AN APPLICATION OF NICHE MARKETING FROM TURKISH PHARMACEUTICAL SECTOR; ORPHAN DRUGS

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IŞIK UNIVERSITY

2016

IŞIK UNIVERSITY

INSTITUTE OF SOCIAL SCIENCES

EXECUTIVE MBA (THESIS OPTION,ENGLISH)

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M.A., EXECUTIVE MBA, IŞIK UNIVERSITY, 2016

Submitted to the Graduate School of Social Sciences in partial fulfillment of the requirements for the degree of Master of Arts

in

Business and Administration

IŞIK UNIVERSITY

2016

IŞIK UNIVERSITY

GRADUATE SCHOOL OF SOCIAL SCIENCES

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APPROVAL DATE: 23 / 6 / 2016

ABSTRACT

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English; Within this research, with the application of niche marketing to the Turkish pharmaceutical sector the issue of orphan drugs and treatment of rare diseases which are not only Turkey's but also other countries' problem are evaluated from the marketing point of view. The point which the private and public organizations play crucial role, the aim of this cooperative work is not only to increase its revenue but also its goodwill at pharmaceutical sector. Different areas where public and private organizations work, importance of new product development and R&D, importance of public health, and importance of public education about the usage of appropriate medicine in an appropriate way (rational usage of medicines) are some of the examples.

Throughout this research, the subject of orphan medicines and treatment of rare diseases are being evaluated from the perspective of a private pharmaceutical company's niche marketing applications. Within context of this research, the subjects of legislation contents and market dynamics which are assumed to have a direct link to the niche marketing application of orphan medicines and treatment of rare diseases.

A course of action and possible research made within the context of niche marketing applications which are believed both to increase the goodwill of the company in the market and to alleviate a public health concern while putting forth improving the health conditions of public with maintaining the financial returns at a sufficient level are emphasized with detailed explanations.

ÖZET

TÜRK İLAÇ SEKTÖRÜNDEN BİR NİŞ PAZARLAMA UYGULAMASI; YETİM İLAÇLAR

Türkçe; Bu araştırmada niş pazarlama uygulamalarının Türk ilaç sektörüne uygulanması ile sadece Türkiye değil ancak diğer ülkelerin yaşadığı en büyük sağlık sorunlarından biri olan yetim ilaç ve nadir görülen hastalıkların tedavisi sorununa pazarlama bakış açısı ile ele alınmıştır. Hem özel sektörün hem de devletin önemli bir rol oynadığı bu noktada, ortak yapılacak araştırmalar ile Türk ilaç sektörü hem gelirini artırması hem de marka değerini yükseltmesi amaçlanmıştır. Devlet ile özel sektörün ortaklaşa çalışacağı farklı alanlar, yeni ürün geliştirme ve AR&GE'nin önemi, halk sağlığının önemi ve halkın doğru ilacı doğru bir biçimde kullanması ile ilgili eğitimler örnek verilen araştırmalardan bazılarıdır.

Araştırma boyunca yetim ilaçlar ve nadir hastalıklar konusu özel bir ilaç şirketinin niş pazar uygulamaları bakış açısıyla ele alınmıştır. Araştırmanın kapsamı içerisinde bu alanda yatırım yapmak isteyen bir ilaç firmasının karşılaşabileceği aynı zamanda yetim ilaçlar ve nadir hastalıklar niş pazar uygulamasını doğrudan etkileyebilecek mevzuat içeriği ve pazar dinamikleri de detaylı bir şekilde yer verilmiştir.

Firmanın, hem pazarda iyi bilinirliğini artıracak hem de toplumsal bir sağlık sorununa çözüm olacak şekilde, insan sağlının iyileştirilmesini ön plana alırken aynı zamanda finansal geri dönüşünü de yeterli seviyede tutacak bir dizi eylem planı ve muhtemel araştırmalar niş pazarlama kapsamında detaylı anlatımlarla vurgulanmıştır.

