunders

[14] K. Wolf-Maier et al., "Hypertension Prevalence and Blood Pressure Levels in 6 European Countries, Canada and the United States", *JAMA* 289:2363-2369, 2003

[15] J. S. Vizlayno et al., "Studies on Hypertension and Risk Factors in Selected Populations of the Philippines, Japan and Korea", *Philippine Journal of Cardiology*, 11(1): 1-10, 1983

[16] "Fact sheet of cardiovascular disease: prevention and control", WHO, retrieved in March 2005 from http://www.who.int/dietphysicalactivity/publications/facts/cvd/en/

[17] Y. Suzuki, et al. "Dietary Supplementation of Fermented Soybean, Natto, Suppresses Intimal Thickening and Modulates the Lysis of Mural Thrombi After Endothelial Injury in Rat Femoral Aartery", *Life Science*, 25; 73(10): pp. 1289-98, July 2003

[18] M. Maruyama, H. Sumi. "Effect of Natto Diet on Blood Pressure", *JTTAS*, 1995

[19] D. Yam et al., "Omega-3 Fatty Acids Reduce Hyperlipidaemia, Hyperinsulinaemia and Hypertension in Cardiovascular Patients", *Journal of Clinical and Basic Cardiology*, 5 (Issue 3): pp. 229-231, 2002

[20] Heart Center Online document on hypertension and treatments, retrieved in March 2005 from, http://www.heartcenteronline.com/myheartdr/common/artprn_rev.cfm?filename=&ARTID=382

[21] American Heart Association official website, retrieved in March 2005 from http://www.americanheart.org/presenter.jhtml?identifier=593

[22] B. M. Psaty, S. R. Heckbert et al., "The Risk of Myocardial Infarction Associated with Antihypertensive Drug Therapies", *JAMA*, 274: pp. 620-625, 1995

[23] M. Pahor, J. M. Guralnik et al., "Calcium-Channel Blockade and Incidence of Cancer in Aged Populations", *Lancet*, 348: pp. 493-497, 1996

[24] M. Pahor, B. M. Psaty et al., "Health Outcomes Associated with Calcium Antagonists Compared with Other First-Line Antihypertensive Therapies: A Meta-Analysis of Randomised Controlled Trials", *Lancet*, 356: pp. 1949-1954, 2000

[25] *2004 OECD Health Database*, (purchased from OECD, www.oecd.org)

[26] National Institute of Mental Health, National Institute of Health (NIH), http://www.nimh.nih.gov

[27] WebMD health guide, retrieved in March 2005 from http://my.webmd.com/medical information/condition centers/depression/default.htm

[28] M. D. Blehar, D. A. Oren, "Gender Differences in Depression: Medscape Women's Health", revised from: "Women's Increased Vulnerability to Mood Disorders: Integrating Psychobiology and Epidemiology", *Depression*, 3:3-12, 1995

[29] Kathryn Schulz, "Did Antidepressants Depress Japan?", *The New York Times Magazine*, August 22, 2004

[30] Suicide prevention and special programmes, The World Health Organization, http://www.who.int/mental health/prevention/suicide/suicideprevent/en/

[31] Yoshitaka Kaneita, "Epidemiology of Depression and Sleep Disturbances: A Nationwide General Population Survey", *The 132nd Annual Meeting of American Public Health Association (APHA)*, November 8, 2004

[32] T. Munakata, "The Socio-Cultural Significance of the Diagnostic Label 'Neurasthenia' in Japanese Mental Health Care System", *Culture, Medicine, and Psychiatry*, 13, pp. 203-213, 1989

[33] Rosie Goldsmith, "Suicide 'Epidemic' Among Japan's Elderly", *BBC news*, March 19, 2003, http://news.bbc.co.uk/1/hi/programmes/crossing continents/2862051.stm

[34] M. Hachisu, Y. Ichimaru, "Pharmacological and Clinical Aspects of Fluvoxamine (Depromel), the First Selective Serotonin Reuptake Inhibitor Approved for Clinical Use Employed in Japan", *Nippon Yakurigaku Zasshi*, 115(5):271-9, May 2000

[35] Weissman et al., "Cross-National Epidemiology of Major Depression and Bipolar Disorder", *JAMA* vol. 276 (4), pp. 293-299, July 1996

[36] Afschin Gandjour et al., "Costs and Quality in the Treatment of Acute Depression in Primary Care: A Comparison Between England, Germany and Switzerland", *International Clinical Psychopharmacology*, 19(4): pp. 201-208, July 2004

[37] German Association of Research-based Pharmaceutical Companies, "Code of the Members of the Association of Research-based Pharmaceutical Companies", November 2001, http://www.vfa.de/en/vfa_en/kdx_en.html