The Pharmacist's Substitution Strategy in the Presence of Manufacturer Quantity Discounts and an Empirical Study on the Cost Effects of Rx-To-OTC Switch in Turkey

by

Ayşe Başak Çizmeci

A Thesis Submitted to the
Graduate School of Engineering
in Partial Fulfillment of the Requirements for
the Degree of

Master of Science
in
Industrial Engineering

Koc University

August 2008

Koc University

Graduate School of Sciences and Engineering

This is to certify that I have examined this copy of a master's thesis by

Ayşe Başak Çizmeci

and have found that it is complete and satisfactory in all respects,
and that any and all revisions required by the final
examining committee have been made.

Committee Members:

_____

Özden Gür Ali, Ph. D. (Advisor)

_____

Fikri Karaesmen, Ph. D.

_____

Yalçın Akçay, Ph. D.

Date: 23/07/2008

ABSTRACT

This thesis consists of an empirical and a theoretical study focused on pharmaceutical industry.

In Turkey, more than a hundred drugs have been removed from reimbursement since July 2006. Government's recent reimbursement policy is interpreted as switching some drug categories from Rx (Prescription) to Over-the-Counter (OTC). In the first part of this thesis study, we analyze the effects of the change on consumption of both the switched drugs and their equivalent alternatives that are still reimbursed by the government. Our results suggest that there has been a significant decrease in the demand for the removed drugs, as expected. More importantly, in absolute terms, the increase in the equivalent drugs sales go beyond the decrease in removed drug sales for some of the ATC groups. Therefore, it is possible that the removal of these drugs from reimbursement may not produce the expected decrease in spending, and could even lead to an increase in total pharmaceutical expenditures. For the first time in the literature of Rx-to-OTC switches, we draw attention to the risk of increased cost to third-party payers due to the demand switch to reimbursed equivalent alternatives of the drugs that are made OTC available.

In the second part of this study, we develop a mathematical model of the profit maximizing pharmacist who can substitute the requested drug with an alternative in the presence of manufacturer discounts. In pharmaceutical industry, it is common that pharmaceutical manufacturers provide attractive quantity discounts to the pharmacist in order to benefit from his substitution power. Our aim is to provide insights into pharmacist's substitution strategy in the presence of manufacturer quantity discounts. The results of the study suggest that full substitution is optimal only when substitution is profitable for the pharmacist and the gain from quantity discount and substitution exceeds the holding cost. When the pharmacist incurs a positive substitution cost, no substitution is

optimal if the discount benefit cannot compensate for the holding cost. Otherwise, the pharmacist engages in partial substitution by substituting all demand up to a point in the order cycle, beyond which holding costs make it unprofitable to substitute. To our knowledge, this study is the first to consider such a temporal partial substitution pattern. In addition, we show its optimality under specified conditions.

ÖZETÇE

Bu tez çalışması ilaç endüstrisi ile ilgili bir veriye dayalı bir de teorik çalışmadan oluşmaktadır.

Türkiye'de, 2006 yılı Temmuz ayından itibaren yüzden fazla ilaç geri ödemeden çıkarılmıştır. Hükümetin bu politikası, bazı ilaç kategorilerinin reçeteliden tezgah üstü (OTC) statüsüne geçişinin ilk adımı olarak yorumlanmıştır. Tez çalışmasının ilk bölümünde, bu değişikliğin hem geri ödeme kapsamından çıkarılan ilaçların hem de onların muadili olabilecek ve halen geri ödenen ilaçların tüketimine etkisi incelenmiştir. Çalışma sonucunda geri ödemeden çıkarılan ilaçların talebinde anlamlı derecede düşüş görülmüştür. Daha önemlisi, incelenen bazı ATC gruplarında, muadil ilaçlara yapılan harcamada, geri ödeme kapsamından çıkarılan ilaçlara yapılan harcamada görülen düşüşten mutlak değerce daha fazla bir artış gözlenmiştir. Bu nedenle, hükümetin yeni geri ödeme politikasının hedeflendiği gibi harcama düşüşü sağlamaması, hatta ilaca yapılan toplam harcamada artışa neden olması mümkündür. Bu çalışmada, konu ile ilgili literatürde ilk kez olmak üzere, ilaçların reçeteli durumdan OTC statüsüne geçişinin üçüncü parti ödeyiciler için, alternatif ilaçlara talep kayması ile açıklanan, bir maliyet artışı riski taşıdığına dikkat çekilmiştir.

Çalışmanın ikinci bölümünde, ilaç ikamesi yapabilen bir eczacının, üretici miktar iskontoları varlığında, kar maksimizasyonu modeli geliştirilmiştir. İlaç üreticilerinin, eczacının ikame gücünden faydalanma amacıyla cazip miktar iskontoları sunması ilaç endüstrisinde yaygın bir durumdur. Bu çalışmada; üretici miktar iskontoları durumunda, eczacının rasyonel ikame stratejisi ortaya konmuştur. En uygun sipariş miktarı ve ikame stratejisi konusunda çıkarımlarımız, tam ikamenin yalnızca ikame etmenin perakendeciye kar getirdiği durumda en iyi sonucu verdiğini, ayrıca iskontodan ve ikameden elde edilen toplam getirinin stok maliyetini karşılaması gerektiğini göstermiştir. İkamenin belirli bir maliyet getirdiği durumda, iskonto getirisi stok maliyetini karşılayamıyorsa perakendeci

ikame etmemeyi seçer. Aynı durumda iskonto getirisi stok maliyetine göre yüksek ise, stok döngüsünde belli bir zamana kadar bütün talebi ikame edip kalan zamanda ikame etmeyecek şekilde bir kısmi ikame stratejisi en iyi sonucu vermektedir. Bu şekilde bir kısmi ikame stratejisi bildiğimiz kadarıyla literatürde ilk kez incelenmiş ve belirli koşullar için en iyi sonucu verdiği gösterilmiştir.

ACKNOWLEDGEMENT

First, I wish to express my gratitude to my supervisor Dr. Özden Gür Ali for her invaluable advice and guidance throughout my research as well as her inspiration and encouragement. I am fortunate to have been able to work with her since the beginning of my master study.

I would like to thank Dr. Fikri Karaesmen and Dr. Yalçın Akçay for taking part in my thesis committee and contributing with their readings and comments.

I thank TÜBİTAK for its generosity in funding my graduate study. I am honored to be the recipient of this award.

I also thank Bahadır Pakiş and Gamze Alatan from Novartis Turkey for their assistance in providing us valuable data about Turkish pharmaceutical market, and Can Adamoğlu from Eczacıbaşı-Zentiva for sharing his knowledge and experience with us.

RxMediaPharma source provided relevant data for my study. I want to thank Prof. Dr. Levent Üstüneş, the editor of RxMediaPharma, for all his support to my thesis.

I am grateful to Professor Dr. Mehmet Melli, the president of Turkish Pharmacological Society, Assistant Professor Hakan Ergün, Dr. Pınar Kutluana, Dr. Hakan Kamışoğlu and Dr. Erdal Mehmet Aksoy for sharing their knowledge that influenced the study.

I appreciate all my friends Figen, Müge, Ferda, Selim, Sezer, Seray, Pelin and Güven for being invaluable colleagues all along my years in Koç University.

I present my special thanks to my parents Semiha and Cevat Çizmeci, and my brother Doğacan Çizmeci for their endless support, love and belief on me. And the last but not the least, I want to thank my darling Suat Topaler who understand my efforts and always stand by me with great love, support and encouragement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Nomenclature

i	drug (firm) indices
P_i	regular price of drug i
Q_i	order quantity for drug i
t_0	substitution period
t_1	cycle time
pm_i	profit margin of pharmacies for drug i regulated by the government
D_i	known annual demand for drug i
a	generic manufacturer's discount parameter
K	fixed order cost for generic drug
c	complaint cost for substituting one unit of branded demand with the generic drug
h	per unit holding cost for the generic drug
CR	the pharmacist's revenue per cycle
AR	the pharmacist's annual revenue
AC	annual total cost
AP	annual profit
C_t	cost of transferring one unit of branded demand to the generic drug

Chapter 1

1. INTRODUCTION

The pharmaceutical industry is an important component of the healthcare system throughout the world. It is comprised of many public and private organizations that discover, manufacture and market products that both treat and help prevent diseases. Spending on medical goods, especially in pharmaceuticals, has risen rapidly across most OECD countries, consuming an increasing share of overall health expenditure. On average across OECD countries, pharmaceutical expenditures accounted for 1.5% of GDP in 2007 [1].

In Turkey, health expenditures as a share of GDP was 7.7% in 2006 [2] and pharmaceutical spending accounts for 40% of total health expenditures which is much higher than the average share of pharmaceuticals in OECD countries [3]. As it is discussed in Pharmacoeconomy Meeting [4], looking towards EU accession, government health spending as a percentage of GDP has to be reduced. Turkish Healthcare System is undergoing significant change under the radical reform known as "Transformation in Health" Programme. One important aspect of the programme is to adopt urgent cost-containment measures for pharmaceutical expenditures [5].

Over-the-counter drugs are available to consumers without a physician's prescription. In Turkey, it is suggested that drugs which are likely to be listed in OTC category be gradually delisted from the reimbursement list. Since 2006, more than a hundred drugs have been removed out of reimbursement.

In the first part of this thesis study, we analyze the effects of the recent Rx-to-OTC switch on pharmaceutical consumption of these drugs and their equivalent alternatives that

are still reimbursed by the government in Turkey. Therefore, our results provide insights for the government strategy regarding the patient out-of-pocket expenses.

In Turkey, as well as in many countries, pharmaceutical manufacturers offer attractive discounts to the pharmacists for the purpose of getting substitutions in their favor. Due to regulations on drug prices, pharmacy discounts are not in the form of a percent reduction in price; rather manufacturers offer an extra amount of drug for each specific amount of purchase. The purpose of these quantity discounts are similar to trade promotions offered by manufacturers to pharmacists for the purpose of stimulating sales [6].

Gür Ali and Çavdaroğlu [7] developed a model for understanding pharmacy and manufacturer decisions in the Turkish pharmaceutical industry where the pharmacist can dispense most drugs without prescription to cash patients and for patients reimbursed by the government they can substitute the prescribed drugs with cheaper bioequivalent alternatives. In this study, the role of the inventory cost was not considered.

In literature, retailer substitution is considered as an opportunity to reduce holding cost, although the retailer has to incur a particular cost. The aim is to determine optimal stocking levels and the substitution rules that should be followed in different settings. Most of the studies focus on “one-way substitutability” which means that the products can be used to substitute each other in a hierarchical order. One example is Drezner et al. [8] who develop a variation on the standard EOQ model for the case of two products where product 1 can substitute for product 2 at transfer cost per unit. Gurnani and Drezner [9] extend this analysis to the case of n drugs with strict ordering on substitutions.

A different stream of research studies the optimal purchase quantities in the presence of quantity discounts offered by manufacturers. Buyer’s lot sizing problems and supplier’s optimal strategy in the presence of quantity discounts have been studied in literature [10]. Recently, researchers have also focused on joint profit maximization using quantity discounts as a tool to achieve channel coordination [11].

Although the optimal ordering decisions of the retailer in the case of substitution and in the case of quantity discounts are separately studied in different settings, there is a gap in the literature about the effect of manufacturer discounts on the retailer's substitution decision.

In the second part of this thesis, we analyze the optimal order quantity and one-way substitution strategy for the retailer (the pharmacist) selling two-products in the presence of quantity discount offers from one of the manufacturers. This study is the first attempt, to our knowledge, to model the role of the discounts offered by manufacturers on retailer's optimal stocking levels and substitution decision. Our aim is to explain how the quantity discounts offered by the manufacturers affect retailer's optimal order quantity and substitution decision, considering the inventory cost and penalty for substitution. The retailer is faced with the quantity discount incentive for substitution as well as inventory holding costs. The trade-off is an issue when the holding cost is comparable with the discount benefit gained from substitution. The results of the study show that when there is a positive substitution cost, partial substitution strategy can be optimal depending on the discount offered for the generic product and the cost of holding the generic product at hand. The portion of branded demand satisfied with the generic product increases with the discount offer. When the discount benefit is not comparable with the holding cost, the profit maximizing retailer chooses not to substitute the branded product with the generic one.

The rest of the study is structured as follows; Chapter 2 presents an overview of the Turkish pharmaceutical industry, describes the drug reimbursement system and governmental regulations. In this chapter, we also provide our limited survey on pharmacy discounts to give a sense of the current practice that is critical in the pharmacist's decision. Chapter 3 gives a brief overview of literature on Rx-to-OTC switches and the empirical study on the effects of the recent governmental reimbursement policy changes on

pharmaceutical expenditures in Turkey. In Chapter 4, we provide an overview of the literature on quantity discounts and substitution and discuss our contribution. Moreover, we model the pharmacist's rational substitution and ordering strategy in the presence of manufacturer quantity discounts and provide managerial implications of the insights obtained.

Chapter 5 concludes with a summary of the performed study, conclusions, managerial implications, limitations and future research work.

Chapter 2

2. TURKISH PHARMACEUTICAL INDUSTRY

2.1. Health Expenditures

Spending on pharmaceuticals has risen rapidly across most OECD countries, consuming an increasing share of overall health expenditure. Since 1995, growth in pharmaceutical spending in real terms has averaged 4.6% per year, higher than the 4.0% annual rise in overall total health spending over the same period [1].

In Turkey, health expenditures constitute 7.7% share of gross domestic product (GDP) [2]. In terms of pharmaceutical consumption Turkey is in third place in the Middle East & Africa [4]. In 2006, having a growth rate of 10%, the Turkish pharmaceutical market reached $ 9.9 billion in consumer prices [12].

On average across OECD countries, 60% of pharmaceutical expenditure is borne by public funds, the remainder being met by out-of-pocket payments and, to a lesser extent, by private insurance. In Turkey, the portion of the pharmaceutical expenditure reimbursed by the government is really high compared to the EU countries and the OECD average [1]. Public sector finances roughly 78% of the total pharmaceutical spending [3]. Other sources of income are contributions obtained from members of the social security schemes, out-of-pocket spending and private sector financing. Out-of-pocket payments account for 27.6% of the total health spending. The remaining portion is relatively trivial and comes from private insurance and corporations [13].

Moreover, pharmaceutical spending in Turkey accounts for 40% of total health expenditures which is much higher than the average share of pharmaceuticals in OECD countries [3]. This major burden in public health spending resulted in cost containment measures such as reference pricing and shifting of some reimbursed drugs to non-reimbursed OTC status.

2.2. Stakeholders

In this subsection we will briefly discuss how main stakeholders in the Turkish pharmaceutical system operate and give an overview of governmental regulations. Key stakeholders in the pharmaceutical system are:

- Government and its agencies
- Health insurance agencies
- Patients
- Physicians
- Pharmaceutical manufacturers
- Wholesalers & Pharmacies

2.2.1. Pharmaceutical Manufacturers

Technically, original drug manufacturers focus their efforts on innovative drug inventions and invest in R&D, whereas generic manufacturers specialize in generic production of drugs whose patent has expired. Unlike the practice in EU countries and the US, in Turkey, generic drugs also have brand names as their original versions. Consumers (patients) are usually not informed whether their medication is an original patent holder or not.

Pharmaceutical manufacturers in Turkey differ with respect to their drug profiles. Besides the original and generic manufacturers, there exist foreign and domestic pharma firms manufacturing both original and generic drugs. There was not a patent protection until 1999 when the new regulation similar to the one implemented in EU countries came into effect. Technically, this regulation provides protection for the patent of the drugs introduced to the market after 1995 [14]. However, this regulation has not come into effect yet [15].

Promotion activities

In the Turkish pharmaceutical market, promotions directly targeting final consumers are very limited due to the restrictions on direct-to-consumer (DTC) advertising activities of pharmaceutical companies. Most commonly, it is the original manufacturer that uses consumer-focused promotions, such as campaigns increasing social awareness.

Pharmaceutical manufacturers provide professional education, growth opportunities and sponsorship to physicians and medical journals. Both original and generic drug manufacturers introduce their products to physicians through their sales representatives. Personal communication is the most effective method of presenting a new drug to the physicians who have the potential of prescribing it. This type of promotion is called detailing. Promotions directed to physician usually constitute the largest proportion of marketing expenditures for original manufacturers.

The profit margin of each party involved in the pharmaceutical transaction is strictly defined by the government. However, deviations occur in actual profit margins due to informal discounts given to wholesalers and retailers. Discounts are in the form of free goods for specific amounts of purchase and they are legal even in low-volume transactions. Generic manufacturers focus their marketing efforts on pharmacies more frequently than

original manufacturers and predominantly use discounting activities in order to increase their sales volume.

2.2.2. Wholesalers and Pharmacies

The current regulations in Turkey, limit the distribution of pharmaceuticals solely through pharmacies and hospitals [13]. Generic and original drug manufacturers sell their products to pharmacies via pharmacy co-operatives and wholesalers.

Wholesalers are in the position of intermediary institutions between pharmaceutical companies and pharmacies. They negotiate with manufacturers for the amount of discount and term of the payment in return for access to pharmacies working with these wholesalers [7]. Hedef Alliance and Selçuk Ecza, account together for over 70% of this market. In addition, there are regional pharmacy co-operatives which hold an estimated 10% of the market [13]. Wholesalers have an expansive distribution channel and they can provide fast response in delivery.

Pharmacists are key players in the pharmaceutical market. In Turkey, pharmaceuticals are only available and for sale in pharmacies. The pharmacy profit margin is regulated by the government, like the profit margins of other players in the supply chain. The pharmacist is allowed for substitution if the price of the equivalent drug to be substituted is less than the price of the prescribed drug. This equivalent drug can be one of the generic substitutes listed for reimbursement. Also in the US, pharmacists can substitute the prescribed drug with its generic version.

In considering substitution, pharmacists are heavily influenced by the financial incentives such as the free goods (“mal fazlası”) and a flexible pay back period ("terms") [13]. Pharmacy discounts are also critical in the pharmacist’s inventory decision, since there is an incentive to procure from and stock the drug that carries the highest discount.

Generic manufacturers try to take advantage of the pharmacist's substitution power and focus their marketing efforts on pharmacies more frequently than original manufacturers.

Patients may actually prefer the original drug to the generic one. However, when generic substitution is presented as purchase option associated with less out-of-pocket spending, patients usually respond positively. On the other hand, with generic substitution, the physicians transfer some of their professional authority to the pharmacists [13]. In the long run, pharmacist may undertake a cost for patient's or physician's objection to the substitution.

2.3. Drug Reimbursement Policy and Transformation in Health Programme

Looking towards EU accession, government health spending as a percentage of GDP has to be reduced in Turkey [4]. Turkish health care system is undergoing significant change under current government's reform programme: "Transformation in Health". The central objective of the programme is to establish a high quality and effective health care system covering all the society [5]. The new drug policy in Turkey operates on the following basis according to Kanavos et al. [13]:

- A unified positive list that provides access to all insurees.
- An inter-ministerial reimbursement committee that is established according to the Pharmaceutical Pricing Decree.
- Detailed policies that will affect physician prescribing and overall authorizing behavior.

The drug reimbursement issue is one of the major problems in Turkish health care system. Recently, a general health insurance covering all the insurees is established under Transformation in Health Programme. The Social Security Institution (SSI) is presently working as an umbrella organization for all of the former insurance institutions- SSK, Emekli Sandığı, and Bağ-Kur and Green Card scheme- [16], and it has started to take over

the major responsibility for conducting a drug policy in Turkey [13]. The objective of this integrated insurance system is to improve the quality of services as well as delivering the health-care service to patients in an equitable way [5].

2.4. Regulations Concerning Over-the-Counter (OTC) Drugs Market

The drug market mainly consists of; prescription submarket, hospital submarket and the over-the-counter (OTC) submarket. These three markets usually differ with respect to the reimbursement dynamics [17]. In this subsection, we focus on the over-the-counter drugs submarket and discuss new governmental policies concerning drug reimbursement.

2.4.1. Over-the-Counter Drugs

Over-the-counter drugs are available to consumers without prescription of physician and mostly used for treatment of relatively minor health problems. These drugs are assumed to be safe for self-treatment when advised by the pharmacist. The OTC pharmaceuticals cover the analgesics, cough and cold preparations, indigestion preparations, vitamins and minerals, medicated skin products and other OTC health care products [18].

The OTC market is much like other competitive commodity markets where there is a high degree of substitutability and demand is relatively sensitive to changes in price. In most European countries, OTC drugs are not reimbursed and the consumers of these drugs pay out of pocket [17]. Prices of OTCs have been liberalized in the majority of OECD countries except when they are reimbursed by health insurance [13]. Although, OTCs are usually available at pharmacies or drugstores, other retail outlets are allowed to sell these products in some countries including the Netherlands and the US.

In Turkey, there is no clear distinction between prescription-only medicines (POM or Rx) and over-the-counter drugs. OTCs are classified as drugs that do not necessitate a prescription. However, patients can also supply most prescription drugs from the pharmacy without a prescription. OTC drugs mainly fall into therapy classes like cough & cold preparations, pain killers and vitamins. Several medications, which should in principle be available over-the-counter can be reimbursed by government when prescribed. It is estimated that 58% of the OTC market is financed by the public sector [13].

2.4.2. Rx-to-OTC switch

Prescription to OTC switch refers to over-the-counter marketing of a product that was once a prescription drug for the same indication, strength, dosage, form and duration of use [19]. Allowing prescription-only (Rx) medicines to be available over-the-counter termed as de-listing or "Rx-to-OTC switch". Over-the-counter drugs are typically available at the consumers' out-of-pocket expense. Therefore, many countries view delisting as a means of relieving some of the pressure on pharmaceutical budgets [13].

The OTC market has a market share of 6-10% in most EU countries and it has a growing share in most pharmaceutical markets due to the increase in Rx-to-OTC switches in recent years. The main motivation behind this trend is to enhance patient access to medicines, to shift drug distribution costs from governments to individual consumers and to encourage greater public responsibility in self-medication. Patient's choice of OTC drugs is generally driven by experience of benefit and safety, out-of-pocket spending and advice from physicians, general practitioners and pharmacists [13].

Literature on the effects of Rx-to-OTC switch indicates that the practice reduces cost to third party payers and provides saving in general practitioners' time due to a decline in overall dispensing. On the other hand, there are the risks of inaccurate diagnosis by

patients, use of suboptimal therapy and perceived loss of control by physicians. When the drug that is made OTC available is also removed from the reimbursed list, patients with low ability to pay or cope with these changes may suffer adversely and this will cost the system in the long run. Therefore, Rx-to-OTC switch has to be evaluated in all its aspects, achieving overall cost saving is not always the case [20]. We investigate a third effect of this switch: a potential move from the non-reimbursed to similar reimbursed drugs in order to save the patient from the out-of-pocket costs.

2.4.3. OTC Drugs Market Regulations: European Countries and Turkey

The sale of over-the-counter medicines might require pharmacist supervision or they may be for general sale. In the US, OTC drugs can be sold in retailers like supermarkets with medical departments. Pharmacist-only or behind-the-counter drug class may fall somewhere between the prescription-only and OTC designations, allowing certain medications to be dispensed without a prescription but requiring them to be stocked behind the pharmacy counter instead of retailer's shelves. It is like an orientation of the pharmacist on how to use the drug before handing it over-the-counter with the objective of protecting consumer safety [21]. For example in Portugal, OTCs are freely priced and not reimbursed, but can be sold only through pharmacies [22]. Currently in Turkey, OTC-type products are required to undergo the same registration procedures as other prescription drugs, and are available only through pharmacy outlets.

In OECD countries, over-the-counter drugs are typically excluded from reimbursement. In many countries including the UK and the Netherlands, a criterion for reimbursement is OTC exclusion and non-reimbursed drug prices are not controlled by the government. However, in Turkey, until recently almost all of the OTCs were reimbursed when they are prescribed by a physician. Their prices are regulated by the government. Provided that all

pharmacies were attended by pharmacists at all times and the drugs are only dispensed by the pharmacist, it would make sense to have a third category of "behind the counter" drugs that are available from a pharmacy without a physician prescription.

2.4.4. Proposed OTC Classification in Turkey

In Turkey, there is a need to limit the increase in health care expenditures and to use health care resources more efficiently. The burden of pharmaceutical expenditures for the public budget is quite high. Delisting the OTC type drugs from reimbursement is an obvious approach to reducing patient incentives for overuse.

There are several controversial issues concerning the pharmaceutical system in Turkey. The proponents of OTC introduction claim that public resources will be used more productively and significant cost savings can be achieved if the reimbursement system is regulated. In the heart of the discussion, the following issues on parliament's agenda constitute the basis of the new OTC system [23]:

a) *Advertising for OTCs and pharmaceuticals*: Direct-to-consumer (DTC) advertising for prescription drugs is restricted in most European countries. Within the context of current regulations, pharmaceutical companies in Turkey are not allowed to advertise even the over-the-counter drugs. A clear distinction of prescription-only medicines and non-prescription drugs and a clearly defined OTC policy may bring in liberty for the over-the-counter drug promotion activities. Pharma companies hope to benefit from this advertisement market in the future, although there are strong objections from Turkish Medical Association and Turkish Pharmacists Association. AIFD (Association of Research-Based Pharmaceutical Companies) claim that if certain drugs are made over-the-counter, the marketing expenditures will be added to the cost and this will result in an increase in prices.

b) *Arrangement for Pharmaceuticals and Medical Devices*: Until very recently, almost all OTCs could be reimbursed by governmental social security organizations if they were prescribed by the physician. In Turkey; 503 million boxes of drugs can be sold without a prescription and 292 million of these are under government reimbursement programs. Accordingly to the OTC report of İstanbul Akademi Danışmanlık, if those 292 million boxes of drugs are shifted to non-reimbursed status, government would achieve significant cost saving [24].

Assuming that the OTC drugs market is explicitly introduced, the reimbursement structure as well as price regulations concerning OTC drugs will be strategically important. It is suggested that products which are likely to be listed in OTC category be gradually delisted from the reimbursement list. Cost-cutting implications of de-listing are likely to prove attractive in the current financial environment [13].

OTC prices have been liberalized in the majority of OECD countries. Turkey may follow a similar arrangement in the long run, while keeping the prices for the reimbursed drugs (Rx or OTC) still under the government's control determined on the basis of multiple criteria in order to determine value and therapeutic benefit.

c) *Sale of Pharmaceuticals in Retailers Other than Pharmacies*: Another item of discussion is the authorized sales channels for the over-the-counter drugs. Currently, only licensed pharmacists are allowed to deliver drugs. After the mentioned bill, OTCs may still only be available from pharmacies or more widely available, e.g. supermarkets [13]. The pharmacists in Turkey are concerned about the introduction of direct competition from supermarkets and other non-pharmacy retail chains in the future.

In the Pharmacoeconomy Meeting [25], it has been discussed that besides providing significant cost saving an OTC model will be instrumental in the following issues:

- European Union Legislation (adaptation process)
- Reducing the patient burden in health care system (reduced physician visits)

- Rational prescribing behavior
- Increase health consciousness and self-medication in the long term

Health consciousness is crucial for successful self-medication. In Turkey, it is necessary to initiate legislation on self-medication if an OTC system is introduced. OTC products and the way of treatment should be clearly defined. Moreover, in order to increase public awareness, patients should be informed about the benefits as well as the related risks of self-medication. Otherwise, there is a risk of inaccurate diagnosis by patients and use of suboptimal therapy which may lead to increased costs in the long-run [20].

In summary, there is an ongoing debate among the government, doctors and pharmacists concerning the introduction of an explicit OTC category in Turkey. General Directorate of Pharmacy and Pharmaceuticals is currently working on the list of non-prescription drugs [26]. Ministry of Finance excluded more than a hundred OTC-type drugs from reimbursement with it's circulars in July and September 2006. These changes were interpreted as the indirect execution of a new OTC system. On the other hand, the opposing party physicians and pharmacists draw attention to the lack of a cost-effectiveness analysis and overall rationale in those regulations [27].

In this thesis, in chapter 3, we empirically study the demand shift due to prescription of reimbursed alternatives after the removal of these drugs from reimbursement.

2.5. Pharmacy Discounts

In Turkey, pharmacists are paid on a regressive profit margin basis from health insurance funds. Moreover, they are allowed to perform a substitution if the price of the drug substituted is less than the price of the prescribed drug. Especially generic

manufacturers try to benefit from this substitution power of the pharmacist by offering attractive discounts [13].

Since the profit margin of the pharmacist is strictly defined by the government, discounts are not given as direct percent rebates. Similar to the quantity discount approach in the retail sector, pharmacy discounts are in the form of free goods for specific amounts of purchase. Given that the substitution is among products with the same molecule conforming to the quality standards set by the health authorities, the principal factor affecting the decision of the pharmacist concerning substitution is mainly commercial. In this context, discounts provide a potentially significant source of income to pharmacists in addition to their margins.

Gür Ali and Çavdaroğlu [7] conducted a research to assess the effects of pharmacy discounts on profit maximizing behavior of both pharmacies and manufacturers. The results of the study suggest that the pharmacist's profit maximizing decision for substitution is driven by the discount rates offered by manufacturers weighted by other factors such as the likelihood that the patient will pay the out-of-pocket expense for the drug, relative to the complaint costs.

Currently, there is no sufficient data to understand the dynamics affecting the dispensing patterns of pharmacists and the interactions among the supply chain. In order to gain some insight into the general structure, we collected and analyzed the pharmacy discount data for some specific ATC groups in a certain time period from a convenience sample of pharmacies in Turkey. Since there are no publicly available statistics, this summary itself is considered a contribution to understanding the nature of quantity discounts offered by pharmaceutical manufacturers. The main features of a typical discount, based on the sample can be listed as follows:

- The discount offer consists of the number of units that the pharmacist has to pay for ("main"), and the number of free units that the buyer gets with paid main quantity.
- The effective discount increases with the number of units purchased.
  Effective Discount (%) = free /(main + free) .
- The term is the due date for all payments by the pharmacist to the supplier.
- Length of Promotion is the time period that drug is available on that discount
- Frequency of promotion

The discounts offered for a certain drug may depend on various factors such as the amount of inventory that the manufacturer has at hand, the region, seasonality and trend in drug prices. Assuming that wholesalers act as intermediaries between the manufacturers and pharmacies, the discount offers of a particular firm should be more or less the same in the same region at the same time. Otherwise it is possible that factors such as the amount of inventory that the wholesaler has at hand affect the discount offers.

The ATC groups; *R05-Cough and Cold Preperations* and *P01-Antiprotozoals* are selected for our analysis. Since 2006, some of the drugs that belong to *R05-Cough and Cold Preperations* have been removed from the reimbursement list. For this survey, we selected an additional ATC group (*P01*) that is not affected from this change. The wholesaler discount offers data is collected for July 2007-March 2008 time interval from pharmacies in different regions. The offers belong to two wholesalers from İstanbul, four wholesalers from Kocaeli and one from Muğla.

In this survey, the aim is to understand the general characteristics of quantity discounts in the pharmaceutical market. More specifically, we want to find answers to the following questions:

1. What is the range of effective discount offers?
2. How do the discounts for original and generic drugs differ?

3. What is the frequency of discount offers for a particular drug?
4. Is it possible that the same manufacturer gives different discounts to pharmacies in the same region at a particular time?

The statistics have been calculated for *those drugs that were discounted, at least once, over the time-interval*. The following four graphs show the frequency of discounts and payment terms (days) offered in a particular month for both of the *R05* and *P01* ATC groups:

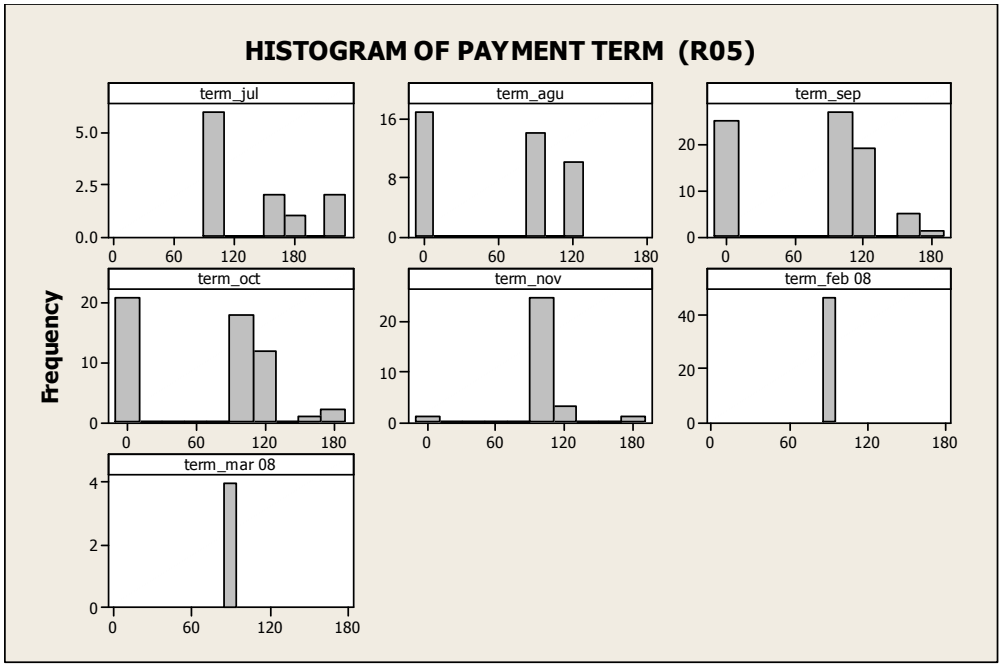


Figure 2.1 Histogram of term for R05 Cough & Cold Preperations

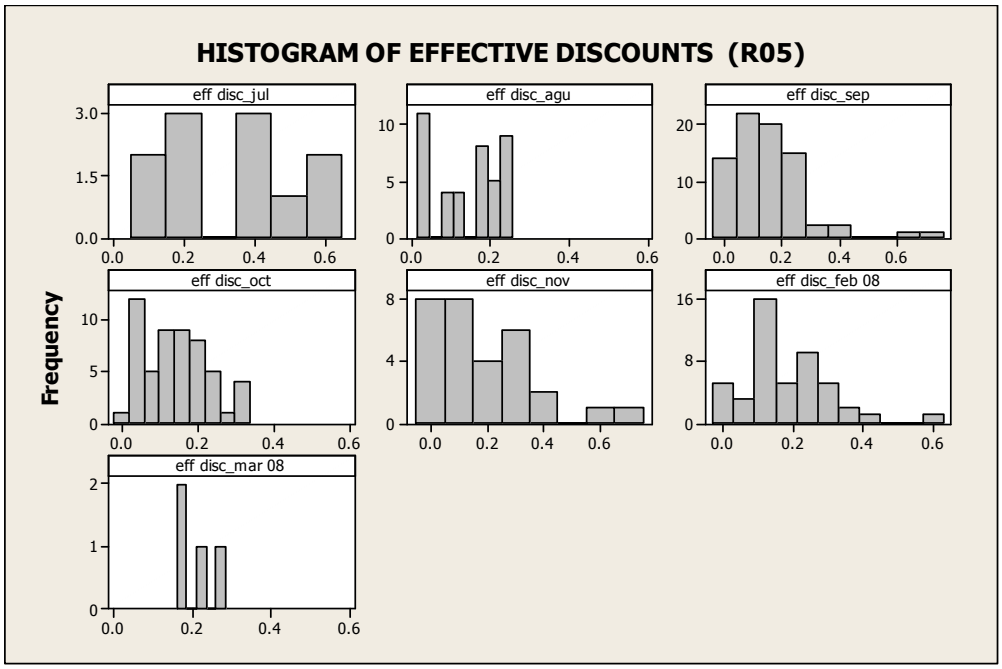


Figure 2.2 Histogram of effective discount for R05 Cough & Cold Preperations

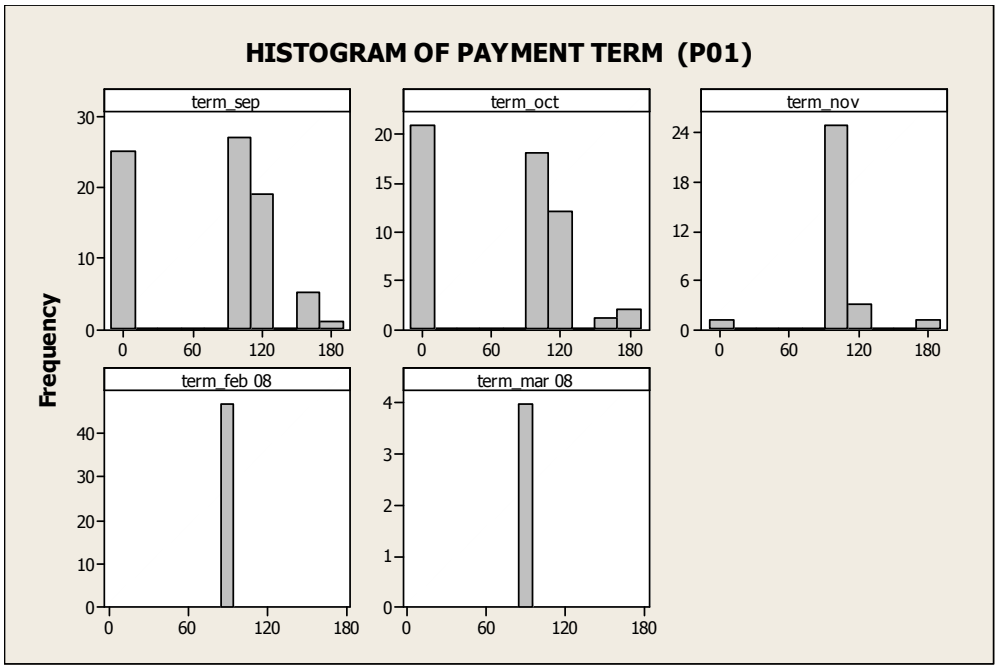


Figure 2.3 Histogram of term for P01 Antiprotozoals

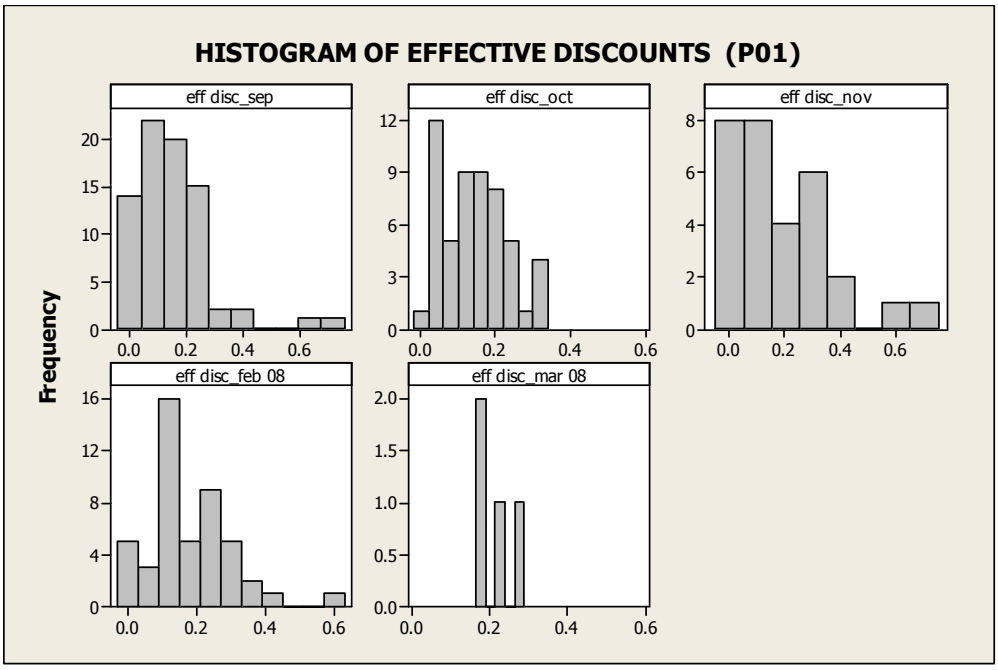


Figure 2.4 Histogram of effective discount for P01 Antiprotozoals

The payment term for the discount offers varies between 0 and 210 days, whereas the effective discount offer varies between 2% and 73%. *Table 2.1* shows the effective discount range for the *R05* and *P01* ATC groups on different wholesalers.

EFFECTIVE DISCOUNT					
region	wholesaler	R05		P01	
		min	max	min	max
Kocaeli	wholesaler 1	2%	73%	2%	51%
	wholesaler 2	5%	70%	22%	50%
	wholesaler 3	2%	13%	N/A	N/A
	wholesaler 4	23%	67%	N/A	N/A
İstanbul	wholesaler 5	2%	70%	9%	38%
	wholesaler 6	2%	39%	11%	51%
Muğla	wholesaler 7	9%	23%	9%	9%

Table 2.1 Effective discount across ATC groups and wholesalers

We also figured out the frequency of offers for a particular drug. *Table 2.3* shows the discount frequency for the drugs that are discounted, at least once, over the whole time-interval. Here, discount frequency represents "number of discounts for the drug/number of discounts" over the corresponding time-interval.

ATC	frequency	drug	discount frequency
R05	max	SEKROL	64%
	median	A FERIN	14%
	min	VICKS VAPOSYRUP	7%
P01	max	ORNİSİD FİLM TABLET	64%
	median	ORNİTOP FİLM TABLET	43%
	min	BİTERAL FİLM KAPLI TABLET	21%

Table 2.2 The discount frequency

A final important observation is that; concurrent discount offers for a particular drug only marginally differ across wholesalers in the same region (9 out of 10 offers of this type showed this pattern). The observation indicates that wholesalers are only acting as intermediaries between pharmaceutical manufacturers and pharmacies.

Chapter 3

3. OTC STUDY

In Turkey, OTC financing places a significant burden on public budget, since almost all OTCs can be reimbursed by governmental social security organizations [13]. As mentioned before, there is an ongoing debate concerning the introduction of an explicit OTC category.

General Directorate of Pharmacy and Pharmaceuticals is currently working on the list of non-prescription drugs. The objective is to make the distinction between prescription and non-prescription drugs as well as preventing the supply of prescription-only medicines without a prescription. It seems that the drugs that are classified as non-prescription (or OTC) will still be reimbursed by the government. The rationale behind this strategy rests on patient's sensitivity to out-of-pocket spending. If the cost to a patient for an OTC medication exceeds the cost for an alternative prescription drug, then more expensive reimbursed alternatives may be prescribed instead of OTC drugs. This tendency may lead to an increase in public expenditures [26].

In Turkey, recent regulations on drug reimbursement list gave us the opportunity to analyze the effects of the OTC availability of some drug categories on pharmaceutical expenditures. Starting from July 2006, more than a hundred OTC type drugs have been removed from the positive list. In this section, we will first present the literature on Rx-to-OTC switches and then discuss the effects of the recent reimbursement list changes on pharmaceutical expenditures in Turkey.

3.1. Literature

The literature on Rx-to-OTC switch focused on the effects of OTC availability on physician prescribing patterns, frequency of physician visits, cost to third party payers or cost to the patients. A vast majority of studies argue that Rx-to-OTC switches reduce cost to third party payers and provide saving in general practitioners' time due to a decline in overall dispensing, as discussed below.

Brass [20] studied the effects of switches from prescription-only to over-the-counter availability on health care. According to the study, the main potential benefits are increased access to effective drugs (access without a prescription or physician visit), lower health care costs and increased autonomy of patients. On the other hand, there is the risk of inaccurate diagnosis by patients, use of suboptimal therapy, increased costs to patients and perceived loss of control by physicians.

Ryan and Yule [28] estimated the economic benefits of over-the-counter availability of loperamide and hydrocortisone. The study suggests that, making these products available from the pharmacy without a prescription reduced cost to consumers and provided savings in general practitioners' time. Gurwitz et al. [29] examined the impact of the prescription-to-OTC switch of vaginal antifungal products on prescribing patterns and utilization of physician services. Their findings suggest that, over-the-counter availability of vaginal antifungal treatments reduced health care costs to the insurer in the managed care setting. The descriptive study of Carlsten et al. [30] showed that total sales increased for 14 out of 16 drugs that were changed from prescription-only status to the Swedish OTC market. Moreover, the prescription of OTC packs decreased on average by 26% during the first 2 years after the switch which led to an estimated saving $30 million for the national budget.

Andrade et al. [31] found statistically significant reductions in the prescriptions for H_2-receptor antagonists dispensed to patients, chronic users of these agents, following OTC

availability. Whereas the dispensings for other gastrointestinal agents apparently increased to a small degree, the substitution of those alternative therapies did not account for the observed reduction in dispensings of H_2-receptor antagonists. Although their results suggest that costs of prescription H_2-receptor antagonists were reduced for the health maintenance organization (HMO) after OTC availability, the overall use and costs of OTC H_2-receptor antagonists were not determined and therefore the change in overall health care cost is not explained in this study.

Lundberg and Isacson [32] studied the effects of switching nasal spreys from prescription to over-the-counter status in Sweden. The study showed that there had been a significant decrease in prescribing of nasal decongestants and number of physician visits for rhinitis and sinusitis as well as the public expenditures estimated for these, after the switch from prescription to over-the counter status of these drugs in 1989.

Harrington and Shephard [33] report that Flowers et al. [34] study involving 1.5 million Health Maintenance Organization members in 3 drug plans for the period 1999-2000, found that spending increased on prescription antifungals following the switch from prescription to OTC status of Lamisal cream and Nizoral shampoo in spring 1999. While coverage of these OTC products was excluded, there was an increase in the cost of antifungal agents to the HMO.

Using simulation, Sullivan et al. [35] assessed the cost-effectiveness of transitioning second-generation antihistamines (SGA) to over-the-counter status from a societal perspective. Their results suggest that even if patients completely replaced prescription SGA with substitute drugs as expensive as the most expensive alternative, making SGA available OTC would be cost saving for society.

As Brass [20] proposed; the effects of switching a drug from prescription-only to over-the-counter status on the distribution of health care costs are uncertain. Moreover, it is possible that a switch may increase the cost to patients while decreasing the cost to third-

party payers ((Andrade et al., 1999), (Harrington and Shepherd, 2002)). On the other hand, Gurwitz et al. [29] draw attention to the risk of increased costs to the insurer or health plan. If the cost to a patient for an OTC medication exceeds the cost for an alternative prescription drug available through a prescription benefit plan, patients may prefer to request the prescription drug from their physician.

In this study, we analyze the effects of Rx-to-OTC switches in Turkey on pharmaceutical consumption of both these drugs and their equivalent alternatives that are still reimbursed by the government. Therefore, our results provide insights into the right strategy for the government considering that out-of-pocket expenses can affect patients purchasing decision.

3.2. Data Analysis Study

3.2.1. Drug Groups that are affected from the changes

119 drugs have been removed from the government's reimbursement list in July 2006. In September, this list was extended to include 141 drugs including the chemotherapy drug Neupogen (Appendix A). The removed drugs mainly belong to the ATC (Anatomical Therapeutic Chemical) groups of *R05 Cough and Cold Preperations, A11 Vitamins, A12 Mineral Supplements and R02 Pharyngeal Preperations*.

It is expected that there will be a fall in the demand for the removed drugs after the change. On the other hand, we need to keep track of the possible demand shift from the switched drugs to the reimbursed alternatives. In each of the ATC groups, the following categories of drugs will be affected from the policy:

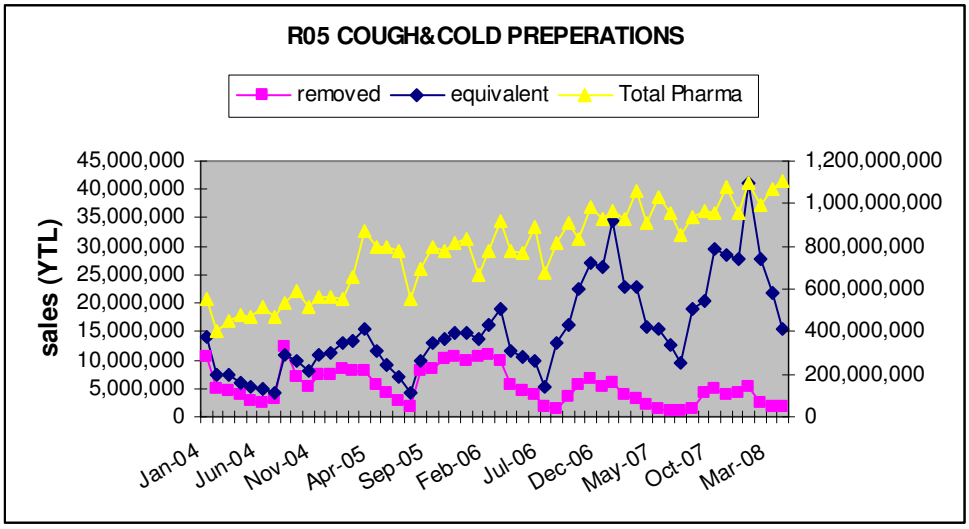
a. Group 1 (Removed drugs): The drugs that are excluded from government reimbursement

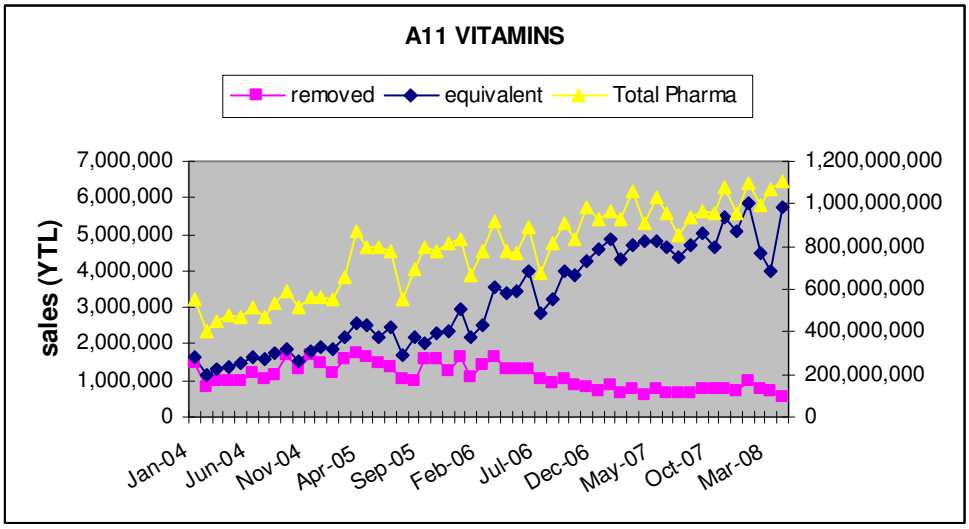
b. Group 2 (Equivalent Drugs): The drugs that can be prescribed by the physician as the reimbursed alternatives for the removed ones, although they are not always the pharmaceutical equivalents.

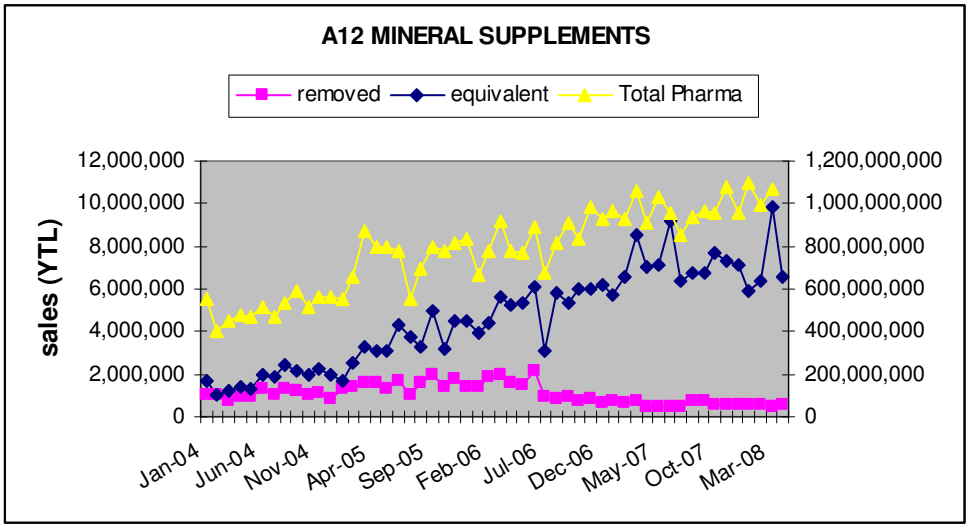
In our empirical study, RxMediaPharma 2007 interactive source provided us the data of reimbursement status and bioequivalent list of a particular drug [36]. Group 2 (Appendix B) is determined in accordance with the views of Professor Dr. Mehmet Melli, the president of Turkish Pharmacological Society, Assistant Professor Hakan Ergün, Dr. Pınar Kutluana, Dr. Hakan Kamışoğlu and Dr. Erdal Mehmet Aksoy. For each of the drugs in Group 1 the doctors suggested two-three drugs that they can prescribe as a reimbursed alternative, especially when there is a request from the patient.

We analyzed the effects of the OTC switch on pharmaceutical consumption of both removed drugs and their equivalent alternatives that are still reimbursed by the government using the wholesale drug sales data from IMS Health for the period January 2004-April 2008. Any removed drug has equivalent alternatives within the same ATC group. Therefore, for each ATC, there exist one removed and one equivalent group.

Throughout this data analysis we make use of the statistical software Minitab 15 and MS Excel. The sales trend for the related drug groups before and after the changes can be traced from the time-series in *Figure 3.1*.


R05 COUGH&COLD PREPERATIONS
removed
equivalent
Total Pharma
sales (YTL)
45,000,000
40,000,000
35,000,000
30,000,000
25,000,000
20,000,000
15,000,000
10,000,000
5,000,000
0
1,200,000,000
1,000,000,000
800,000,000
600,000,000
400,000,000
200,000,000
0
Jan-04
Jun-04
Nov-04
Apr-05
Sep-05
Feb-06
Jul-06
Dec-06
May-07
Oct-07
Mar-08


A11 VITAMINS
removed
equivalent
Total Pharma
sales (YTL)
7,000,000
6,000,000
5,000,000
4,000,000
3,000,000
2,000,000
1,000,000
0
1,200,000,000
1,000,000,000
800,000,000
600,000,000
400,000,000
200,000,000
0
Jan-04
Jun-04
Nov-04
Apr-05
Sep-05
Feb-06
Jul-06
Dec-06
May-07
Oct-07
Mar-08



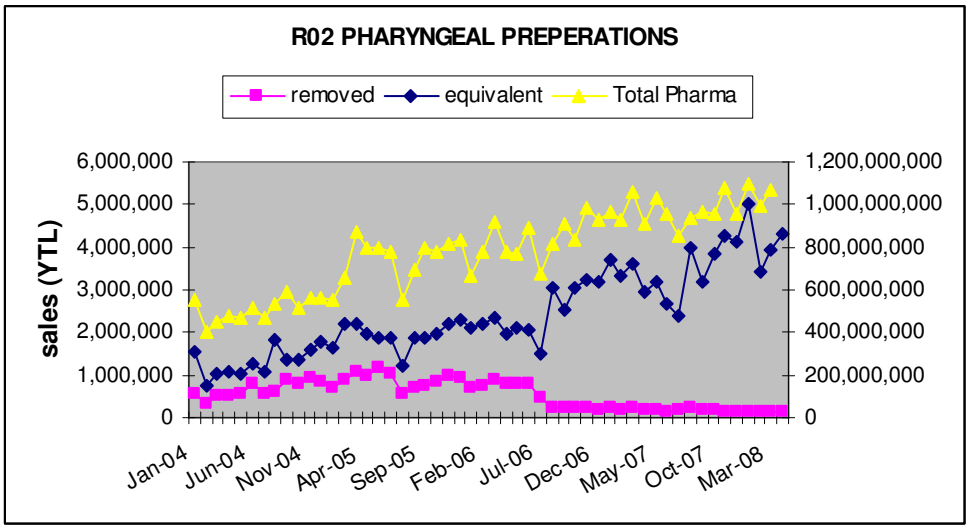
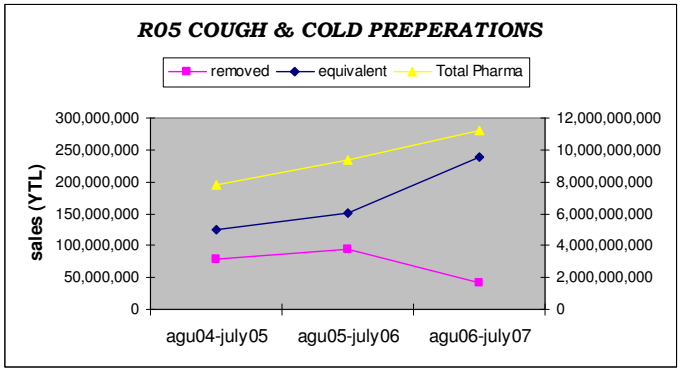
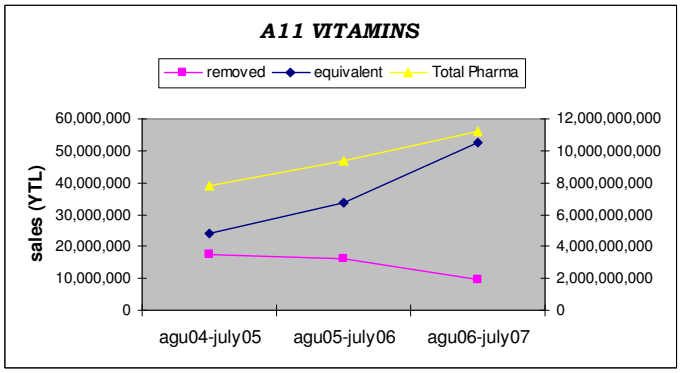
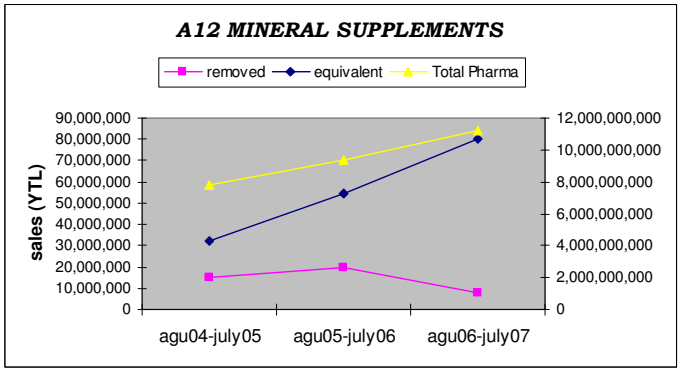


Figure 3.1 *Time-series for different ATC group sales (YTL)*

After the change, as expected, the removed drug sales have downward trend whereas the equivalent drug sales has an increasing trend. The same effect can be seen from the time-series of yearly expenditures before (2 years) and after (1 year) the change:


R05 COUGH & COLD PREPERATIONS
removed
equivalent
Total Pharma
sales (YTL)
300,000,000
250,000,000
200,000,000
150,000,000
100,000,000
50,000,000
0
12,000,000,000
10,000,000,000
8,000,000,000
6,000,000,000
4,000,000,000
2,000,000,000
0
agu04-july05
agu05-july06
agu06-july07


A11 VITAMINS
removed
equivalent
Total Pharma
sales (YTL)
60,000,000
50,000,000
40,000,000
30,000,000
20,000,000
10,000,000
0
12,000,000,000
10,000,000,000
8,000,000,000
6,000,000,000
4,000,000,000
2,000,000,000
0
agu04-july05
agu05-july06
agu06-july07


A12 MINERAL SUPPLEMENTS
removed
equivalent
Total Pharma
sales (YTL)
90,000,000
80,000,000
70,000,000
60,000,000
50,000,000
40,000,000
30,000,000
20,000,000
10,000,000
0
12,000,000,000
10,000,000,000
8,000,000,000
6,000,000,000
4,000,000,000
2,000,000,000
0
agu04-july05
agu05-july06
agu06-july07

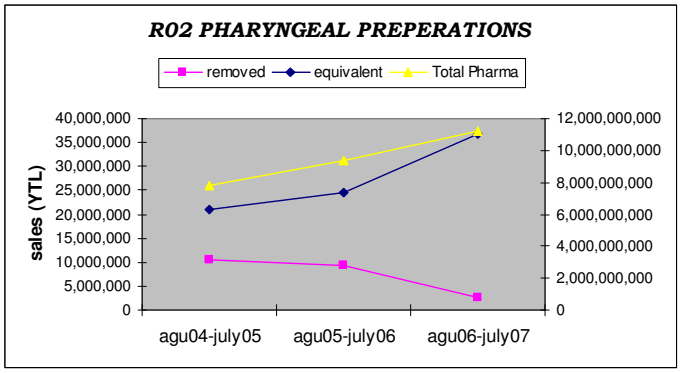


Figure 3.2 Yearly sales before and after the change

Taking inflation rate and population growth into account:

	BEFORE (YTL)	BEFORE (UNITS)	$ratio_1$	AFTER (YTL)	AFTER (UNITS)	$ratio_2$	$ratio_1 / ratio_2$
R05 REMOVED	205,221,968	75,259,417	2.73	71,194,216	22,744,439	3.13	**1.15**
R05 EQUIVALENT	326,718,721	114,731,202	2.85	470,075,389	156,258,615	3.01	**1.06**
A11 REMOVED	41,216,110	16,034,934	2.57	16,121,113	5,543,849	2.91	**1.13**
A11 EQUIVALENT	68,245,831	26,306,413	2.59	97,540,560	28,315,090	3.44	**1.33**
A12 REMOVED	42,230,127	15,998,015	2.64	13,420,198	3,922,819	3.42	**1.30**
A12 EQUIVALENT	96,928,750	18,646,666	5.20	144,368,554	15,411,203	9.37	**1.80**
R02 REMOVED	23,718,296	2,804,710	8.46	3,965,894	363,349	10.91	**1.29**
R02 EQUIVALENT	53,048,961	18,123,385	2.93	72,919,728	21,352,383	3.42	**1.17**
Total Pharma	20,541,790,411	2,811,864,180	7.31	20,334,577,885	2,466,245,160	8.25	**1.13**

If we define "price" as YTL/UNITS ratio; we can see that increase in price for removed and equivalent drug groups are similar except for A12 equivalent group.

Moreover, we have Total Pharma market as the control group and this group shows the same pattern with the ATC groups in the analysis.

3.2.2. Control Group

In order to precisely measure the impact of changes we first have to understand if there is an outside factor, other than the reimbursement policy, affecting drug sales. "Total

Turkish Pharma Market" has been selected as the control group. If the trend in control group sales for the whole time period (β_2) is not significantly different (between $\pm 2\sigma$), than its trend before the changes (β_1), we can conclude that there is not an irregular component (outside effect) on drug sales. *Figure 3.3* shows the time-series regression analysis results for the control group sales before the changes (Jan2004-Jul2006) and for the whole time period (Jan2004-Apr2008).

Regression Analysis: Total Tr Pharma Market (before) versus time
The regression equation is
Total Tr Pharma Market (before) = **4.48E+08 + 13386455 time**

Predictor	Coef	SE Coef	T	P
Constant	448455113	33241225	13.49	0.000
time	13386455	1813457	7.38	0.000

S = 90309454 R-Sq = 65.3% R-Sq(adj) = 64.1%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	4.44409E+17	4.44409E+17	54.49	0.000
Residual Error	29	2.36518E+17	8.15580E+15		
Total	30	6.80927E+17			

Regression Analysis: Total Tr Pharma Market versus time
The regression equation is
Total Tr Pharma Market = **4.70E+08 + 11911220 time**

Predictor	Coef	SE Coef	T	P
Constant	470436684	22814210	20.62	0.000
time	11911220	749115	15.90	0.000

S = 81074178 R-Sq = 83.5% R-Sq(adj) = 83.2%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	1.66181E+18	1.66181E+18	252.82	0.000
Residual Error	50	3.28651E+17	6.57302E+15		
Total	51	1.99046E+18			

Figure 3.3 Time-series regression results for total pharma market sales

Total Tr Pharma Market			
period	−σ	slope	+σ
before	11,572,998	13,386,455	15,199,913
whole	11,162,105	11,911,220	12,660,335

Table 3.1 Total pharma market sales trend

As it can be seen from *Table 3.1*, general slope β_2 is between (β_1- σ, β_1 +σ). This implies that the control group "Total Turkey Pharma Market" sales do not show a significant difference after the changes. Therefore, there is not an outside factor, other than the policy changes, affecting drug sales.

Since there is not an outside factor that has significant effect on sales, we can assume that the removed and equivalent drug groups would have their regular trend if no change had taken place.

In order to figure out the effect of changes on pharmaceutical expenditures, we tried the following methods in finding the expected sales after the change:

- Regression Analysis
- Year-over-year Growth
- Decomposition Method
- Winter's Method

The decomposition method and the Winter's method take the seasonality into account [37]. Considering the ATC series, *R05* and *R02* clearly have seasonality. The year on year growth method averages away the seasonality by using whole years.

In order to analyze the sales trend before the change, we performed time-series regression for January 2004 - July 2006 period. However, when there is seasonality, linear regression is not able to capture the relationship.

MSE (mean squared error) is a common accuracy measure for Regression analysis, Decomposition method and Winter's method. Among these methods regression performs worst as can be seen from the MSE (for January 2004 - July 2006 period) comparison in *Table 3.2*. The reason for that is the seasonality effect in drug sales especially for R05 and R02 groups.

METHOD	MSE							
	R05		A11		A12		R02	
	removed	equivalent	removed	equivalent	removed	equivalent	removed	equivalent
REGRESSION	9.71E+12	1.30E+13	6.54E+10	1.31E+11	7.37E+10	4.40E+11	3.49E+10	9.46E+10
DECOMPOSITION	1.97E+12	3.39E+12	4.99E+10	9.11E+10	3.76E+10	3.35E+11	2.79E+10	6.91E+10
WINTER'S	2.36E+12	3.48E+12	4.84E+10	8.87E+10	3.40E+10	3.71E+11	1.71E+10	6.05E+10

Table 3.2 Performance of methods that are used for the analysis

3.2.3. The Regression Method

In this method, first the trend before the changes is estimated by time-series regression for the Jan2004- July2006 period. Then, this trend is reflected to find the expected sales after the changes. The difference between the actual and the expected values gives the effect on sales in terms of YTL.

REGRESSION (YTL)				
ATC		agu06-july07 (expected)	agu06-july07 (actual)	effect
R05	removed	90,863,042	41,058,807	**-49,804,235**
	equivalent	169,517,760	238,943,994	**69,426,234**
A11	removed	17,586,437	9,423,413	**-8,163,024**
	equivalent	43,705,540	52,528,239	**8,822,699**
A12	removed	23,428,036	8,031,614	**-15,396,422**
	equivalent	74,227,258	79,879,823	**5,652,565**
R02	removed	11,075,703	2,530,284	**-8,545,419**
	equivalent	29,736,497	36,829,006	**7,092,509**

Table 3.3 The expected sales and the effect of the policy changes for the full year after enactment based on Regression Method

As mentioned before, regression results may be misleading due to seasonality effects.

3.2.4. Year-over-Year Growth Method

An alternative method is to use the previous period's growth rate in finding the expected sales for each whole year after the change.

period	Total Pharma Market	growth
agu04-jul05	7,787,999,261	_
agu05-jul06	9,411,684,506	1.21
agu06-jul07	11,176,768,304	1.19

Table 3.4 Control group growth

Table 3.4 shows that control group growth rate does not change much over time. Therefore, we can use "the previous period's growth rate" as an indicator of "the current periods expected growth". The effect of changes according to this method can be traced from the following table:

YEAR-OVER-YEAR (YTL)							
ATC		agu 04-july 05	agu 05-july 06	slope	agu 06-july 07 (expected)	agu 06-july 07 (actual)	effect
R05	removed	78,377,750	94,350,102	1.2	113,577,409	41,058,807	**-72,518,602**
	equivalent	125,009,480	152,136,170	1.2	185,149,272	238,943,994	**53,794,722**
A11	removed	17,454,109	16,174,973	0.9	14,989,579	9,423,413	**-5,566,166**
	equivalent	24,272,399	33,767,654	1.4	46,977,411	52,528,239	**5,550,828**
A12	removed	15,431,795	19,753,198	1.3	25,284,734	8,031,614	**-17,253,120**
	equivalent	32,376,267	54,207,737	1.7	90,760,270	79,879,823	**-10,880,447**
R02	removed	10,430,443	9,410,691	0.9	8,490,637	2,530,284	**-5,960,353**
	equivalent	20,912,805	24,431,018	1.2	28,541,109	36,829,006	**8,287,897**

Table 3.5 The expected sales and the effect of the policy changes for the full year after enactment based on Year-over-year growth method

From *Table 3.5*, we see that *A12* equivalent group sales has been less than expected after the changes (diff= *-10,880,447*). This is due to the huge growth in *A12* equivalent group sales before the changes (which can be explained by the huge increase in Calcimax D3 sales, especially between July 2004 and July 2006). The following figure shows the mentioned situation.

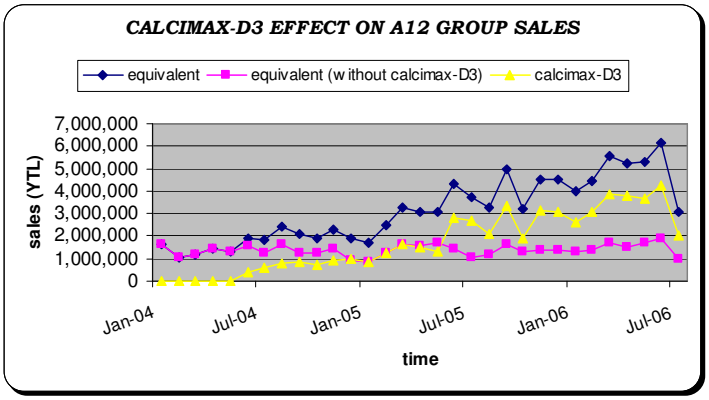


Figure 3.4 Time-series of A12 group sales before changes

3.2.5. Winter's Method

A seasonal pattern appears to exist in most ATC groups. Therefore, Winter's method might represent the data better and reduce forecast error. *Table 3.6* gives the effect of changes based on Winter's method. The Minitab outputs for the analysis are given in Appendix C.

WINTER'S METHOD (YTL)				
ATC		agu06-july07 (expected)	agu06-july07 (actual)	effect
R05	removed	101,593,495	41,058,807	**-60,534,688**
	equivalent	181,171,296	238,943,994	**57,772,698**
A11	removed	15,420,176	9,423,413	**-5,996,763**
	equivalent	47,646,674	52,528,239	**4,881,565**
A12	removed	20,443,861	8,031,614	**-12,412,247**
	equivalent	66,838,821	79,879,823	**13,041,002**
R02	removed	6,988,402	2,530,284	**-4,458,118**
	equivalent	26,867,983	36,829,006	**9,961,023**

Table 3.6 The expected sales and the effect of the policy changes for the full year after enactment based on Winter's method

3.2.6. Decomposition Method

In this method, first the data is deseasonalized by applying moving averages, and seasonal factors are determined. Forecasts for each group sales after the changes give the expected sales. The effects can be seen from *Table 3.7* and related Minitab results are given in Appendix D.

DECOMPOSITION METHOD (YTL)				
ATC		agu06-july07 (expected)	agu06-july07 (actual)	effect
R05	removed	103,031,369	41,058,807	**-61,972,562**
	equivalent	183,819,390	238,943,994	**55,124,604**
A11	removed	17,452,810	9,423,413	**-8,029,397**
	equivalent	43,004,536	52,528,239	**9,523,703**
A12	removed	23,489,229	8,031,614	**-15,457,615**
	equivalent	73,446,702	79,879,823	**6,433,121**
R02	removed	10,837,198	2,530,284	**-8,306,914**
	equivalent	30,337,480	36,829,006	**6,491,526**

Table 3.7 The expected sales and the effect of the policy changes for the full year after enactment based on the Decomposition method

3.3. The Results

In this before-after analysis, we determined the effects of the recent reimbursement policy changes on the related drug group sales and total pharmaceutical expenditures. Decomposition analysis and Winter's method best suit the objectives of this study. We also used previous year's growth as an indicator of the expected growth for a particular time-period. The table below summarizes the effects on drug group sales:

METHOD		IMPACT ON PHARMACEUTICAL EXPENDITURES (agu06-july07)							
		regression		year-over-year		decomposition		winter's	
		change	percent	change	percent	change	percent	change	percent
R05	Δ removed	-49,804,235	-55%	-72,518,602	-64%	-61,972,562	-60%	-60,534,688	-60%
	Δ equivalent	69,426,234	41%	53,794,722	29%	55,124,604	30%	57,772,698	32%
	Δ total	19,621,998	-	-18,723,880	-	-6,847,959	-	-2,761,989	-
A11	Δ removed	-8,163,024	-46%	-5,566,166	-37%	-8,029,397	-46%	-5,996,763	-39%
	Δ equivalent	8,822,699	20%	5,550,828	12%	9,523,703	22%	4,881,565	10%
	Δ total	659,675	-	-15,338	-	1,494,306	-	-1,115,198	-
A12	Δ removed	-15,396,422	-66%	-17,253,120	-68%	-15,457,615	-66%	-12,412,247	-61%
	Δ equivalent	5,652,565	8%	-10,880,447	-12%	6,433,121	9%	13,041,002	20%
	Δ total	-9,743,858	-	-28,133,567	-	-9,024,494	-	628,754	-
R02	Δ removed	-8,545,419	-77%	-5,960,353	-70%	-8,306,914	-77%	-4,458,118	-64%
	Δ equivalent	7,092,509	24%	8,287,897	29%	6,491,526	21%	9,961,023	37%
	Δ total	-1,452,911	-	2,327,544	-	-1,815,387	-	5,502,905	-

Table 3.8 Impact of change on pharmaceutical sales

As expected, all of the methods point out a significant decrease in removed drug sales after the changes. The sales do not decrease to zero due to non-reimbursed purchases.

3.4. Potential Improvements

After the changes, since the removed drugs are no longer reimbursed, the patients who were demanding those drugs may either switch to the reimbursed alternatives (a_1), continue to purchase them and pay out-of-pocket (a_2) or give up taking these drugs (a_3) where $a'=a1+a2+a3$ and $a_1, a_2, a_3 \geq 0$.

GROUP	PRICE	before		expected		after	
		reimbursed	*cash*	*reimbursed*	*cash*	*reimbursed*	*cash*
removed	P_R	a	b	a'	b'	0	$b' + a_2$
equivalent	P_E	*reimbursed*	*cash*	*reimbursed*	*cash*	*reimbursed*	*cash*
		c	d	c'	d'	$c' + a_1$	d'

Table 3.9 Impact of change

The effects of the reimbursement policy changes on the related drug groups are summarized in *Table 3.9*. Our analysis on wholesale data gives insights on the effects of changes on total pharmaceutical expenditures in Turkey. On the other hand, the following calculation suggests that we also have an insight on public expenditures (with a certain error).

Impact of changes on total expenditures (our conclusion in this study) =

$$P_R\ (b'+a_2-a'-b')+P_E\ (c'+a_1+d'-c'-d') = (P_E-P_R)\ a_1-P_R\ a_3$$

Impact of changes on public expenditures =

$$P_E\ (c'+a_1-c')-P_R\ a' = (P_E-P_R)\ a_1-P_R\ (a_2+a_3)$$

Therefore, working with the data including the cash and reimbursed sales, we are underestimating the reduction in government expenses by $P_R\ a_2$, i.e., those who continue to purchase them and pay out-of-pocket.

In order to precisely measure the impact of changes on public expenditures, it is necessary to analyze the prescription data of the Social Security Institution.

3.5. Interpretation

In the case of an OTC switch, there is the risk of increased cost to third party payers. If the cost to a patient for an OTC medication exceeds the cost for an alternative prescription drug available through a prescription benefit plan, patients may prefer to request the prescription drug from their physician [29]. Likewise, our hypothesis was that the demand for the removed drugs would switch to reimbursed equivalent alternatives in the pharmaceutical market. The results of the data analysis study suggest that there is a significant increase in the equivalent group sales for all ATC groups, except the *A12* equivalent group for the year-over-year method, after the changes. This finding is in line

with the suggestion that patients and physicians may switch to the reimbursed alternative drugs, which may lead to an increase in governments pharmaceutical spending.

Our findings also suggest that, in absolute terms, the increase in the equivalent drugs sales go beyond the decrease in removed drug sales for some of the ATC groups. Therefore, it is possible that the removal of these drugs from reimbursement may not produce the expected decrease in spending, and could even lead to an increase in total pharmaceutical expenditures.

Chapter 4

4. THE PHARMACIST'S SUBSTITUTION STRATEGY IN THE PRESENCE OF QUANTITY DISCOUNTS

4.1. Literature

The literature related to our research can be grouped into two categories; quantity discounts and substitution problem.

4.1.1. Quantity discounts

On their exploratory study on thirty-nine companies concerning the real-world implementation of quantity discounts, Munson and Rosenblatt [38] found that nearly all of the firms either offer or receive some type of all-units quantity discounts. Another finding was that nearly one third of these firms offered or received incremental quantity discounts. The popularity of quantity discounts in practice stems from the fact that suppliers' discount offers can influence buying firms' purchasing behavior by providing economic incentives and encouraging larger orders [11].

The uniform price schedule is formed when there is a linear relationship between the amount ordered, q, and the charge for an amount q, R(q). In this type of a schedule, the average price paid is independent of the amount ordered. Any price schedule not satisfying the linearity condition can be an example of nonlinear schedule [39]. Quantity discount may be offered in the form of many different nonlinear price schedules.

In general, quantity discounts have four characteristics [38]:

a) The form may be either *incremental* where the units in each price break interval receive that interval's discount or *all-units* where the price schedule contains specified break points $q_0, q_1, \ldots, q_r$, where $q_0 = 0$ and all items of an order which falls in the interval q_i to $q_{i+1} - 1$ has a discount price of P_i.

b) The item aggregation describes whether the discount applies to one or multiple products. A "business volume discount" represents item aggregation where the price breakpoints are based on the total dollar volume of business across all products purchased from the vendor.

c) The time aggregation describes whether the discounts apply to individual purchases or multiple purchases over a given time frame.

d) The number of price breakpoints may be one, multiple, or infinite. Taking the charge for an amount q, R(q), discrete or continuous represents a trade-off between implementation concerns and power of analytical results obtainable. Modeling infinite price breakpoints by specifying R(q) as a continuous function can provide insights on the role of different pricing schedules, although these schedules are not always implementable [39].

The vast majority of the operations literature on inventory management has used the criterion of minimization of costs. The assumption behind this objective function is that inventory decisions do not significantly affect the revenue stream [40]. As well as minimizing the operational costs, most of the supplier firms try to push their products through the pipeline by offering some kind of an incentive to buyers. For instance, manufacturers offer special incentive programs to their distribution channel members either in the form of discounts or free case offers. Research from the marketing perspective mostly focuses on this kind of trade promotion activities.

In literature, many useful applications have been suggested for quantity discounts. The main uses are achieving economies of scale for transportation and operating costs, price

discrimination and channel coordination. Suppliers also make use of discounts in pushing their products through the pipeline. On the other hand, buyers expect a price break for purchasing larger amounts of the seller's product. It is shown that, quantity discounts can provide optimal means for achieving coordination between supply chain members [41].

Buyer's lot sizing problems and supplier's optimal strategy in the presence of quantity discounts have been studied separately in literature. Recently, researchers have also focused on joint profit maximization using quantity discounts as a tool to achieve channel coordination. The literature on lot sizing model with different variations of the quantity discount schemes is classified in Benton and Park [10] with the following categories: (i) buyer's perspective models, (ii) seller's perspective models, and (iii) channel coordination models.

The use of supplier-oriented quantity discount policies to influence a buyer's purchasing behavior has received considerable attention. The supplier planning to offer quantity discounts decides on the type of the discount to offer and the parameters for the chosen type of quantity discount. Most authors consider one of the most common discount policies; all-units or incremental discount schedules. Lal and Staelin [42] take a slightly different approach and develop a unified pricing policy which motivates the buyer to increase its ordering quantity and reduce the joint ordering and holding costs in this way. Shin and Benton [11] modeled the use of all-units discounts to coordinate inventory decisions between a single buyer and a single supplier as well as relaxing the conventional assumptions of deterministic demand and constant use of single price break.

In the marketing literature, supplier-oriented discount policies are in the context of manufacturer trade promotions. In response to trade promotions, retailers either forward buy or pass through a proportion of this discount to consumers. These promotions increase manufacturer's long-run sales only if they are able to generate consumer sales. Otherwise, merely short-run pipeline inventories will increase due to the forward buying behavior of

the retailer. In order to understand and measure the effects of trade promotions, Blattberg and Evin [43] presented a model including the consumer and the retailer and applied it to a manufacturer's shipment data. Their analysis on the profitability of the manufacturer's past promotion activities suggested that most of the manufacturer's trade promotions were not profitable and the firm would have been better off with more stringent contractual requirements (concerning issues like consumer pass through), increase consumer promotional spending or change its current promotion strategy. Neslin et al. [6] showed that as well as consumer response to promotions, retailer inventory carrying cost and promotion wearout is critical in manufacturer's optimal trade promotion strategies. Lal et al. [44] studied the dynamic effects of forward buying by the retailer through a game theoretic model that includes the manufacturers, the retailer and the consumers. The main conclusion of the study was that forward buying behavior of the retailer yields higher profits to the manufacturers due to a decrease in the intensity of competition.

Pass-through represents the portion of the promotion value provided by a manufacturer to its retailers that ultimately reaches the consumer. Kumar et al. [45] examined the pass-through decision of a retailer responding to a trade deal and showed that the optimal strategy of the retailer is to pass through trade deals on certain occasions and post ‘‘regular’’ prices on other occasions.

In Turkey, strict governmental regulations on pharmaceutical promotion activities and pharmacy profit margins do not allow for pass-through and any discount offered by the manufactures to the pharmacies becomes a hidden source of income for the pharmacist. Therefore, we do not focus on the pass-through behavior as in trade promotions literature [45].

The order size and delivery time of materials play a major role in any inventory system. The general assumption is that buyer uses the economic order quantity (EOQ) model to determine his optimal order size. In the classical EOQ model, as the quantity purchased

increases, the unit cost remains constant, the cost of procurement decreases and the holding cost increases. The EOQ is the quantity at the minimum cost on the total cost curve [46].

In the presence of quantity discounts, the buyer's managerial interest is to come up with the optimum purchasing decision considering the trade-off between the costs and benefits of larger orders [10]. Sadrian and Yoon [47] describe a procurement decision support system which is used to improve the purchasing activities in the presence of business volume discounts. The system provides the flexibility for uncertainties in the demand and procurement budget by combining different types of purchasing strategies. Using the system they were able to achieve significant cost saving.

One of the main issues of supply chain management is to coordinate the channel members' decisions in order to achieve overall maximal profit. Quantity discounts represent a mechanism for profit sharing between the supplier and the buyer. If the two parties coordinate with each other, it is possible to identify a pricing strategy that improves both parties' performance [48]. The supplier is usually the active party who offers the discount schedule to the buyer in order to entice the buyer to place a larger order quantity. When the buyer purchases more than the economic order quantity ($Q > EOQ$), the supplier's profit increases due to potential savings in order processing cost, manufacturing setup costs and transportation costs. With a few exceptions, in the literature on quantity discounts, models are developed where suppliers offer all unit quantity discounts with a single price break point [49]. The literature has shown that the application of all-units discounts contributes to reducing the buyer's inventory cost and improving the supplier's profit simultaneously, improving the channel profits. This finding justifies the wide-spread use of discounting motivated earlier.

4.1.2. Substitution

The origins of the analysis of substitution can be traced to the firm's assortment problem where the main aim is to satisfy all demand by producing only m items, while the firm has the ability to produce n different items (m<n). Any superior item may be substituted to satisfy demand for an inferior item with the objective of minimizing waste and therefore total cost. Pentico [50] classifies the assortment problem models in the literature with respect to the following problem characteristics:

a. Demand: deterministic - stochastic
b. Demand pattern: discrete- continuous
c. Dimensions: one - multiple
d. Number of sizes to stock: fixed - to be determined
e. Substitution cost structure: linear - non linear
f. Stocking pattern: stationary - non stationary

Substitution literature deals with problems in which all sizes are stocked or the set of sizes to stock has been predetermined and the basic issues are to determine the optimum stocking levels and substitution rules to be followed. Most of the studies focus on *one-way substitutability* which means certain products can be substituted with others in a hierarchical order [50]. The assumption is that products with higher grades can be used to substitute for products with lower grades. However, in practice substitution may occur both ways and as presented in Parlar and Goyal [51] for two end-products in a generalized version of the single period newsboy problem.

Substitution problem may either be in firm-driven or consumer-driven context. Consumers who do not find their first-choice product in the current inventory may substitute a similar product for it which is called *consumer-driven substitution*. Here,

substitution decisions are not made by the retailer, instead they are made by a large number of self-interested consumers. A retailer can only indirectly affect customer's decisions through his inventory policy. In this context, Smith and Agrawal [52] obtained a number of insights regarding inventory systems that include substitution effects. Their study showed that in the presence of fixed costs, substitution decreases the optimal number of items to stock. Moreover, when items have different profit margins, substitution effects can reduce the optimal assortment size even when the fixed costs are zero. Mahajan and Ryzin [53] proposed a model to understand inventory decisions in retail assortments when consumers choose dynamically based on the on-hand stock. They showed that under substitution, popular variants should be stocked relatively more and unpopular variants relatively less when compared to what the traditional newsboy analysis indicates.

On the other hand, a supplier firm may choose to fill demand for one product with inventory of another product with the objective of minimizing total cost or maximizing profit. We are mostly interested in this *firm-driven substitution* problem.

Deterministic firm-driven substitution models investigated the dynamics of production and cycle inventory with the presence of economies of scale. Chand et al. [54] considered a manufacturing problem where some components or parts may be used to substitute for others in an assembly process. In this study, the purchase price of a lot is allowed to be any non-linear function of its purchase quantity. They showed the optimality of a segmented policy where stocked parts are grouped into segments and largest number part in each segment serves as a source for all parts in the segment. Drezner et al. [8] developed a variation of the standard EOQ model for the case of two products where product 1 can substitute for product 2 at a transfer cost per unit. They showed that in a deterministic setting with proportional positive substitution costs, full substitution is never optimal. In the case of partial substitution, the substituted quantity increases with the holding cost of the second product whereas it decreases with the holding cost of the first product and the

transfer cost. Gurnani and Drezner [9] extended the two-product analysis by Drezner et al. [8] to the case of *n* products with hierarchical ordering on substitutions.

Stochastic models deal with demand and supply uncertainties and study issues such as the effect of inventory pooling with product substitution. Pentico [55] analyzed the substitution problem with concave production costs and different linear substitution costs and showed that an optimal stocking policy is either segmented or quasi-segmented. Pasternack and Drezner [56] compared the optimal stocking levels with single substitution to the corresponding inventory levels without substitution for the case of two products where the substitution probability is one. They showed that in the general case, if the revenue available from substitution of one product for another increases, the optimal order quantity for the substitute item increases whereas the quantity for the other one decreases. Bassok et al. [57] studied a single-period, multi-product, one-way substitution problem and showed that the benefit of considering substitution at the ordering stage is higher when demand variability and salvage values are higher, substitution cost is lower and products are similar in terms of price and costs.

Gür Ali and Çavdaroğlu [7] developed a model for understanding pharmacy and manufacturer decisions in the presence of competitive manufacturer discounts and complaint costs resulting from substitution. The results of the study suggest that the pharmacist's profit maximizing decision for substitution is driven by the discount rates offered by manufacturers weighted by other factors such as the likelihood that the patient will pay the out-of-pocket expense for the drug, relative to the complaint costs. Modeling the substitution cost function quadratically increasing in the quantity substituted, they were able to explain the empirical observation that the pharmacist may prefer partial substitution. In this study, the role of inventory was not taken into consideration.

Motivated by the work Gür Ali and Çavdaroğlu [7], we explore the role of inventory in pharmacist's optimal decisions. Our model is able to explain the empirical observation of

partial substitution by considering inventory costs together with quantity discounts and linear substitution cost.

With respect to the substitution literature, our study is in the class of firm-driven, one dimensional, deterministic, one-way substitution problems with stationary stocking pattern and linear substitution cost. Pentico [55] proposed additive and proportional- linear-substitution costs. The purchase price function in Chand et al. [54] covers all non-linear pricing schemes for quantity discounts and can be thought as a generalization of the one in Pentico [55]. Although we present a linear substitution cost structure, the purchase cost in our model is a decreasing function of the order quantity. To our knowledge, this quantity discount integration is new in the substitution literature, since Chand et al. [54] focused on the assortment problem.

Moreover, we consider retailer's strategic substitution behavior. In our model, substitution is not considered as a remedy for stock-outs, instead it is the direct choice of the retailer/pharmacist) with the purpose of selling more from the more profitable item. The incentive for the retailer's substitution comes from the quantity discounts offered by the manufacturers. In this setting, the optimal strategy may be partial substitution by substituting all demand up to a point in the order cycle beyond which the additional cost burden makes it unprofitable to substitute.

4.1.3. Our contribution

In Turkey, pharmacists have the authority to substitute the drug that is prescribed by a physician with an equivalent alternative. We got our motivation from the pharmacist's substitution behavior in the presence of quantity discounts offered by pharmaceutical companies. These discounts provide incentives to the pharmacist to substitute the requested drug with a more profitable alternative. Given that the substitution is among products with

the same molecule conforming to the quality standards set by the health authorities, the principal factor affecting the decision of the pharmacist concerning substitution is mainly commercial. Usually, the patient is not the only decision maker in purchasing; the pharmacist, has a great influence on drug choice.

Therefore, we study a firm-driven, one-way substitution problem with linear substitution cost. Instead of considering substitution as a remedy for stock-outs, we focus on the quantity discount incentive as the primary driver of pharmacist's substitution. Our main contribution to the literature is to associate firm-driven substitution with the firm's quantity discount incentive.

Many useful applications have been suggested for quantity discounts including price discrimination [41]. Our model reflects manufacturer's/supplier's price discrimination in the sense that size of the pharmacy dictates the amount that the pharmacy purchases. Smaller pharmacies or the ones in rural areas where little competition exists may be willing to order in smaller sizes for higher unit prices.

As far as we know, the firm-driven substitution literature considers stock-out based substitution pattern where the retailer substitutes in a predetermined way throughout the cycle. In this study, rather than constructing a prescriptive model we wanted to provide insights into retailer's (pharmacist's) substitution strategy in the presence of manufacturer quantity discounts. In our model, the retailer retails two products and quantity discounts from one of the manufacturers provide incentive for substituting the other item with this more profitable one. Therefore, the retailer favors purchasing the discounted item in larger lots. However, both the holding cost and the cost of substitution increase as the order quantity increases. Our second contribution in terms of modeling is to consider the temporal partial substitution strategy with full substitution up to a point in the order cycle and no substitution afterwards.

We showed that, full substitution is optimal only when substitution is profitable for the

retailer and the retailer's gain from the discount and substitution exceeds the holding cost. When the retailer incurs positive substitution costs, and the discount benefit can not compensate for the holding cost, no substitution becomes optimal. Otherwise, the retailer engages in partial substitution by substituting all demand up to a point in the order cycle, and not substituting afterwards.

4.2. The Pharmacist: The Characteristics Specific to Turkey

Generally, consumer population is assumed to consist of brand loyals and switchers. However, in pharmaceutical markets, demand is usually affected by patient/consumer, the prescriber and the pharmacist. In most developed countries, patients covered by the reimbursement system are partially or completely financed by a third party payer.

In Turkey, pharmaceuticals are only available in pharmacies under the supervision of a licensed pharmacist. For patients coming with a prescription, pharmacists can substitute the prescribed drugs reimbursed by the government with cheaper bioequivalent alternatives. On the other hand, almost any drug can be supplied from the pharmacies without a prescription. Patients directly going to the pharmacy either request a specific drug or ask for pharmacist's advice for treatment. It is worth emphasizing that pharmacists play an important role in purchase decision.

In the retailing context, trade promotions are temporary price cuts that manufacturers offer retailers with the intent of encouraging them to reduce retail prices [45]. In response to trade promotions, retailers either pass through a portion of the promotion value to the consumer or hold inventory in order to take advantage of the special incentives being offered. The latter is known as forward-buying.

Trade promotions in Turkish pharmaceutical industry have a different structure. Due to the strict governmental regulations both on promotional activities and pharmacy profit

margins, pharmaceutical manufacturers can not give direct price discounts. Instead, they provide free goods with purchase of a certain quantity. These quantity discounts are legal even in low-volume transactions. As mentioned before, passing through the discount is not applicable in pharmacy setting since drug prices are regulated by the government. As a result, any quantity discount offered by the manufactures becomes a hidden source of income for the pharmacist.

In Turkey, drug prices have been either stable or decreasing in recent years. Therefore, unlike the earlier inflationary environment, where the inventory can increase in value due to frequent price increases, the inventory decision is important for the pharmacist. Moreover, pharmacists can procure the pharmaceuticals just in time; the supply process is fast and free of expense. Pharmacists opt to cut back on goods on hand due to the market characteristics mentioned above. On the other hand, manufacturer quantity discounts give an incentive to purchase in larger lots and the terms of payment offered by the manufacturer (or wholesaler) are also critical in pharmacist's purchase decision.

In general, substitution is either considered as a remedy for stock-outs or an opportunity to reduce the retailer's holding cost burden. On the other hand, discounts offered by the pharmaceutical manufacturers provide an incentive to the pharmacist to substitute drugs with more profitable equivalent alternatives. The pharmacist incurs a cost for substitution which emanates from the cost of dealing with complaining patients who are not satisfied with the substitution made by the pharmacist or objection from physicians. Therefore, the structure of the substitution cost is also different than the transformation or modification cost that the retailer faces.

4.3. The Problem Characteristics

In this study, we analyze the optimal order quantity and one-way substitution strategy for the pharmacist selling two-products in the presence of quantity discount offers from one

of the manufacturers. The presented situation, although similar to the retailer's substitution problem, is different in many aspects.

Most importantly, we position the quantity discount incentive as the primary driver of substitution. The generic manufacturer offers attractive quantity discounts to the pharmacist to induce substitution of the branded product demand with its generic product. We assume that the manufacturer/seller uses a non-linear price schedule similar to the one presented in Lal and Staelin [42], where the price of the seller's product is a monotonically decreasing function of the amount ordered by the buyer. The objective here is to provide insights rather than practical use.

Substitution has a particular cost to the pharmacist; the complaint cost from unsatisfied consumers plus the revenue difference between the branded and the generic drug. The complaint cost can be represented as a fixed cost of substitution per unit drug substituted.

The local availability of products/services is an important factor in the consumer choice decision. However, in the pharmacy setting "lost sales due to stockouts" is not very common. As mentioned before, couriers deliver the required drugs throughout the day and we assume zero lead time in the supply process.

4.4. The Model

We present a mathematical model of the profit maximizing pharmacist selling the branded and generic versions of a particular drug when there is a quantity discount offers from the generic manufacturer. The demand for both versions is fixed but the demand for the branded version can be satisfied by substituting it with the generic version. By doing so, the pharmacist incurs a substitution cost which has two components. The first one is the cost of dealing with complaining patients who are not satisfied with the substitution made by pharmacist, which can be considered as loss of future revenue. The second component of the substitution cost is the profit difference between the branded and the generic drug,

which can be positive or negative.

The pharmacist decides on the order quantity of the generic drug when there is an available discount. The branded drug is not discounted and the pharmacist can always procure it just in time without incurring holding cost. Therefore, there is no reason for the pharmacist to keep inventory of the branded drug. In this setting, substitution is not a remedy for stock-outs; instead it is an opportunity to make maximum use of the quantity discounts offered by the generic manufacturer.

When there is a positive cost for substitution, the pharmacist's trade-off is to balance the benefit from the discounts with the cost of substitution and the holding cost of the generic drug. We are interested in the case when this holding cost is comparable with the discount benefit gained from substitution. Otherwise, the trade-off is not much of an issue and the cycle time tends to go to infinity due to a stockpiling behavior. The figure below shows how the pharmacist's profit function, the cost elements and the discount benefit change while the substitution period extends:

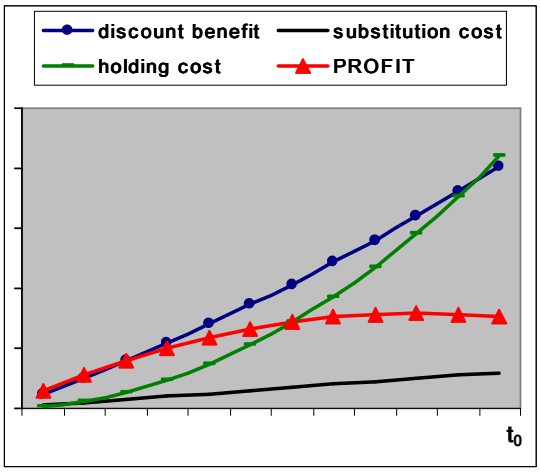


Figure 4.1 The Trade-off

4.4.1. Problem Formulation

In this sub-section we formulate the problem, derive the expression for the total cost and revenue function, and finally give the pharmacist's profit function. A cycle begins with the quantity discount offer from the generic manufacturer at $t= 0$, and ends with the depletion of the generic drug at $t= t_1$. Let the drugs be indexed by $i = 1, 2$ where *1* is the generic version and *2* is the branded version.

In order to benefit from the discounts, pharmacist orders the generic drug (i=1) at the beginning of the cycle. The branded drug (i=2) is either substituted with the generic one or procured just in time as the need arises. P_i (i=1, 2) stands for "the regular wholesale price" and Q_i stands for the order quantity for drug i throughout the cycle.

As mentioned before, the generic manufacturer uses a non-linear price schedule where the price of the drug is a monotonically decreasing function of the amount ordered by the pharmacist. The discounted price function of the generic drug is formulated as:

$$P_1 - a\,Q_1 \tag{4.1}$$

where; a is the coefficient of the quantity discount offered by the generic manufacturer.

In the presence of quantity discount offers for the generic drug, the pharmacist strategically substitutes the branded drug with the generic one up to some particular t_0 ($t_0 \le t_1$). Thereafter, he places the orders for the branded drug simultaneously with the arrival of demand, since there is no lead time for delivery of drugs. The inventory cycle for both drugs can be seen from *Figure 4.2*.

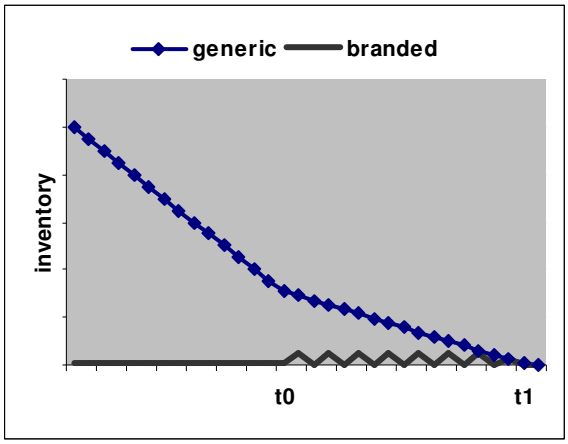


Figure 4.2 Inventory cycle

Total revenue expression

The pharmacist has a profit margin specific to each drug denoted by pm_i (i=1, 2). There is no transformation or modification process in drug substitution. When the pharmacist substitutes the branded with the generic drug, the patient pays for the generic one. Therefore, the expression for revenue per cycle is:

$$CR = Q_1 \; P_1 \; (1 + pm_1) + Q_2 \; P_2 \; (1 + pm_2) \tag{4.2}$$

The order quantity for the generic drug, Q_1, is the sum of the demand for both drugs until t_0 and the demand for only the generic one between t_0 and t_1. Throughout the cycle, the branded product is ordered one by one, only to satisfy its own demand after t_0. Therefore, order quantities can be expressed as:

$$Q_1 = (D_1 + D_2)\, t_0 + D_1 \; (t_1 - t_0) = D_1 \; t_1 + D_2 \; t_0 \tag{4.3}$$

$$Q_2 = D_2 \; (t_1 - t_0) \tag{4.4}$$

where; D_i is the known annual demand for drug i (i=1, 2).

Substituting form (4.3), (4.4) and noting that the cycle length is t_1, the revenue per unit time (AR) can be expressed as:

$$AR = \frac{(D_1\ t_1 + D_2\ t_0)\ P_1\ (1 + pm_1) + D_2\ (t_1 - t_0)\ P_2\ (1 + pm_2)}{t_1} \tag{4.5}$$

Total cost expression

Total cost per cycle has the following components: the cost of purchased drugs, the fixed cost of an order, the holding cost and the cost of substitution. The pharmacist only keeps stock of the generic drug; therefore the holding cost per cycle is:

$$h\left[\left(\frac{Q_1 + \left[Q_1 - (D_1 + D_2)\ t_0\right]}{2}\right) t_0 + \left(\frac{Q_1 - (D_1 + D_2)\ t_0}{2}\right)(t_1 - t_0)\right] \tag{4.6}$$

where; h represents per unit holding cost for the generic drug

Substituting from (4.3) and simplifying gives:

$$h\left[\frac{D_1}{2}\ {t_1}^2 + \frac{D_2}{2}\ {t_0}^2\right] \tag{4.7}$$

Noting that the generic drug is purchased at the discounted price given by (4.1), the purchase cost per cycle can be expressed as:

$$Q_1\ (P_1 - a\ Q_1) + Q_2\ P_2 + K \tag{4.8}$$

where; K is the fixed cost per generic drug order.

The quantity transferred from the generic drug to the branded one is $D_2\ t_0$. Finally, the cost of substitution is $D_2\ t_0\ c$ where *c* stands for the per unit substitution (complaint) cost ($c \geq 0$). After the necessary algebraic manipulations, we have the total cost per unit time (AC) as:

$$AC = \frac{(D_1\ t_1 + D_2\ t_0)\left[P_1 - a\ (D_1\ t_1 + D_2\ t_0)\right] + D_2\ (t_1 - t_0)\ P_2 + K + h\left[\frac{D_1}{2} t_1^{\ 2} + \frac{D_2}{2} t_0^{\ 2}\right] + D_2\ t_0\ c}{t_1} \tag{4.9}$$

Objective function

The pharmacist's objective is to maximize the total profit. Profit per unit time is the difference between the revenue per unit time in (4.5) and total cost per unit time in (4.9). After the necessary algebraic manipulations, the expression for profit per unit time is given as below:

$$AP = \frac{(D_1\ t_1 + D_2\ t_0)\left[P_1\ pm_1 + a\,(D_1\ t_1 + D_2\ t_0)\right] + D_2\ (t_1 - t_0)\ P_2\ pm_2 - h\left[\frac{D_1}{2} t_1^{\ 2} + \frac{D_2}{2} t_0^{\ 2}\right] - D_2\ c\ t_0 - K}{t_1} \tag{4.10}$$

4.4.2. Optimal Decision

The decision variables in the formulation of the problem are the substitution period (t_0) and the cycle time (t_1). The steps for proving concavity of the objective function is given in Appendix E. The profit per unit time function is jointly concave for the following

condition:

$$2K\ (h-2a\,D_2)-D_2\ C_t^{\,2}\geq 0 \tag{4.11}$$

Here, $P_2\ pm_2-P_1\ pm_1$ shows the difference in profit of selling one unit of the branded drug and one unit of the generic drug. The expression $c+P_2\ pm_2-P_1\ pm_1$ includes the marginal profit difference due to substitution together with the per unit substitution cost. Therefore, the cost - positive or negative- of transferring from generic drug to the branded one is specified as:

$$C_t=c+P_2\ pm_2-P_1\ pm_1 \tag{4.12}$$

Optimum values of the cycle time, t_1, and the substitution period, t_0, can be found as:

$$t_1^*=\sqrt{\frac{2\ K\ (h-2\ a\ D_2)-D_2\ Ct^2}{D_1\ h\ (h-2\ a\ (D_1+D_2))}} \tag{4.13}$$

$$t_0^*=\frac{2\ a\sqrt{\frac{D_1\left(2\ K\ (h-2\ a\ D_2)-D_2\ Ct^2\right)}{h\ (h-2\ a\ (D_1+D_2))}}-C_t}{(h-2\ a\ D_2)} \tag{4.14}$$

Concavity implies $2K\ (h-2a\,D_2)-D_2\ C_t^{\,2}\geq 0$. Therefore, in the concave region, we also need the following condition in order t_1^* to be defined and limited:

$$h-2\ a\ (D_1+D_2)\geq 0 \tag{4.15}$$

The condition (4.15) also guarantees that the pharmacist faces a trade-off between the holding cost and discount benefit. As it can be shown in the simple problem of one drug with quantity discount and holding cost, the optimal cycle time goes to infinity when $h - 2\,a\,D \le 0$.

Finally, using the relation in expression (4.3), the optimal order quantity can be formulated as:

$$Q_1^* = \frac{\sqrt{\frac{2\,K\,D_1\,h\,(h-2\,a\,D_2) - D_2\,Ct^2}{(h-2\,a\,(D_1+D_2))}} - D_2\,Ct}{(h-2\,a\,D_2)} \qquad (4.15)$$

4.4.3. The Results

Under the concavity condition, the pharmacist would prefer no substitution when $t_0^* \le 0$. On the other hand, $0 \le t_0^* \le t_1^*$ implies that partial substitution is optimal for the pharmacist. Finally, full substitution becomes the case when $t_1^* \le t_0^*$. The corresponding conditions for each of the three optimal strategies are given below.

$$C_t \ge 0 \quad \delta \quad a \le \frac{h}{D_1 + \sqrt{D_1\left(D_1 + 8\,h\,\frac{K}{C_t^{\,2}}\right)}} \quad \Rightarrow \textit{ No substitution}$$

$$C_t \geq 0 \quad \delta \quad a \geq \frac{h}{D_1 + \sqrt{D_1\left(D_1 + 8\,h\,\frac{K}{C_t^{\,2}}\right)}}$$

OR

$$C_t \leq 0 \quad \delta \quad a \leq \frac{h}{2\,(D_1 + D_2)} - \frac{C_t^{\,2}}{4\,K} \qquad \Rightarrow \textit{ Partial substitution}$$

$$Ct \leq 0 \quad \delta \quad a \geq \frac{h}{2\,(D_1 + D_2)} - \frac{C_t^{\,2}}{4\,K} \qquad \Rightarrow \textit{ Full substitution}$$

The results suggest that full substitution is optimal when the quantity discount is high enough compared to the holding cost and substitution itself is profitable for the pharmacist. When there is a positive substitution cost, either no substitution or partial substitution becomes optimal. The pharmacist does not substitute when the discount benefit can not compensate for the holding cost. Otherwise, the pharmacist engages in partial substitution by substituting all demand up to a point in the order cycle, beyond which the additional cost burden makes it unprofitable to substitute.

4.5. Comparison with Drezner et al. (1995)

Drezner et al. [8] assumed one-way substitution (only product 1 can substitute product 2).
The parameters:

c_{hi}: annual holding cost of product *i*

Di: annual demand for product *i*

Ct: the transfer cost for substituting product 2 with product 1 (including the price differential between the products)

C_0 = the total ordering cost for **both** products

ΔQ = the unknown quantity of product 1 that is transferred to product 2 (the amount of product 2 demand that is substituted with product 1)

Let's define t_1: cycle time. Then, the optimal strategy in the case of partial substitution is given as below:

$$t_1^* = \sqrt{\frac{2\,C_0 - \frac{D_2\,C_t^{\,2}}{c_{h2}-c_{h1}}}{c_{h1}(D_1+D_2)}} \quad = \quad t_1^* = \sqrt{\frac{2\,C_0\,(c_{h2}-c_{h1}) - D_2\,C_t^{\,2}}{c_{h1}(c_{h2}-c_{h1})(D_1+D_2)}}$$

$$Q_1^* = \sqrt{(D_1+D_2)\left[\frac{2\,C_0(c_{h2}-c_{h1}) - D_2\,C_t^{\,2}}{c_{h1}\,(c_{h2}-c_{h1})}\right]} - \frac{D_2\,C_t}{c_{h2}-c_{h1}}$$

$$Q_2^* = \frac{D_2\,C_t}{c_{h2}-c_{h1}}$$

$$\Delta Q = \sqrt{D_2\left[\frac{2\,C_0(c_{h2}-c_{h1}) - D_2\,C_t^{\,2}}{c_{h1}\,(c_{h2}-c_{h1})\,(D_1+D_2)}\right]} - \frac{D_2\,C_t}{c_{h2}-c_{h1}}$$

Substitution rate = $\Delta Q/Q_1$

$$\boldsymbol{\Delta Q/Q_1} = \frac{\sqrt{(D_1+D_2)\left[\sqrt{D_2\,(c_{h2}-c_{h1})(2\,C_0\,(c_{h2}-c_{h1}) - D_2\,C_t^{\,2})} - D_2\,C_t\sqrt{c_{h1}(D_1+D_2)}\right]}}{\sqrt{(D_1+D_2)(c_{h2}-c_{h1})(2\,C_0\,(c_{h2}-c_{h1}) - D_2\,C_t^{\,2}) - D_2\,C_t\sqrt{c_{h1}}}}$$

Our Model:

Let's define ΔQ = the unknown quantity of product 1 that is transferred to product 2 (the amount of product 2 demand that is substituted with product 1) = $D_2 * t_0$

Partial substitution case (for *a=0*):

$$t_1^* = \sqrt{\frac{2\,K\,h - D_2\,C_t^{\,2}}{h^2 D_1}} \qquad t_0^* = \frac{-C_t}{h} \qquad t_0^* \geq 0 \text{ for } C_t \leq 0$$

$$Q_1^* = \frac{\sqrt{\frac{2\,K\,D_1\,h^2 - D_2\,C_t^{\,2}}{h}} - D_2\,C_t}{h} = \sqrt{\frac{2\,K\,D_1}{h} - \frac{D_2\,C_t^{\,2}}{h^3}} - \frac{D_2\,C_t}{h}$$

$$Q_2^* = D_2\,(t_1^* - t_0^*) = D_2\left(\sqrt{\frac{2\,K\,h - D_2\,C_t^{\,2}}{h^2 D_1}} + \frac{C_t}{h}\right)$$

$$\Delta Q = D_2\,t_0^* = \frac{-C_t\,D_2}{h}$$

$$\text{Substitution rate} = \Delta Q / Q_1 = \frac{C_t\,D_2}{\sqrt{\frac{2K\,D_1\,h^2 - D_2\,C_t^{\,2}}{h}} - D_2\,C_t}$$

Comparison:

1. Drezner et al. [8] concludes that full substitution is never optimal since substitution has a positive cost to the retailer. In our model, there is the quantity discount incentive for substitution. Moreover, by allowing negative transfer cost (C_t<=0), we are able to show the optimality of full substitution in the case when the quantity discount is high enough compared to the holding cost and substitution itself is profitable for the retailer.

2. Drezner et al. [8] concludes that when C_t>=0, either partial substitution or no substitution becomes optimal. Whereas we showed that when C_t>=0, if there is no quantity discount (a=0) “no substitution” is optimal for the retailer. The reason for that:

- In Drezner et al. [8], the retailer keeps inventory of the second product. Therefore, even if there is no quantity discount from the first product, partial substitution may become optimal, depending on the value of $(c_{h2} - c_{h1})$.

3. Since, we assume a different partial substitution strategy and a different stocking pattern, there is no meaningful relation between substitution rate in Drezner et al. [8] and our study (a=0).

4.6. Managerial Implications

In this study we determined the pharmacist's rational substitution strategy in the presence of quantity discounts. We showed that when there is a positive substitution cost, partial substitution strategy can be optimal depending on the discount offered for the generic drug and the cost of holding generic drug at hand. The quantity transferred to the branded drug increase with the effective discount. When the discount benefit is not comparable with the holding cost, the pharmacist may choose not to substitute the branded drug with the generic one.

With these insights in mind, we provide implications for the pharmaceutical manufacturer's whose interest is to benefit from pharmacist's substitution power. The pharmaceutical manufacturers can take advantage of the pharmacist's substitution power by offering attractive discounts. An alternative strategy can be reducing the holding cost burden for the pharmacist and this is mainly supported with the terms of payment in practice. Interestingly, increasing the price is also beneficial for the manufacturer. On the defensive move, the manufacturer can block its competitors' substitution power by increasing the cost of substitution for the pharmacist, either by increasing its price or the cost of complaint resulting from substitution.

4.7. Numerical Study

Initial parameters: Branded drug (i=2) is the expensive one and has a regular price (P_2) of 20YTL/unit, whereas the generic drug (i=1) has a price (P_1) of 18 YTL/unit. Their profit margins (pm_i) are the same and 30%. The per unit complaint cost (c) is set to 0.5 YTL/unit. The demand rate for the generic drug (D_1) is 2 unit per day and it is twice as the demand rate for the branded one (D_2). The fixed cost per order (K) is 10 YTL and the holding cost for the generic drug (h) is 2YTL/unit*day. Finally, the discounted price for the generic drug is initially expressed as "P_1 - 0.15 Q_1".

As derived in Appendix E, the pharmacist's profit function is concave for the following condition: $2K\,(h - 2a\,D_2) - D_2\,C_t^{\,2} \geq 0$

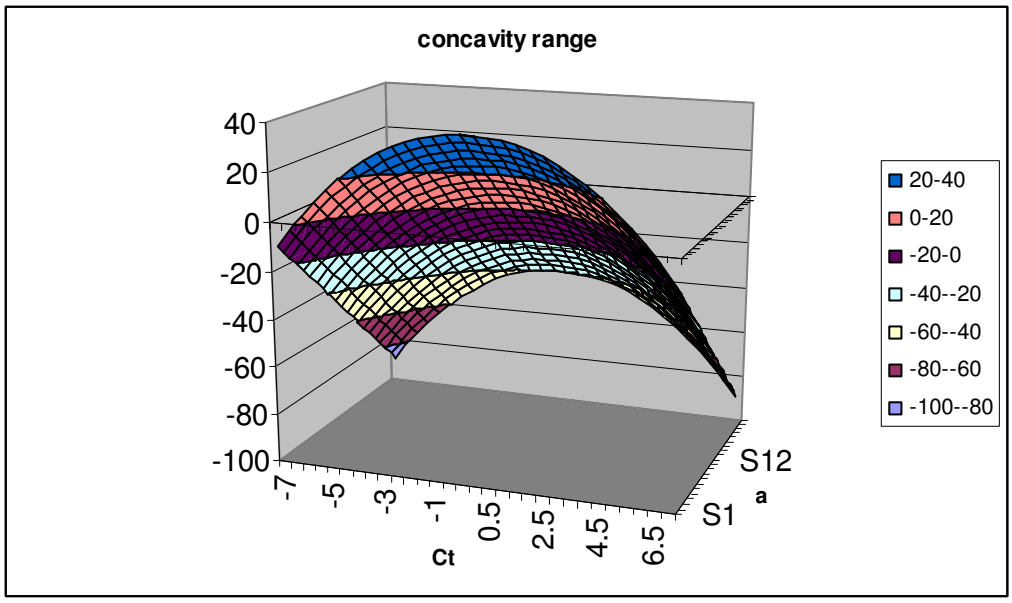


Figure 4.3 Concavity Range

A closer analysis of the range of concavity shows that when substitution is profitable for the pharmacist, ($C_t \leq 0$), concavity range expands as the substitution benefit and the

discount benefit decreases. Otherwise, concavity range expands as the substitution cost and the discount benefit increases.

In order to see the effect of change in model parameters on optimal cycle time and substitution rate (t_0^*/t_1^*), we conducted a numerical study. The corresponding effects can be seen from *Figure 4.4* to *Figure 4.9*.

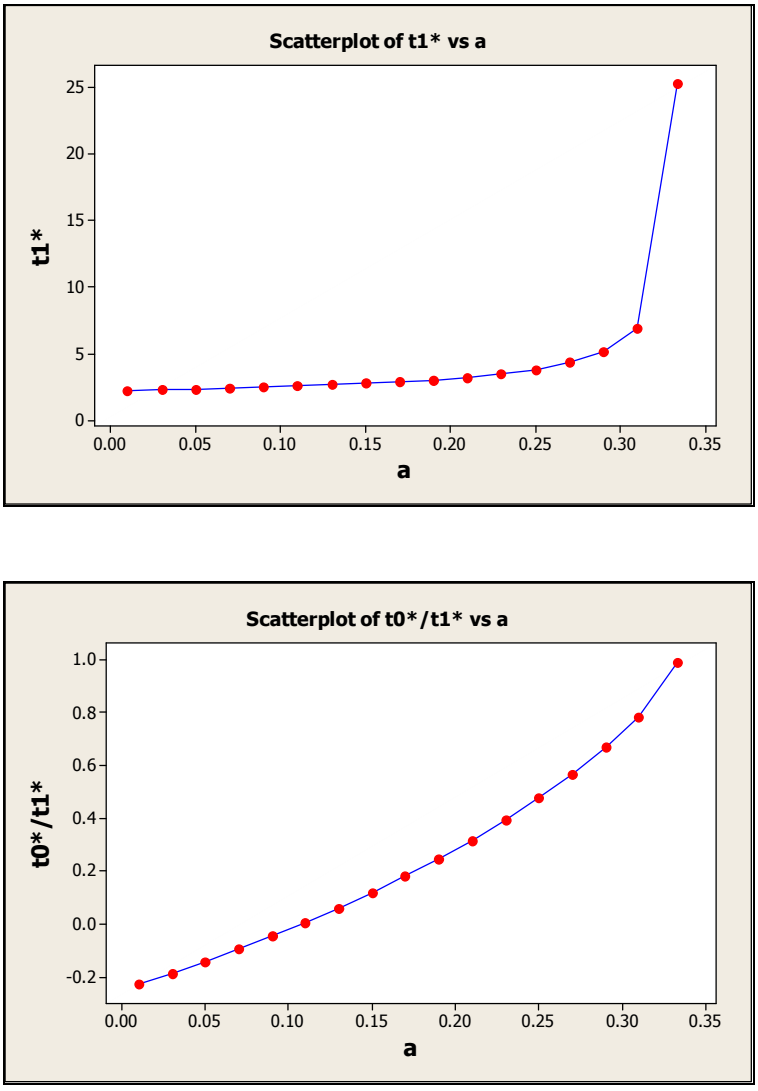
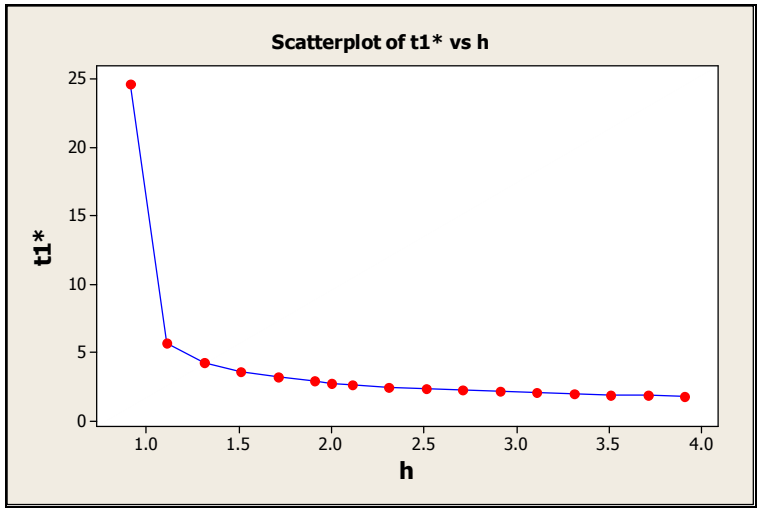


Figure 4.4 The generic discount effect



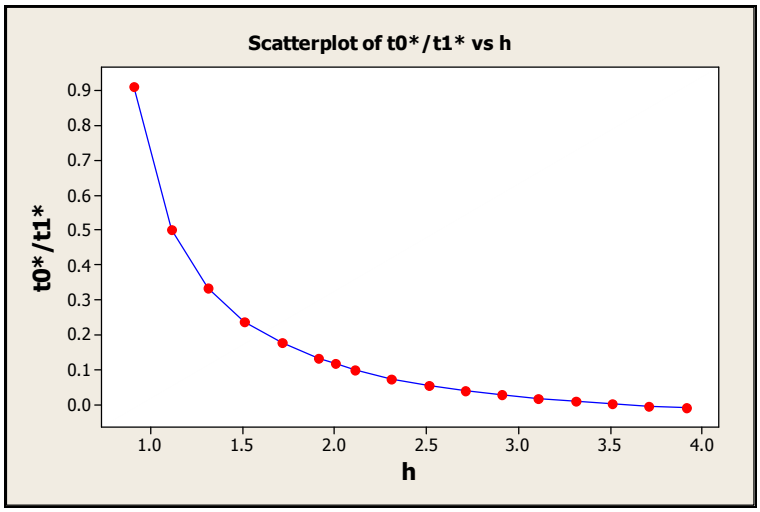
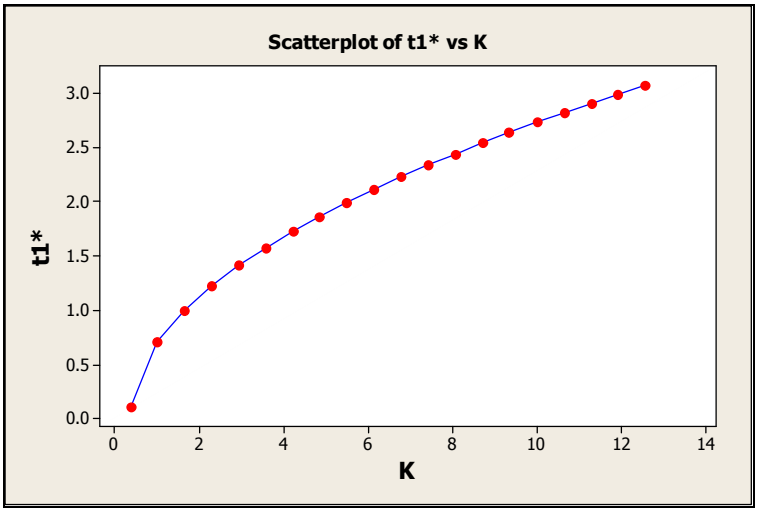


Figure 4.5 The holding cost effect



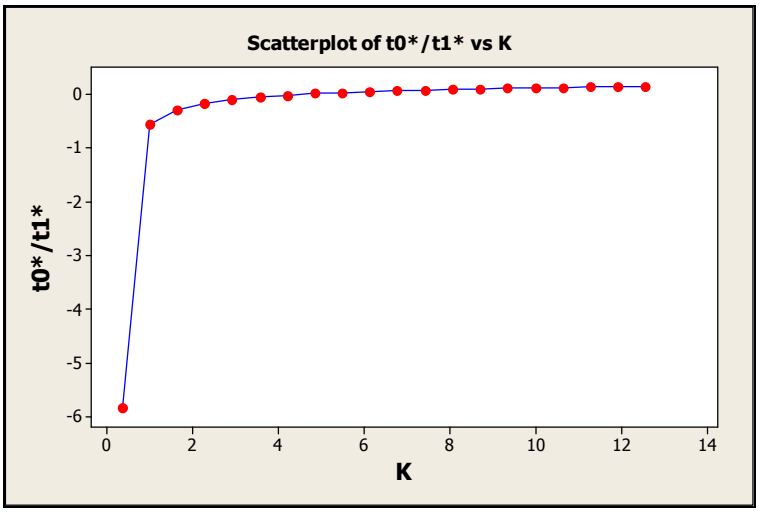


Figure 4.6 Fixed order cost effect

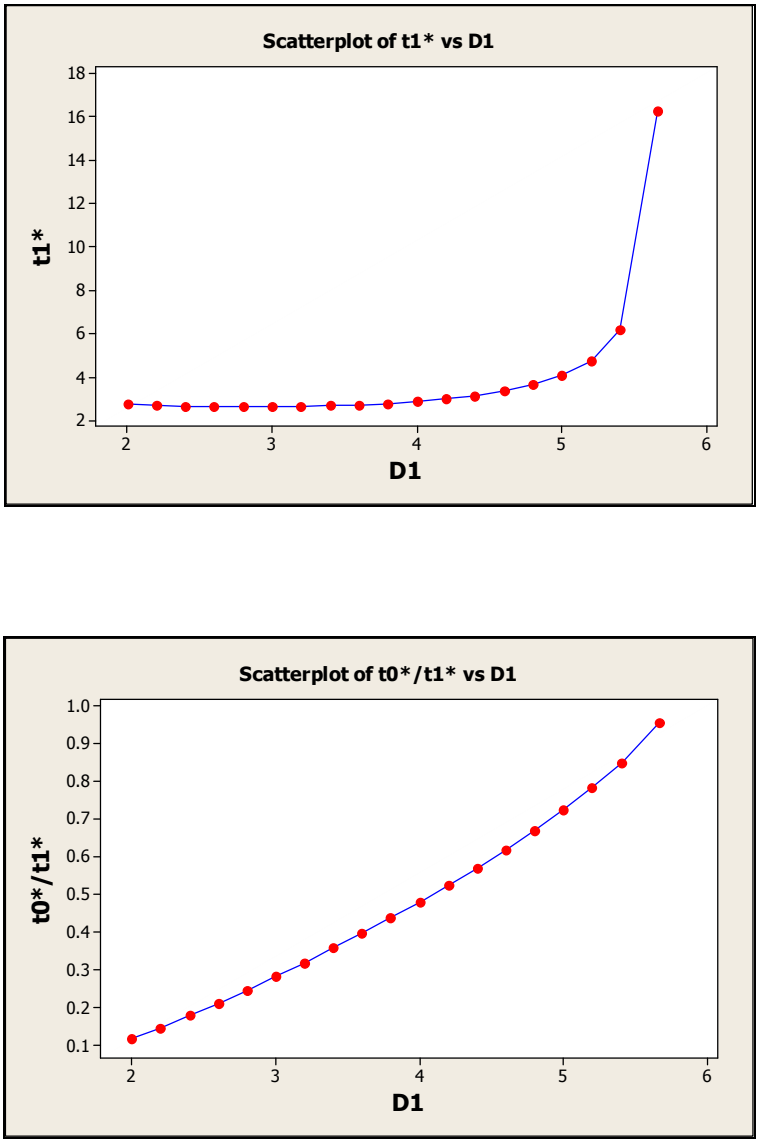


Figure 4.7 Generic demand rate effect

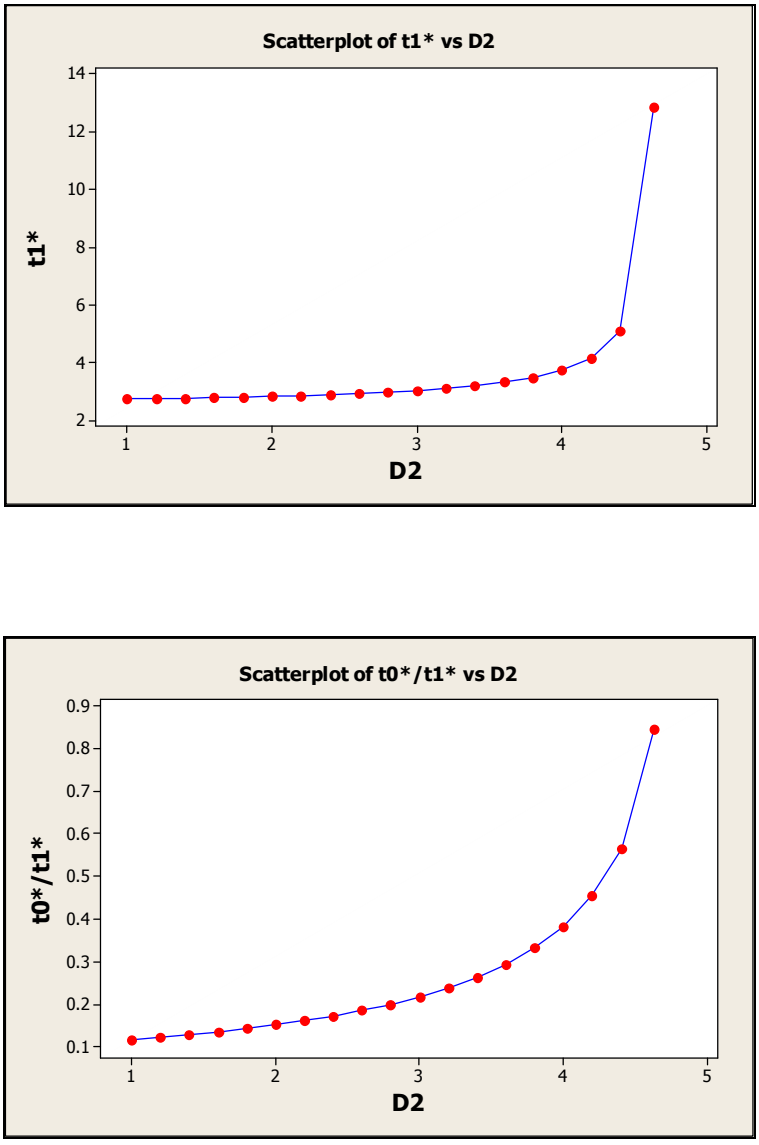


Figure 4.8 Branded demand rate effect

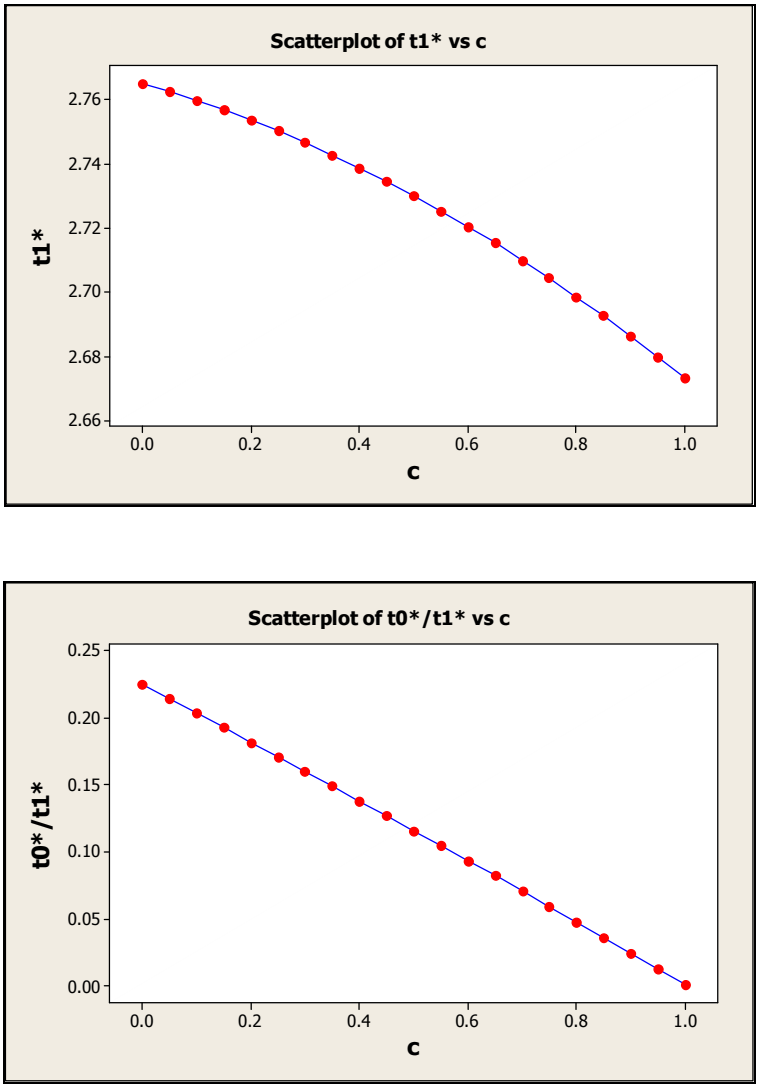


Figure 4.9 Complaint cost effect

The results of the study suggest that as the generic discount parameter *(a)* increases, the length of optimal cycle time as well as the rate of substitution increase. The pharmacist's increases the generic drug inventory in order to benefit the increasing discount. As expected, we observe an opposite pattern when the cost of holding the generic drug increases.

As the fixed cost of an order (K) increases, the cycle time and substitution rate tends to increase, but the effect is weaker when compared to the discount effect.

When the generic or branded demand rate increases, we again see the increasing effect on the cycle time and substitution rate. In this case, the pharmacist satisfies the increasing demand with the discounted item.

Finally, as expected, the cycle time and the substitution rate decreases as the transfer cost (C_t) increases. The increase or decrease in transfer cost depends on the parameters of c, P_1, P_2, pm_1 *and* pm_2. The effects of per unit substitution cost can be seen from Figure 4.9.

Chapter 5

5. CONCLUSION

In this thesis, we have conducted an empirical study on the effects of OTC drugs market introduction related policies on pharmaceutical expenditures and a theoretical study focused on pharmaceutical industry in Turkey. First, we gave an overview of Turkish pharmaceutical market, with special emphasis on the reimbursement system and the cost containment measures on the government's agenda. Next, we discussed our empirical study about the effects of government's reimbursement policy changes on pharmaceutical spending in Turkey. In the penultimate section, we presented the profit maximizing substitution strategy and ordering decision of the retailer in the presence of manufacturer discounts, filling a gap in literature. Motivated by the pharma industry practice, we derived the pharmacist's rational substitution decision incentivized by the generic manufacturer's quantity discount offers. In the empirical study, we evaluated the effect of the recent reimbursement policy changes shifting more than a hundred OTC-type drugs to non-reimbursed status on public expenditure. Removed drugs mainly belong to the therapy classes of Cough & Cold Preperations, Vitamins, Mineral Supplements and Pharyngeal Preperations. In most European countries as well as the US, drugs in these categories are defined as over-the-counter and therefore not reimbursed.

The literature indicates that making drugs OTC available provides significant cost savings to third party payers via reduced reimbursement burden and decreased number of prescriptions for those drugs. However, it is possible that there exist reimbursed equivalents of the switched drugs in the market, and sometimes those alternatives can be even more expensive. At this point, we want to draw attention to the risk of increased cost

to the third party payer due to the demand switch to the reimbursed alternative drugs. In fact, our empirical study showed that Turkish pharmaceutical market faced a similar situation.

We have drawn the following conclusions from the analysis. As expected, there has been a decline in removed drug sales after the change. More importantly, we observed significant increase in the demand for reimbursed alternatives of the removed drugs that can be prescribed by a physician in the case of a patient request, which can wipe out the expected savings. The results of the study justify the concerns of Turkish government regarding the introduction of a non-reimbursed OTC category.

One limitation of the study is that the analysis was done with the wholesaler sales data which includes the sale of both reimbursed and non-reimbursed drugs. While we are able to explain the impact on overall pharmaceutical expenditures, we are unable to observe the portion of patients who are eligible for reimbursement and purchase the drugs that are removed from reimbursement by paying the total amount out-of-pocket. As further research, impact on public expenditures can be clearly determined by repeating the analysis with the prescription data from the Social Security Institution that only includes the reimbursed items

The OTC availability enhanced the role of the pharmacist in many countries. In Turkey, pharmacists are allowed to substitute the prescribed drugs with cheaper bioequivalent alternatives. On the other hand, almost any drug can be supplied from the pharmacies without a prescription. Provided that OTC drugs market is introduced in Turkey, in the absence of physician prescription the pharmacist's role will even be more critical. The second part of this thesis study is inspired by the pharmaceutical product substitution decision in the presence of quantity discounts by the pharma companies. In chapter 2 we have shown with our small scale survey that the effective discount levels are 2% to 73% with 70 drugs offering discounts out of 107 occasions observed. We have studied the

strategic substitution behavior of the pharmacist that is faced with quantity discounts, substitution penalties and one way substitution. To our knowledge, this study is the first attempt to model the role of the discounts offered by manufacturers on retailer's optimal stocking levels and substitution decision. While Chand et al. [54] can be considered in a similar context, they studied the assortment problem.

Getting our inspiration from the study Gür Ali and Çavdaroğlu [7] and Gür Ali and Çavdaroğlu [58], we show the optimality of partial substitution for the pharmacist even if the substitution cost is linearly increasing in the quantity substituted. In the pharmaceutical industry, substitution typically occurs from original drug to its generic alternate and it is called "generic substitution". This study provides the optimal ordering and substitution strategies for the pharmacist in the presence of generic manufacturer's quantity discounts.

In this study, it is emphasized that the manufacturer discounts give an incentive to the pharmacist to substitute a particular product for a more profitable one. If the discount benefit overcomes the cost of holding the product, order quantity for the discounted item increases due to the gain from substitution.

We are interested in the case when the holding cost is comparable with the discount benefit gained from substitution. Otherwise, the trade-off is not much of an issue and the cycle time tends to go to infinity due to a stockpiling behavior. The results suggest that full substitution is optimal only when substitution is profitable for the pharmacist and the pharmacist's gain from the discount and substitution exceeds the holding cost. When the pharmacist incurs positive substitution cost, and the discount benefit can not compensate for the holding cost, no substitution becomes optimal. Otherwise, the pharmacist engages in partial substitution by substituting all demand up to a point in the order cycle, beyond which holding costs make it unprofitable to substitute.

We believe that our results have provided useful insights into the issue of strategic substitution in the presence of manufacturer quantity discounts. There are still interesting

avenues of research worth exploring such as extending the results to the *n*-product substitutable set or assuming different discount offers from all manufacturers. Another promising future direction is to assume probabilistic demand which will help to better adapt the results to real life situations.

Appendix A

DRUGS REMOVED FROM REIMBURSEMENT LIST WITH JULY AND SEPTEMBER 2006 CIRCULARS

LIST OF REMOVED DRUGS (JULY 2006)		
ADANT 25 MG/2.5 ML 3 KULL HAZIR SIRINGA	GINGER 250 MG 10 KP	RINOLAR BUGU 50 ML SOL
A-FERIN HOT 500/60 MG GRANUL 10 POSET	GRIBEX HOT 20 GR 12 POSET	SEKROL 30 MG 20 TB
ALGO WAX TUP 50 G POM	GRIBEX HOT PEDIATRIK 10 GR 12 POSET	SEKROL 30 MG/5 ML 150 ML SURUP
AMBREKS 15 MG/5 ML 100 ML PED SURUP	GRIBEX HOT-D 6 GR 12 POSET	SEKROL 60 MG 20 EFF TABLET
AMBREKS 30 MG/5 ML 150 ML SURUP	HYALGAN 20 MG/2 ML 1 KULL HAZIR ENJ	SEKROL PED 15MG/5ML 100 ML SURUP
AMBROL 15 MG/5 ML 100 ML PED SURUP	HYDRYLLIN 100 ML SURUP	SEKROL PED 15MG/5ML 150 ML SURUP
AMBROL 30 MG 20 TB	KLORHEX %0.2 200 ML GARGARA	SUDAFED EKSPEKTORAN 150 ML SURUP
AMBROL 30 MG/5 ML 150 ML SURUP	KLORHEX %0.2 30 ML ORAL SPREY	SUPERHEKS %0.2 200 ML GARGARA
ANTIBEKSIN 100 ML SURUP	MAXIHOT TEK KULLANIMLIK GRANUL 12 POSET	SUPERHEKS %0.2 30 ML ORAL SPREY
ARCALION 200 MG 30 DRJ	MEGADYN 30 FTB	SUPRADYN 30 DRJ
ARTU 100 ML SURUP	MENTOSEPTOL 100 ML GARGARA	SYNVISC 8MG/ML 2 ML 3 KULL HAZIR ENJ
BATTICON %7.5 100 ML GARGARA	MUKORAL 15 MG/5 ML 100 ML PEDSURUP	THERAFLU-P 10 GR 10 POSET
BECOVITAL-C 30 YUM KP	MUKORAL 15 MG/5 ML 150 ML PED SURUP	TUSEPTIL 100 ML SURUP
BECOZYME 100 ML SURUP	MUKORAL 30 MG 20 TB	TUSILIN 15MG/5ML 150 ML PED SURUP
BECOZYME-C FORTE 30 LAK TB	MUKORAL 30 MG/5 ML 150 ML SURUP	TUSILIN 30 MG/5 ML 150 ML SURUP
BENIL 125 ML SURUP	NEOFEDRIN 100 ML SURUP	TYLOL-HOT 20 GR 12 POSET EFF GRANUL
BENYLIN EKSPEKTORAN SURUP	NEO-SEDEKS 150 ML SURUP	TYLOL-HOT D 6 GR 12 POSET EFF GRANUL
BENYLIN PEDIATRIK SURUP	OLEDRO-HOT 12 EFF GRANUL POSET	TYLOL-HOT PED 10 GR 12 POSET
BENZOLEKS SURUP	OMEKSIN 100 ML SURUP	UNICAP-T 30 FTB
BIBORA 50 ML GOZ BANYOSU	OROHEKS %0.2 200 ML GARGARA	VERMIDON HOT 20 GR 12 POSET
BRODIL 150 ML SURUP	OROHEKS %0.2 30 ML ORAL SPREY	VICKS VAPORUP 38 GR POMAD
BROKSIN 150 ML SURUP	ORTHOVISC 30 MG/2 ML 1 KULL HAZIR ENJ	VICKS VAPOSYRUP EKSPEKTORAN 120 ML SURUP
BROMEK 4 MG/5 ML100 ML SURUP	OSTENIL 20 MG/2 ML 3 KULL HAZIR ENJ	VI-MINERAL 30 CIG TB
BROMEK 8 MG 50 TB	OSTRAM 500 MG 20 EFF TB	VISCOL 8 MG 50 TB
BROMEKSIN 4 MG/5 ML 100 ML SURUP	PECODE 150 ML SIROP	VITABIOL-C FORT 30 DRJ
BROMEKSIN 8 MG 50 TB	PEDILIN 125 ML SURUP	VITADYN 30 DRJ
BUGUMENTOL 40 GR SOL	PEDRIN 100 ML SURUP	XENICAL 120 MG 84 KP
CALCIUM SANDOZ FORT 500 MG 10 EFF TB	PEKTODIN SURUP	ZELIUM 10 MG KP
CALCIUM SANDOZ FORT 500 MG 10 EFF TB	PEREKS 150 ML SURUP	ZELIUM 15 MG 28 KP
CALCIUM SANDOZ+C 1.000/260 MG 10 EFF TB	PERMASOL 250 MG 20 TB	ZINC NUTRIMED 5 MG 20 EFF TB
DECAVIT 30 YUM KP	PINGEL 75 MG 28 FTB	ZINCO-C 15/30 MG 30 TB
EKSOFED 150 ML EKSPEKTORAN SURUP	POLYOD %7.5 GR 100 ML GARGARA	ZINCO-C 2.5/15 MG/ML 50 ML SURUP
EKSOFED 30 MG/5 ML 150 ML SURUP	PULMOR 30 MG/5 ML 150 ML SURUP	ZINCO-C 25 MG TB
EKSOFED 60 MG 30 TB	PULMOR PED 15 MG/5 ML 150 ML SURUP	ZINCO-C 5/30 MG/ML 100 ML SURUP
EKSTO SURUP	RADYOCODIN 100 ML SURUP	ZINCOVER 100 ML PED SURUP
EUPNASE 150 ML SURUP	REDOXON 500 MG 10 CIG TB	
FENIDIN 125 ML SURUP	REDUCTIL 10 MG 28 KP	
FLUIBRON 15 MG/5 ML 150 ML PED SURUP	REDUCTIL 15 MG 28 KP	
FLUIBRON 30 MG 20 TB	RINOGEST 30 MG/5 ML 100 ML SURUP	
FLUIBRON 30 MG/5 ML 150 ML SURUP	RINOGEST EKSPEKTORAN 150 ML SURUP	
GAYABEKSIN 150 ML SURUP	RINOGEST-SR 120 MG 10 MIKROPELLET KP	

LIST OF REMOVED DRUGS (SEPTEMBER 2006)
BEMIKS-C 30 DRJ
BENEXOL 250/250 MG 50 LAK TB
BETADINE GARGARA
BEVITIN-C 30 FTB
BIOKADIN %7.5 100 ML GARGARA
C-PLAN 500 MG 20 CIG TB
DAPTA-12 DAMLA
EPHYNAL 100 MG/2 ML 5 AMP
ESTER-VIT 645 MG 50 TB
HEKSORAL 1 MG/ML 200 ML GARGARA
HEKZOTON 1 MG/ML 200 ML GARGARA
KOMBEVIT-C 30 DRJ
MEFOXIN IM 1 GR 1 FLK
MEFOXIN IV 1 GR 1 FLK
NATABEC 600 MG 25 KP
NEUPOGEN 30 MIO FLK (ENDIKATORSZ)
NEUPOGEN 30 MIU 5 KULL HAZIR ENJ
NEUPOGEN 48 MIO FLK (ENDIKATORSZ)
NEUPOGEN 48 MIU 5 KULL HAZIR ENJ
PARIET 10 MG 28 TB
POLIVIT-C 30 DRJ
POLIVIT-C 30 FTB
POLYBION 2 ML 5 AMP
POLYBION 20 DRJ
PV7 POLIVITAMIN 30 DRJ
REDOXON JUNIOR CIGNEME TB
REMINYL 8 MG 14 FTB
SERALIN 50 MG 14 KP
SERMION 30 MG 30 FTB
TONODEX 100 ML SURUP
ULTRAVIST 370 100 ML 1 FLK
ULTRAVIST 370 200 ML 1 FLK
ULTRAVIST 370 50 ML 1 FLK
ULTRAVIST 370 500 ML FLK
UNIVIT 100 ML SURUP

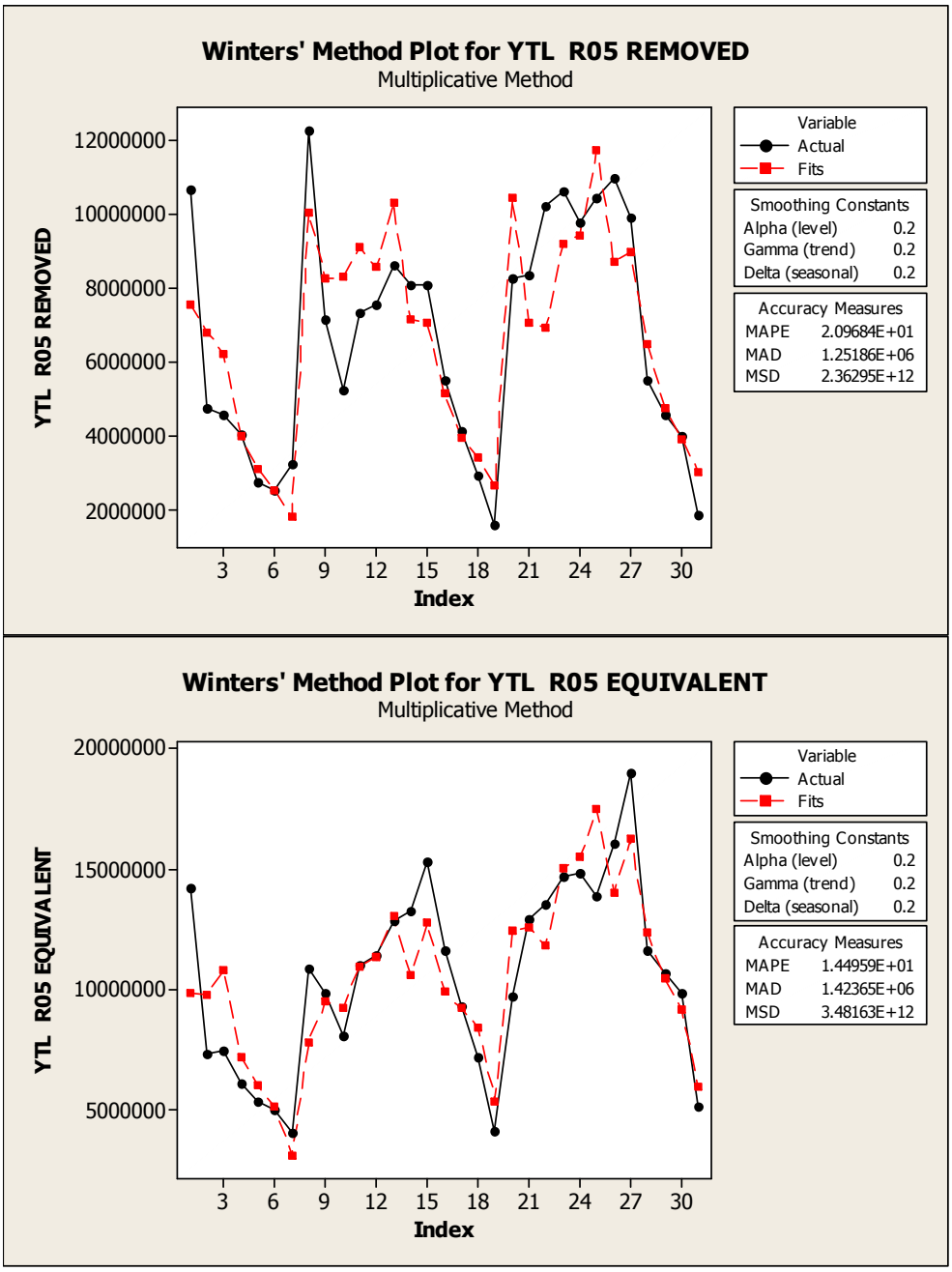
Appendix B

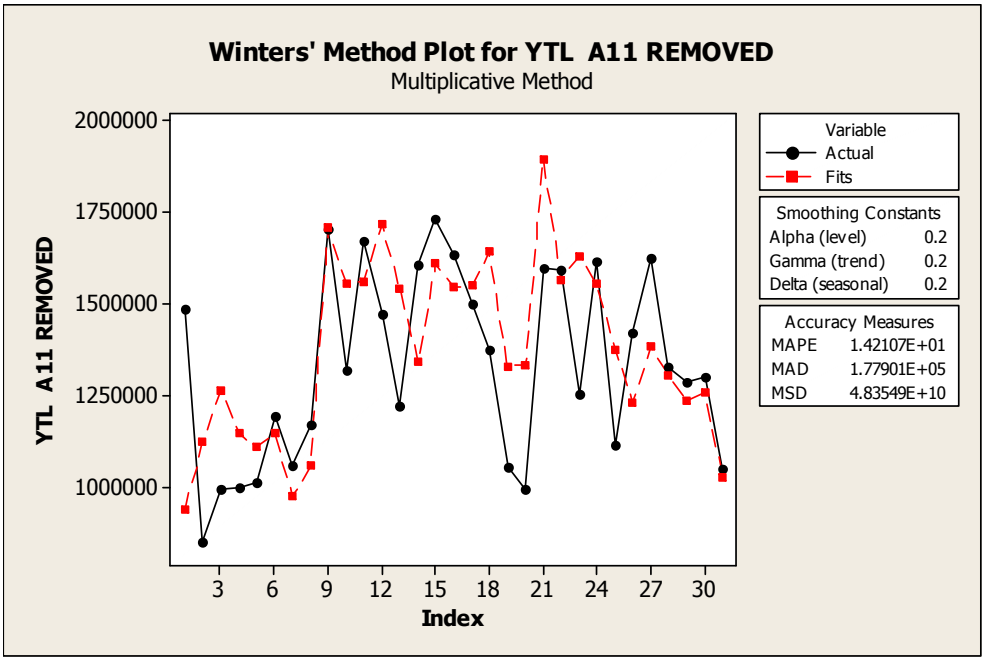
LIST OF EQUIVALENT DRUG GROUPS

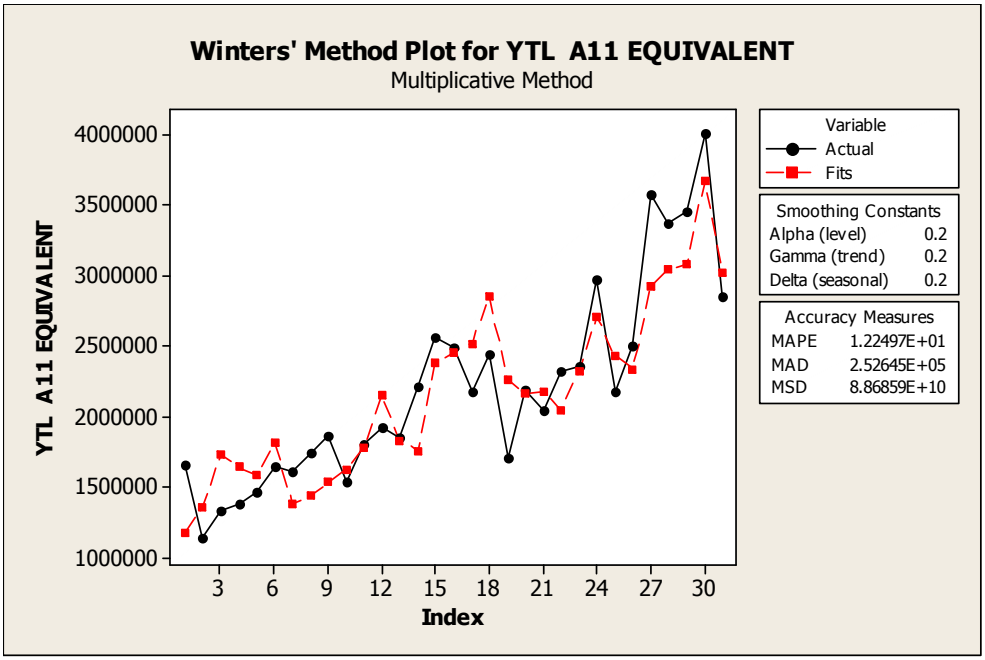
EQUIVALENT DRUGS WITH RESPECT TO ATC GROUPS		
R05 COUGH & COLD PREPARATIONS		***A12 MINERAL SUPPLEMENTS***
PARASINUS	KATARIN	ZINCOVER
GERAKON	NAC	CALCIMAX D3
MEDICOLD	ERDOSTIN	CAL-D-VITA
CETAFLU-FORTE	PEDITUS	ZINCO
VICKS MEDINAIT	ACETYLCYSTEIN	ZENTIUS D
FORZA	MUCONEX 600	CALCIUM D SANDOZ
OLEDRO	BENICAL	***R02 PHARYNGEAL PREPARATIONS***
EXTAL	THERAFLU	TANTUM VERDE
LEVOPRONT	ACTIDEM	ANDOREX
KREVAL	BENICAL COLD	KLOROBEN
SINECOD	KONGEST	FARHEX
PEREBRON	OXXA	TANFLEX
OKSABRON	VICKS VAPODRY	***A11 VITAMINS***
MENTOPIN	A FERIN SINUS	VITABIOL
A FERIN PLUS	MUKOTIK	NEROX B
NUROFEN COLD+FLU	CORSAL	POLIVIT
TYLOL COLD	GAYABEN	VIDAYLIN
TAMOL COLD	DEFLU	SANASOL COLLET
COLDEKS	MUKOLIZ	SUPRAVIT
MUCONEX	VERMIDON COLD	BENEXOL B12
A FERIN		APIKOBAL
ASIST		BEMIKS

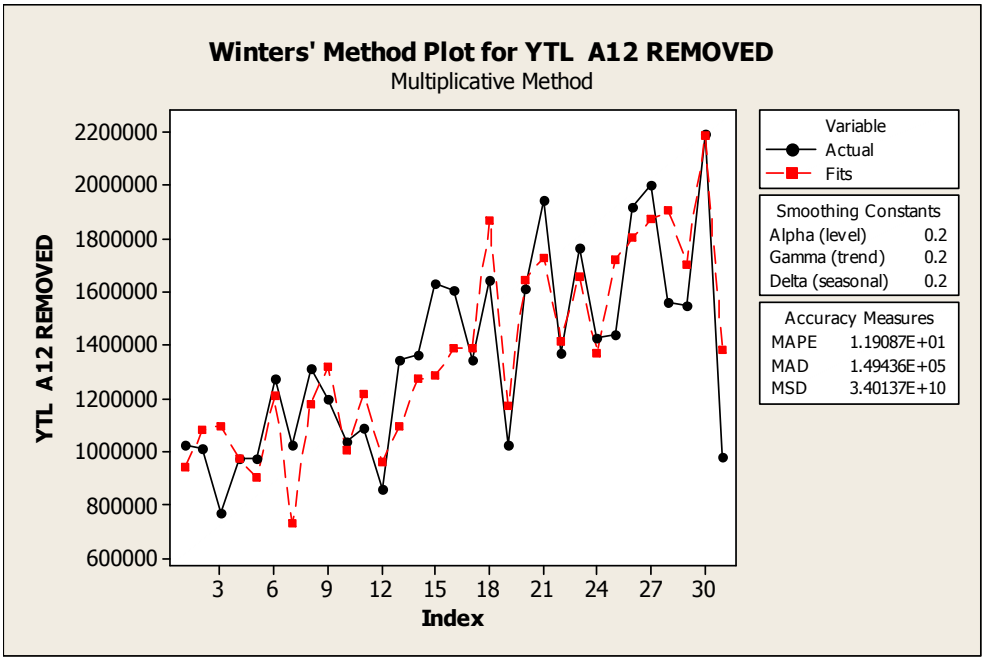
Appendix C

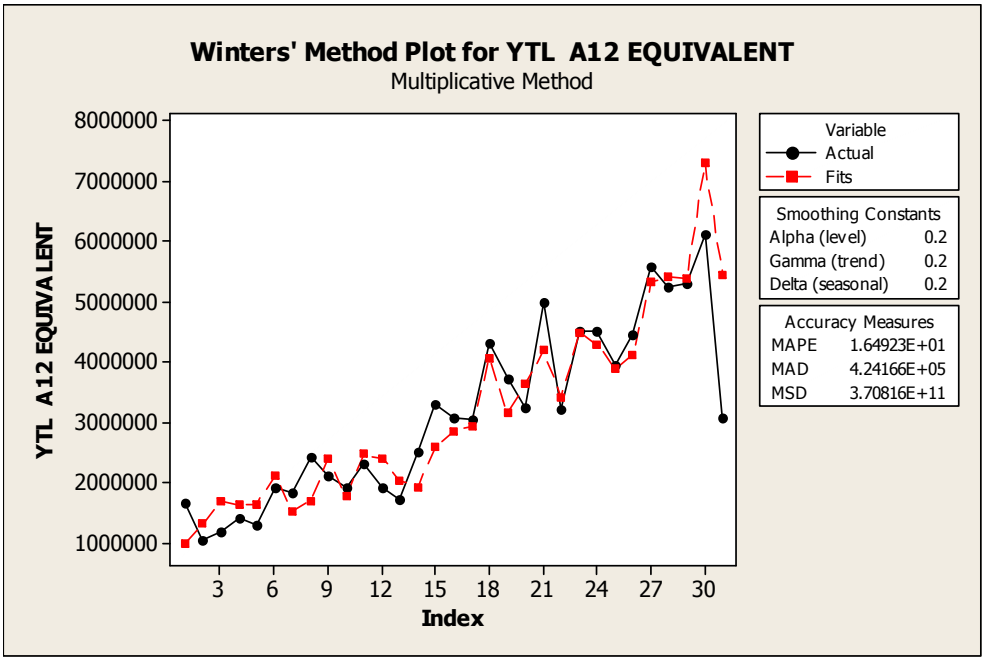
MINITAB RESULTS FOR WINTER'S METHOD

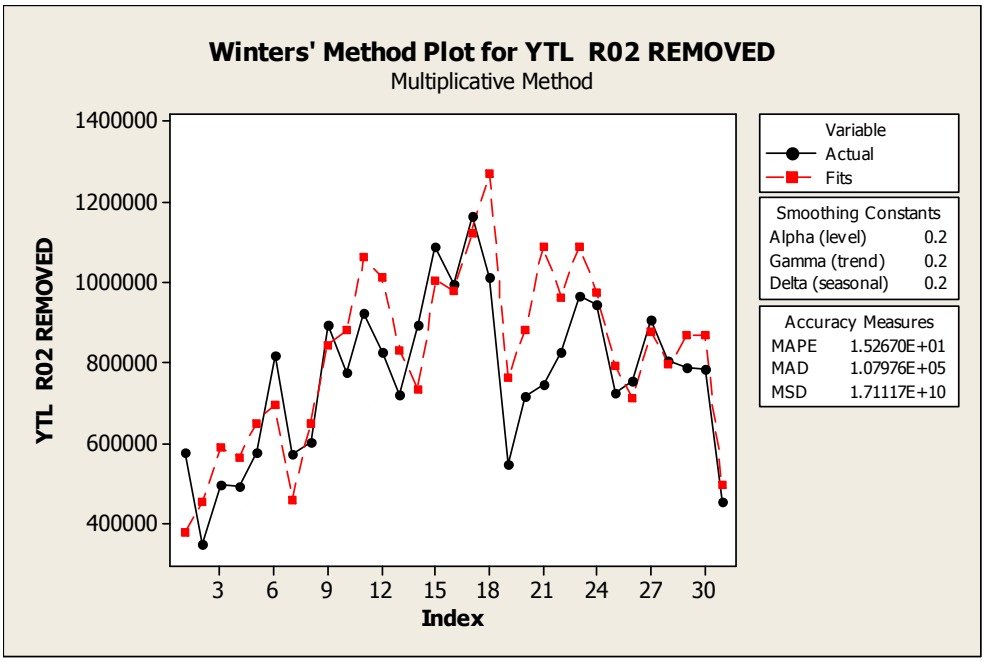


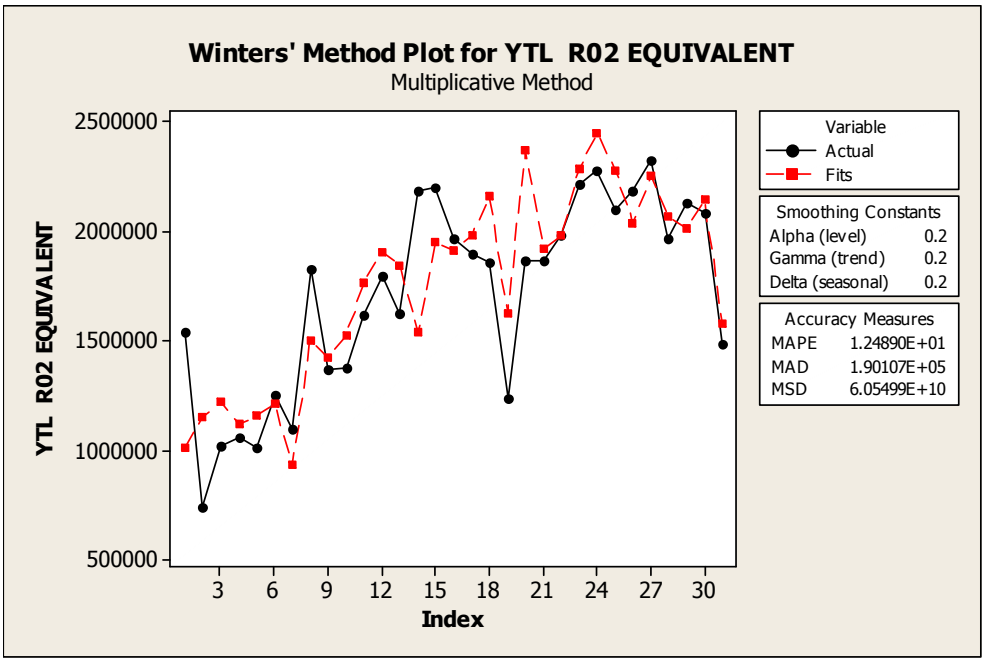

Winters' Method Plot for YTL A11 REMOVED
Multiplicative Method
YTL A11 REMOVED
2000000
1750000
1500000
1250000
1000000
3 6 9 12 15 18 21 24 27 30
Index
Variable
Actual
Fits
Smoothing Constants
Alpha (level) 0.2
Gamma (trend) 0.2
Delta (seasonal) 0.2
Accuracy Measures
MAPE 1.42107E+01
MAD 1.77901E+05
MSD 4.83549E+10


Winters' Method Plot for YTL A11 EQUIVALENT
Multiplicative Method
YTL A11 EQUIVALENT
4000000
3500000
3000000
2500000
2000000
1500000
1000000
3 6 9 12 15 18 21 24 27 30
Index
Variable
Actual
Fits
Smoothing Constants
Alpha (level) 0.2
Gamma (trend) 0.2
Delta (seasonal) 0.2
Accuracy Measures
MAPE 1.22497E+01
MAD 2.52645E+05
MSD 8.86859E+10


Winters' Method Plot for YTL A12 REMOVED
Multiplicative Method
YTL A12 REMOVED
Index
Variable
Actual
Fits
Smoothing Constants
Alpha (level) 0.2
Gamma (trend) 0.2
Delta (seasonal) 0.2
Accuracy Measures
MAPE 1.19087E+01
MAD 1.49436E+05
MSD 3.40137E+10

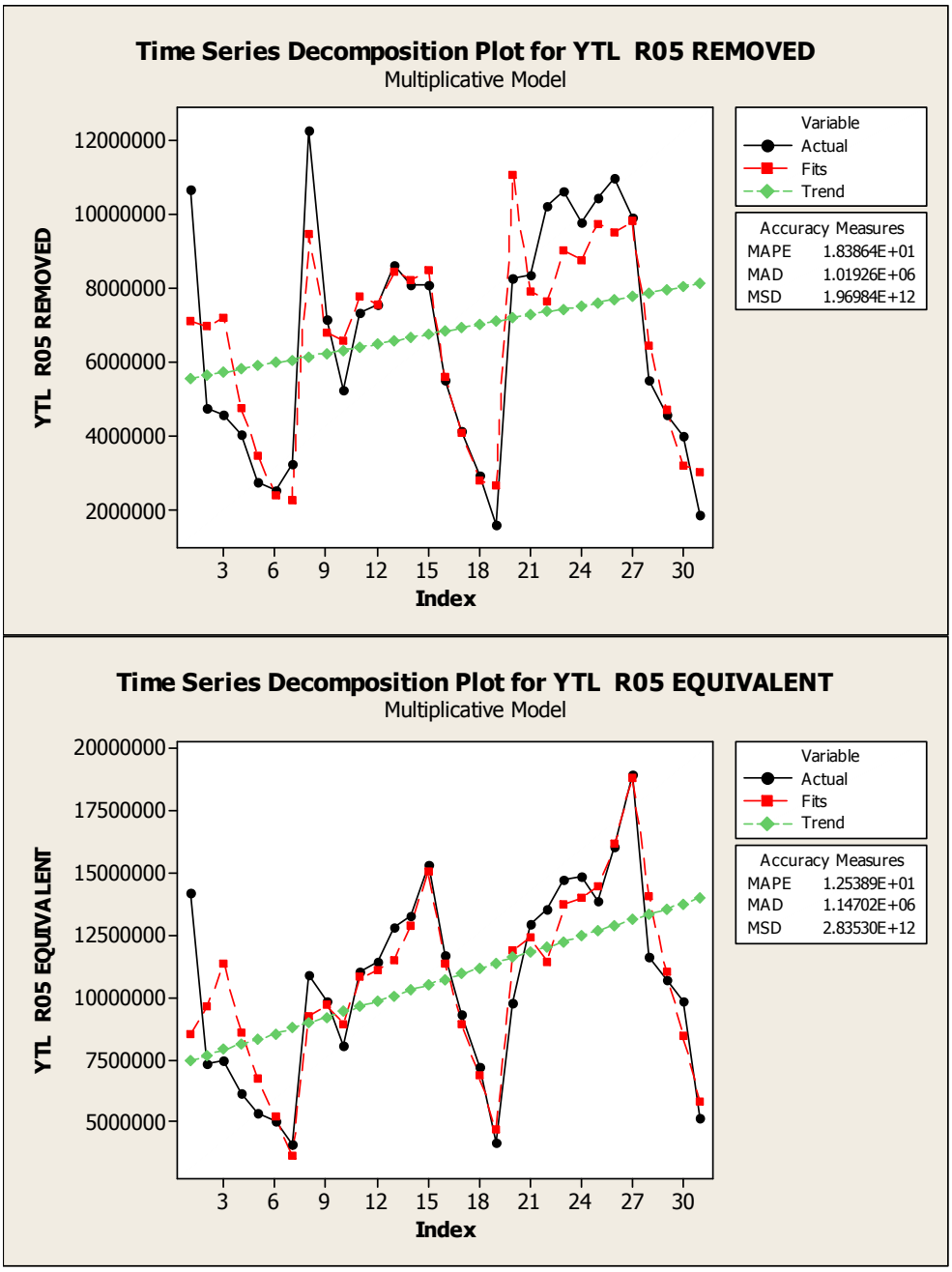

Winters' Method Plot for YTL A12 EQUIVALENT
Multiplicative Method
YTL A12 EQUIVALENT
Index
Variable
Actual
Fits
Smoothing Constants
Alpha (level) 0.2
Gamma (trend) 0.2
Delta (seasonal) 0.2
Accuracy Measures
MAPE 1.64923E+01
MAD 4.24166E+05
MSD 3.70816E+11

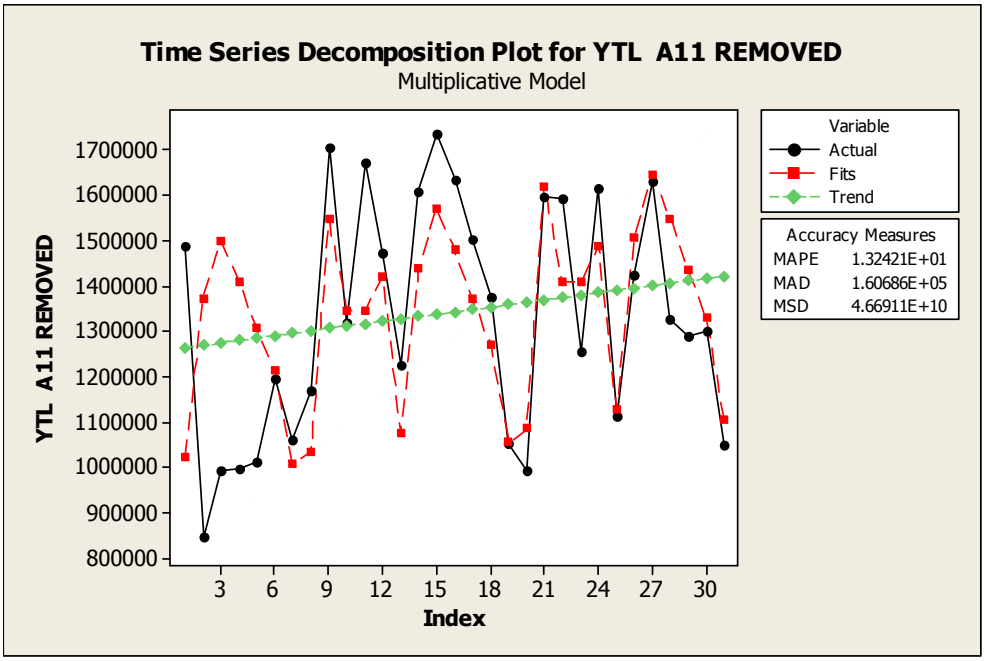

Winters' Method Plot for YTL R02 REMOVED
Multiplicative Method
YTL R02 REMOVED
1400000
1200000
1000000
800000
600000
400000
3
6
9
12
15
18
21
24
27
30
Index
Variable
Actual
Fits
Smoothing Constants
Alpha (level) 0.2
Gamma (trend) 0.2
Delta (seasonal) 0.2
Accuracy Measures
MAPE 1.52670E+01
MAD 1.07976E+05
MSD 1.71117E+10

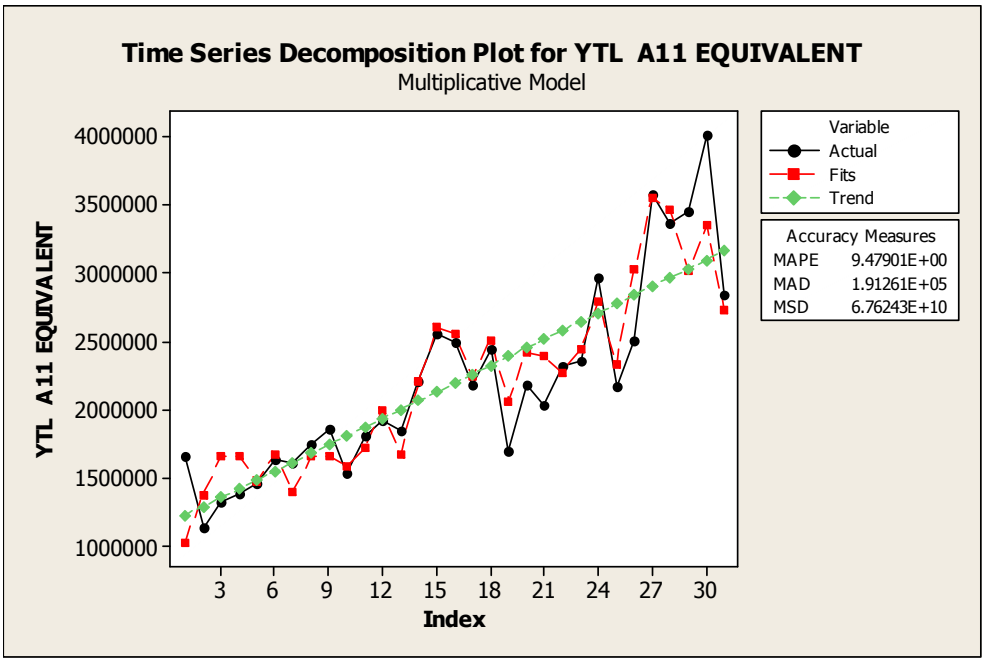

Winters' Method Plot for YTL R02 EQUIVALENT
Multiplicative Method
YTL R02 EQUIVALENT
2500000
2000000
1500000
1000000
500000
3
6
9
12
15
18
21
24
27
30
Index
Variable
Actual
Fits
Smoothing Constants
Alpha (level) 0.2
Gamma (trend) 0.2
Delta (seasonal) 0.2
Accuracy Measures
MAPE 1.24890E+01
MAD 1.90107E+05
MSD 6.05499E+10

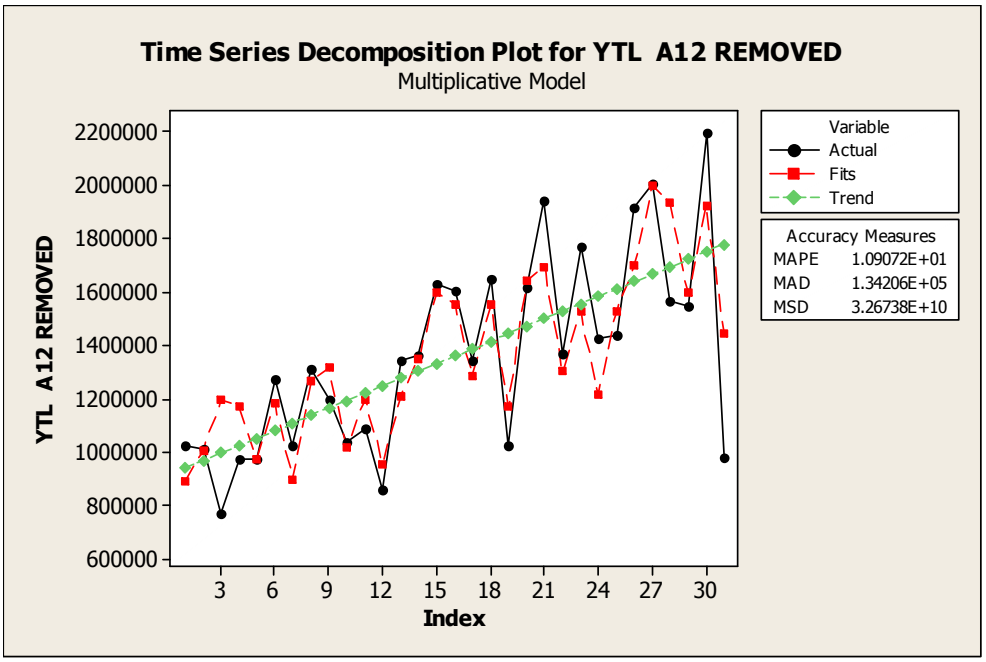
Appendix D

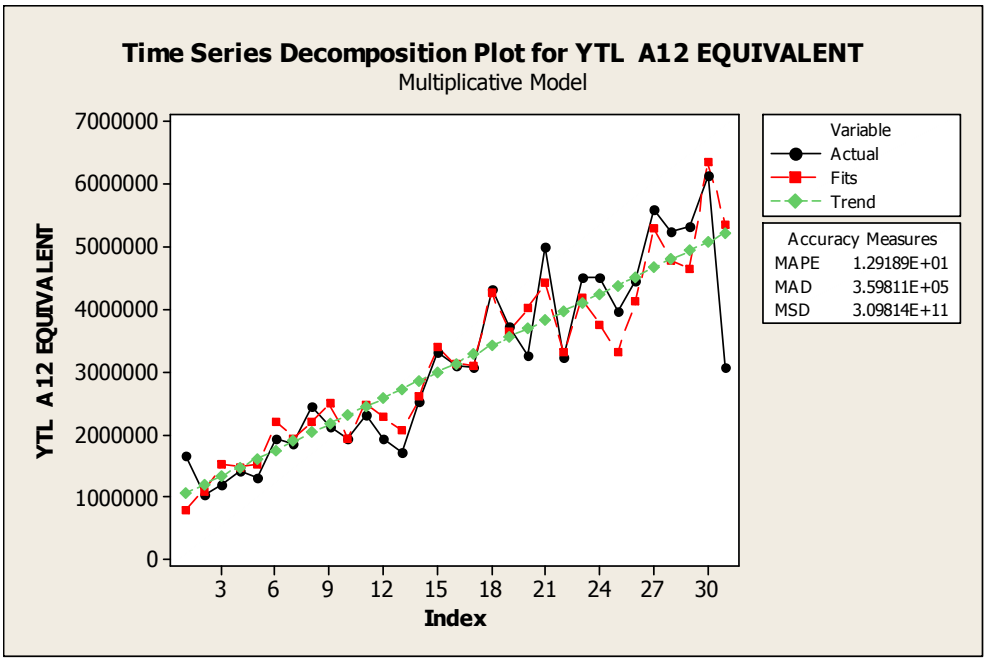
MINITAB RESULTS FOR DECOMPOSITION METHOD

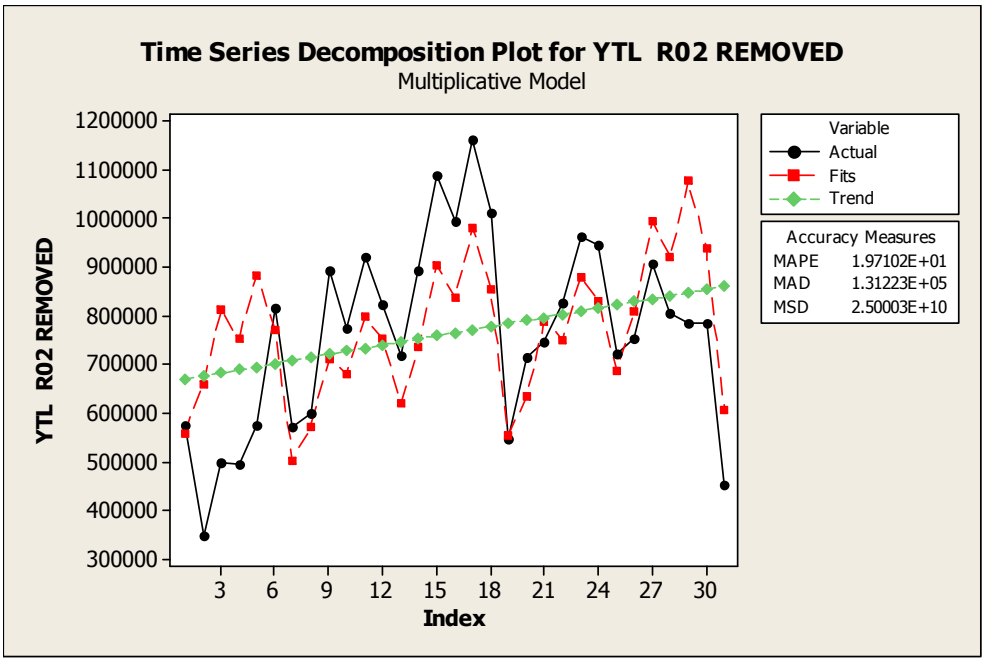


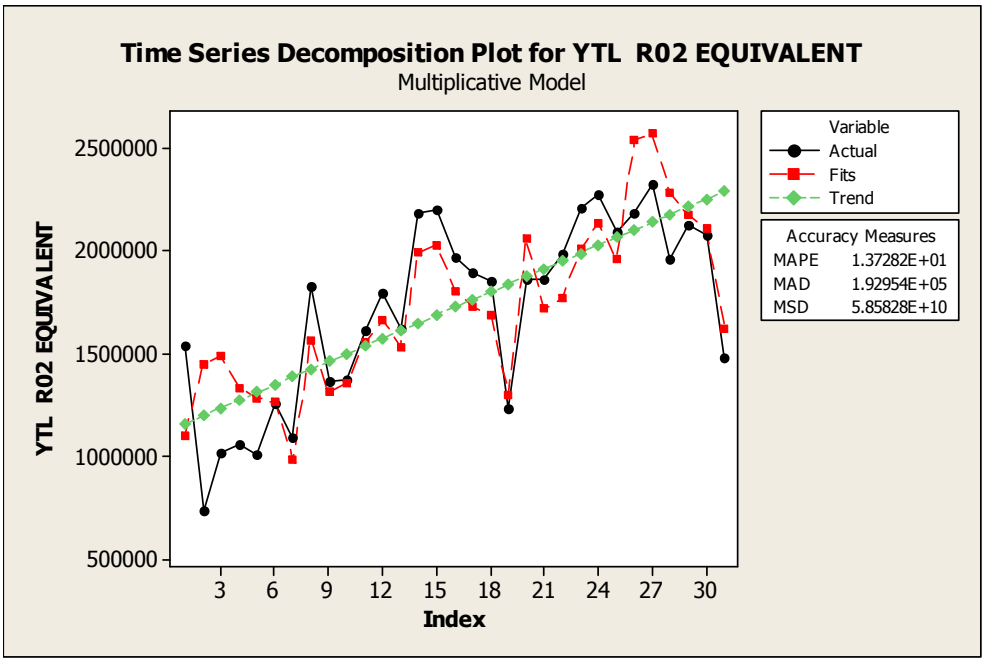

Time Series Decomposition Plot for YTL A11 REMOVED
Multiplicative Model
YTL A11 REMOVED
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
3 6 9 12 15 18 21 24 27 30
Index
Variable
Actual
Fits
Trend
Accuracy Measures
MAPE 1.32421E+01
MAD 1.60686E+05
MSD 4.66911E+10


Time Series Decomposition Plot for YTL A11 EQUIVALENT
Multiplicative Model
YTL A11 EQUIVALENT
4000000
3500000
3000000
2500000
2000000
1500000
1000000
3 6 9 12 15 18 21 24 27 30
Index
Variable
Actual
Fits
Trend
Accuracy Measures
MAPE 9.47901E+00
MAD 1.91261E+05
MSD 6.76243E+10


Time Series Decomposition Plot for YTL A12 REMOVED
Multiplicative Model
YTL A12 REMOVED
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
3 6 9 12 15 18 21 24 27 30
Index
Variable
Actual
Fits
Trend
Accuracy Measures
MAPE 1.09072E+01
MAD 1.34206E+05
MSD 3.26738E+10


Time Series Decomposition Plot for YTL A12 EQUIVALENT
Multiplicative Model
YTL A12 EQUIVALENT
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
3 6 9 12 15 18 21 24 27 30
Index
Variable
Actual
Fits
Trend
Accuracy Measures
MAPE 1.29189E+01
MAD 3.59811E+05
MSD 3.09814E+11


Time Series Decomposition Plot for YTL R02 REMOVED
Multiplicative Model
YTL R02 REMOVED
Index
Variable
Actual
Fits
Trend
Accuracy Measures
MAPE 1.97102E+01
MAD 1.31223E+05
MSD 2.50003E+10


Time Series Decomposition Plot for YTL R02 EQUIVALENT
Multiplicative Model
YTL R02 EQUIVALENT
Index
Variable
Actual
Fits
Trend
Accuracy Measures
MAPE 1.37282E+01
MAD 1.92954E+05
MSD 5.85828E+10

APPENDIX E

PROVING CONCAVITY

In order to determine whether a twice-differentiable function of *many* variables is concave, we need to examine all its second partial derivatives. The Hessian matrix is an NxN symmetric matrix of second derivatives of the function with respect to each variable pair.

$$H = \begin{pmatrix} \frac{\partial^2 f}{\partial x_1^2} & \cdots & \frac{\partial^2 f}{\partial x_1 \partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial^2 f}{\partial x_n \partial x_1} & \cdots & \frac{\partial^2 f}{\partial x_n^2} \end{pmatrix}$$

Proposition 1: Let f be a function of many variables with continuous partial derivatives of first and second order on the convex open set *S* and denote the Hessian of f at the point *x* by *H*(*x*). Then *f* is concave if and only if *H*(*x*) is negative semidefinite for all $x \in S$

Proposition 2: If a square matrix is negative semidefinite then the determinants of the principal matrices have the following pattern:

$$|D_1| \leq 0; |D_2| \geq 0; |D_3| \leq 0...$$

with not all zero [59].

The principal matrices for the Profit per Unit Time (PU) function in our problem:

$$D_1 = \left|\frac{\partial^2 f}{\partial t_1^2}\right| \qquad D_2 = \begin{vmatrix} \frac{\partial^2 f}{\partial t_1^2} & \frac{\partial^2 f}{\partial t_1 \partial t_0} \\ \frac{\partial^2 f}{\partial t_1 \partial t_0} & \frac{\partial^2 f}{\partial t_0^2} \end{vmatrix}$$

Substituting $C_t = c + P_2\, pm_2 - P_1\, pm_1$ in the corresponding determinants we have the following ***concavity conditions***:

1. $$Det\,|D_1| = Det\left|\frac{\partial^2 f}{\partial t_1^2}\right| = \frac{-2\,K + D_2\,t_0\,[-2\,C_t + t_0\,(2\,a\,D_2 - h)]}{t_1^{\,3}} \le 0$$

2. $$Det\,|D_2| = Det\begin{vmatrix} \frac{\partial^2 f}{\partial t_1^2} & \frac{\partial^2 f}{\partial t_1 \partial t_0} \\ \frac{\partial^2 f}{\partial t_1 \partial t_0} & \frac{\partial^2 f}{\partial t_0^2} \end{vmatrix} = \frac{2\,K\,(h - 2\,a\,D_2) - D_2\,C_t^{\,2}}{t_1^{\,4}} \ge 0$$

The maximum of a multivariate function must be found so that all terms of the gradient vector simultaneously equal zero. Again, considering profit per unit time function (PU), we have:

$$\frac{\partial f}{\partial t_1} = 0 \Rightarrow \frac{2K + D_2\,t_0\left(2\,C_t + t_0\,(h - 2\,a\,D_2)\right) + D_1 t_1^{\,2}(h - 2\,a D_1)}{2\,t_1^{\,2}}$$

$$\frac{\partial f}{\partial t_0} = 0 \Rightarrow \frac{D_2\left(2aD_1 t_1 - t_0(h - 2aD_2) - C_t\right)}{t_1}$$

Solving the equations above simultaneously, we find the optimum values of the cycle time (t_1*) and substitution period (t_0*) as:

$$t_1^* = \sqrt{\frac{2\,K\,(h - 2\,a\,D_2) - D_2\,Ct^2}{D_1\,h\,(h - 2\,a\,(D_1 + D_2))}} \qquad t_0^* = \frac{2\,a\,\sqrt{\frac{D_1\left(2\,K\,(h - 2\,a\,D_2) - D_2\,Ct^2\right)}{h\,(h - 2\,a\,(D_1 + D_2))}} - C_t}{(h - 2\,a\,D_2)}$$

Considering t_0 - t_1 relation and assuming $\boldsymbol{t_1,\ t_0,\ D_1,\ D_2 \geq 0}$, the summary of concavity conditions can be given as below:

1. $\left(D_1\,(2\,a\,D_1 - h)\right)^3 \leq 0 \quad \Rightarrow \quad h - 2\,a\,D_1 \geq 0$

$2\,K\,(h - 2\,a\,D_2) - D_2\,C_t^{\,2} \geq 0$

Assuming that the first and second concavity conditions are satisfied, we need $h - 2\,a\,(D_1 + D_2) \geq 0$ for finding an optimal cycle time that is feasible. If the feasibility condition is satisfied, the second concavity condition is already satisfied. Therefore, the second concavity condition does not bring any additional constraint.

Bibliography

[1] OECD Indicators 2007: Health at a Glance. *OECD* Paris; 2007

[2] OECD Health Data 2006, *OECD*, Paris

[3] JHI – John Hopkins International (2004), "Sağlıklı Bir Gelecek: Sağlık Reformu Yolunda uygulanabilir Çözüm Önerileri, *TÜSİAD Publication,* accessed 20th May 2008, Available from World WideWeb: http://www.tusiad.org/turkish/rapor/saglik/saglik.pdf

[4] Zambrowski, J. (2007), "Principles and Methods of Health Economics, Their Role in Evaluation of Medical Practice", Presented at: *Istanbul PharmacoEconomy Meeting*, accessed 15th April 2007, Available from World Wide Web: http://www.farmakoekonomi.org/files/SUNUMLAR/4_MAYIS/ZAMBROWSKI/ZAMBROWSKI.pdf

[5] The Ministry of Health of Turkey (2005), "Sağlıkta Dönüşüm Programı", *T.C. Sağlık Bakanlığı,* accessed 20th March 2008, Available from World WideWeb: http://www.saglik.gov.tr/TR/BelgeGoster.aspx?F6E10F8892433CFF7A2395174CFB32E19ABF9BBCF4C02FA1

[6] Neslin, S., Powell, S., Stone, L. (1995), "The Effects of Retailer and Consumer Response on Optimal Manufacturer Advertising and Trade Promotion Strategies", *Management Science*, Vol. 41

[7] Gür Ali, Ö., Çavdaroğlu, B. (2007), "Pharmaceutical Marketing Mix Optimization and Pharmacy Discounts in Turkey", *14th International Annual Euroma Conference*.

[8] Drezner, Z., Gurnani, H., Pasternack, B.A. (1995), "An EOQ Model with substitutions between products", *Journal of the Operational Research Society*, 46 (7) 887–891

[9] Gurnani, H., Drezner, Z. (2000), "Deterministic Hierarchical Substitution Inventory Models", *Journal of the Operational Research Society*, 51, 129–133

[10] Benton, W.C., Park, S. (1996), "A Classification of Literature on Determining the Lot Size Under Quantity Discounts", *European Journal of Operational Research*, Vol. 92, pp. 219-238

[11] Shin, H., Benton, W.C. (2006), "A Quantity Discount Approach to Supply Chain Coordination", *European Journal of Operational Research,* 180, 601–616.

[12] Araştırmacı İlaç Firmaları Derneği (AIFD). 2006, "Türkiye 2006 Yılı İlaç Harcamaları Değerlendirmesi", accessed 3rd Agu 2007, Available from World WideWeb: http://www.aifd.org.tr/pdf/Haber/140.pdf

[13] Kanavos P., Üstel İ., Costa-Font J. (2005), "Pharmaceutical Reimbursement Policy in Turkey", *Sağlıkta Umut Vakfı (SUVAK) Yayınları*, viewed 19th January 2008, Available from World Wide Web: http://www.suvak.org.tr/kitap-2ingilizce.pdf

[14] *Patent Koruması*, accessed 15th March 2008, Available from World WideWeb: http://www.aifd.org.tr/Yeni-ilac-ve-ar-ge/Patent-Korumasi.aspx

[15] Berkan, İ. (2005, January), "İlaç ve İlaç Sanayi", accessed 5th Feb 2008, Available from World WideWeb: http://www.radikal.com.tr/haber.php?haberno=139369

[16] *Geri Ödeme*, accessed 15th March 2008, Available from World WideWeb: http://www.ieis.org.tr/asp_sayfalar/index.asp?sayfa=250&menuk=12

[17] Ess S. M., Schneeweiss S., Szucs T. D. (2003), "European Healthcare Policies for Controlling Drug Expenditures", *Pharmacoeconomics,* 21 (2), 89-103.

[18] OTC Pharmaceuticals in the United States, Industry Profile, *Datamonito*r, 2006

[19] *Frequently Asked Questions on the Regulatory Process of Over-the-Counter (OTC) Drugs*, accessed 5th July 2007, Available from World WideWeb: http://www.fda.gov/cder/about/smallbiz/OTC_FAQ.htm

[20] Brass, E. (2001), "Changing the Status of Drugs from Prescription Only to Over-The-Counter Availability", *The New England Journal of Medicine*, Vol. 345, No.11

[21] Porter, S. (2007), "FDA Explores Idea of 'Behind-the-Counter' Drugs", accessed 25th May 2008, Available from World WideWeb: http://www.aafp.org/online/en/home/publications/news/news-now/health-of-the-public/20071108fdabtcdrugs.html

[22] Espin, J., Rovira, J. (2007), "Analysis of differences and commonalities in pricing and reimbursement systems in Europe", Final Report

[23] *Basına ve Kamuoyuna 14 Mayis Eczacılık Günü'nde Eczacılar Eylemde! Eczanelerimizin Vitrinlerini Karartıyoruz!*, accessed 16th May 2008, Available from World WideWeb: http://www.istanbuleczaciodasi.org.tr

[24] *Reçetesiz İlaç Sektörü Böldü,* accessed 18th January 2008, Available from World WideWeb: http://www.beo.org.tr/modules.php?name=News&file=article&sid=1122

[25] Örgen, N. (2007), "Sektörel Bakış Açısıyla Akılcı İlaç Kullanımı", Presented at: *Akılcı İlaç Kullanımı ve Farmakoekonomi Sempozyu*mu, accessed 15th April 2007, Available from World Wide Web: http://www.farmakoekonomi.org/files/SUNUMLAR/5_MAYIS/NURGUN_ORGEN/5_MAYIS_AKILCI_ILAC_ENDUSTRI_YAKLASIMI_REVIZE.pdf

[26] *"Raf üstü ilaçlar" ın listesi,* accessed 3rd January 2008, Available from World Wide Web: http://hurarsiv.hurriyet.com.tr/goster/haber.aspx?id=7841048

[27] Türk Tabibler Birliği (2006), "12/09/2006 tarihli Maliye Bakanlığı İlaç Genelgesinin TTB İlaç Danışma Kurulu Değerlendirme Raporu", Available from World Wide Web: www.ttb.org.tr/kutuphane/ilac_danisma_kurulu_raporu.pdf

[28] Ryan, M., Yule, B. (1990), "Switching Drugs from Prescription-Only to Over-the-Counter Availability: Economic Benefits in the United Kingdom", *Health Policy*, 16, 233-239

[29] Gurwitz, J.H., McLaughlin, T.J., Fish, L.S. (1995), "The effect of an Rx-to-OTC switch on medication prescribing patterns and utilization of physician services: the case of vaginal antifungal agents", *Health Serv Res.* 1995;30(5):672-85

[30] Carlsten, A., Wennberg, M., Bergendal, L. (1996), "The Influence of Rx-to-OTC changes on drug sales. Experiences from Sweden 1980-1994", *Journal of Clinical Pharmacy and Therapeutics*, 21, 423-430.

[31] Andrade, S. E., Gurwitz, J. H., Fish, L.S. (1999), "The Effect of an Rx-to-OTC Switch on Medication Prescribing Patterns and Utilization of Physician Services: The Case of H2 - Receptor Antagonists", *Medical Care*, 37 (4), 424-430

[32] Lundberg, L., Isacson, D. (1999), "The impact of over-the-counter availability of nasal sprays on sales, prescribing, and physician visits", *Scandinavian Journal of Primary Health Care*, 17

[33] Harrington, P. and Shepherd, M. (2002), "Analysis of the Movement of Prescription Drugs to Over-the-Counter Status", *Journal of Managed Care Pharmacy*, 8 (6), 499-508

[34] Flowers AS, Cassard SD. (2001), "Coverage exclusion of OTCs and OTC equivalents can lead to higher drug benefit costs", Presented at: 13th Annual Meeting of the Academy of Managed Care Pharmacy; Tampa, FL

[35] Sullivan PW, Follin SL, Nichol MB (2003), "Transitioning the second - generation antihistamines to over - the-counter status: a cost - effectiveness analysis", *Med Care*, 41:1382–95

[36] *RxMediaPharma 2007*, İnteraktif İlaç Bilgi Kaynağı, edited by: Prof. Dr. Levent Üstüneş, 2007

[37] Hanke, E.H., Wichern, D.W., Reitsch A.G., *Business Forecasting*, 7 ed., Prentice Hall, New Jersei, 2001

[38] Munson, C., Rosenblatt, M. (1998), "Theories and Realities of Quantity Discounts: An Exploratory Study", *Production Oper. Management*, 7, 352-369

[39] Dolan, R. (1987), "Quantity Discounts: Managerial Issues and Research Opportunities", *Marketing Science*, 6 (1), 1-22

[40] Edward A. Silver (1981), "Operations Research in Inventory Management: A Review and Critique", *Operations Research*, 29 (4), 628-645

[41] Jeuland, A., Shugan, S. (1983), "Managing Channel Profits", *Marketing Science*, 2 (3), 239-272

[42] R. Lal, R. Staelin (1984), "An approach for developing an optimal discount pricing policy", *Management Science,* 30 (12) 1524–1539

[43] Blattberg R. C., Evin A. (1987), "Modeling the Effectiveness and Profitability of Trade Promotions", *Marketing Science*, 6 (2), 124-146

[44] Lal, R., Little, J., Villas-Boas, J.M. (1996), "A Theory of Forward Buying, Merchandising, and Trade Deals", *Marketing Science*, 15 (1), 21-37

[45] Kumar, N., Rajiv, S. and Jeuland, A. (2001), "Effectiveness of Trade Promotions: Analyzing the Determinants of Retail Pass-through", *Marketing Science*, 20 (4), 382–404

[46] Whitin, T.M. (1954), "Inventory Control Research: A Survey", *Management Science*, 1 (1), 32-40

[47] Sadrian, A. A., Yoon, Y. S. (1994), "A Procurement Decision Support System in Business Volume Discount Environments," *Operations Research*, 42 (1), 14-23.

[48] Li, J., Liu, L. (2005), "Supply chain coordination with quantity discount policy", *International Journal of Production Economics*, 101, 89–9

[49] Sarmah, S.P., Acharya, D., Goyal, S.K. (2006), "Buyer vendor coordination models in supply chain management", *European Journal of Operations Research*, 175, 1-15

[50] Pentico, D.W. (2007), "The assortment problem: A survey", *European Journal of Operational Research*, 190 (2), 295-309.

[51] Parlar, M. and Goyal, S. (1984), "Optimal ordering decisions for two substitutable drugs with stochastic demands", *Operation Research*, 10, 96–100.

[52] Smith, S.A., Agrawal, N. (2000), "Management of Multi-Item Retail Inventory Systems with Demand Substitution", *Operations Research*, Vol. 48, No. 1, pp. 50-64.

[53] Mahajan, S. and Ryzin, V. (2001), "Stocking Retail Assortments Under Dynamic Consumer Substitution", *Operations Research*, 49(3), 334-351

[54] Chand, S., Ward, J.E. and Weng, Z.K. (1994), "A parts selection model with one-way substitution", *European Journal of Operational Research*, 73, 65-69.

[55] Pentico (1976), "The assortment problem with nonlinear cost functions", *Operations Research*, 24, 1129-1142

[56] Pasternack, B., Z. Drezner (1991), "Optimal Inventory Policies for Substitutable Commodities with stochastic demand", *Naval Research Logistics*, 38, 221-240

[57] Bassok, Y. Anupindi. R. and Akella, R. (1999), "Single period multi-drug inventory models with substitution", *Operations Research*, 47, 632-642

[58] Gür Ali, Ö., Çavdaroğlu, B. (2008), "Pharmacy Discounts Under Competition and Interactions with Pull Efforts", *Under review at International Journal of Research in Marketing*

[59] Bazaraa, Mokhtar S., Hanif D. Sherali, C. M. Shetty (2006), Nonlinear Programming: Theory and Algorithms, John Wiley, New Jersey

Vita

Ayşe Başak Çizmeci was born in İstanbul, on August 3, 1984. She graduated from Kocaeli Körfez Science High School in 2002. She received her B.S. degree in Industrial Engineering from Yıldız Technical University, İstanbul, in 2006. In September 2006, she joined the Industrial Engineering Department of Koç University, Istanbul, as a teaching and research assistant.