DEDICATION

To my parents for their moral support,

and

To my advisor Prof. Dr. Murat Ferman for sharing his guidance and expertise…

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LIST OF ABBREVIATIONS

Bağ - Kur: Esnaf ve Sanatkârlar ve Diğer Bağımsız Çalışanlar Sosyal Sigortalar Kurumu (Social Security Organization for Artisans and the Self Employed)

BTC: Behind The Counter

CAD: Computer Aided Design

CAM: Computer Aided Manufacture

E.S. : Emekli Sandığı (Social Security Organization for Civil Servants)

EFPIA: European Federation of Pharmaceutical Industries and Associations

EU: European Union (Avrupa Birliği)

EUR : Euro

FDA: Food and Drug Administration

GBP: Great Britain Pounds

GMP : Good Manufacturing Practices

IEIS : İlaç Endüstrisi İş Verenleri Sendikası (Pharmaceutical Industry Employers Union)

INRUD : International Network for Rational Use of Drugs

JPPI: Joint Public Private Initiatives

MEA: Middle East and Africa

MSB : Milli Savunma Bakanlığı (Ministry of National Defense)

NGO : Non - Governmental Organization

OTC: Over The Counter

R&D: Research and Development

SAN - TEZ : Sanayi Tezleri AR&GE Programları (Industry Thesis R&D Programs)

SGK : Sosyal Güvenlik Kurumu (Social Security Institutions)

SPC : Supplementary Protection Certificate

SSK : Sosyal Sigortalar Kurumu (Social Insurance Institute)

TEYDEB : Teknoloji ve Yenilik Destek Programları Başkanlığı (Technology and Innovation Funding Programs Directorate)

TİG: Teşhis İlişkili Gruplar (Diagnosis Related Groups)

TL: Turkish Liras

TRIPS: Trade Related Intellectual Property Rights

TSK : Türk Silahlı Kuvvetleri (Turkish Military Forces)

UNFPA: United Nations Population Fund

USD: United States Dollars

VAT : Value Added Tax

WHO : World Health Organization

WTO : World Trade Organization

INTRODUCTION

Niche marketing applications are gaining importance day by day on the field of marketing. Within the context of this research study; the issue of orphan drugs is researched from the niche marketing point of view. Niche marketing as its characteristic features is expected to answer all the objectives of this study. Within the context of this study, we are looking for the possible actions which can be taken both as preventive and as solution to rare diseases through the applications within the context of marketing of orphan drugs and treatment of rare diseases. According to the field of marketing, the patients who are suffering from rare diseases are considered and mentioned as niche markets. In this graduate thesis study, we discuss that how can the niche marketing applications can be applied to the orphan drugs issue and treatment of rare diseases.

There are approximately 5000 to 8000 rare diseases recorded and only %1 of those diseases has an approved orphan drug used for their treatment. Rare diseases are usually life threatening, chronic and devastating diseases. Most of the rare diseases underneath causes are still unknown which leads to latency and errors at diagnosis and prognosis of those diseases. Despite the very small amount of patients, if multiple of those rare diseases are combined and focused together, with the combination of the both foreign and domestic markets, the outcome of this graduate thesis study not only creates an opportunity for the alleviation of a problem of public health but also creates a financially viable and profitable business opportunity for the firm which has interest about making investments in orphan drugs and treatment of the rare diseases.

According to the statistics published online and from other resources, one can easily see that many countries, especially the countries located at the African continent and eastern Europe countries are unaware of those rare diseases presence and most of the countries are unable to take preventive and total solution oriented action against this orphan drug and rare diseases issue. If a marketing analyst looks at the issue from only the diseases point of view he or she can easily see that there are very few number of patients who are suffering from rare diseases.

However, if that analyst can combine both domestic and foreign markets he or she can bring the same issue to both local and foreign governments' attention both, he or she may not only generate an important financial profit to his or her company but also addresses a public health problem at the same time. If we take into consideration that in many markets around the world the applications of the WTO's TRIPS and high selling prices to the high cost of orphan drugs; these factors are making difficult for the patients to purchase the orphan drugs. Therefore the importance of this graduate thesis study can be summarized around this focus point; the application of the niche marketing to the orphan drugs and treatment of rare diseases is important because running a pharmaceutical company is not only about making profits but also saving lives especially at the right time and at the right place. For a pharmaceutical company being at the right place and at the right time is possible with niche marketing applications which are going to be explained throughout this graduate thesis study.

Since the discipline of this graduation thesis study is marketing, our viewpoint of medicine and pharmaceutical applications will be primarily focused on marketing of orphan drugs and treatments of rare diseases. Subjects which are going to be explained (again within the niche marketing context) can be briefly given as follows; market components of pharmaceutical industry, basic specifications of product and services of pharmaceutical markets, product components of Turkish pharmaceutical industry, market of niche drug (orphan drugs and rare diseases), niche marketing applications at pharmaceutical sector, market analysis, coordination of public institutions at reaching niche markets, niche markets strategies, niche markets and competition and conclusion. Overall conduct of this graduate thesis study will be focused generally on Turkish pharmaceutical industry, however information about foreign niche markets will be given within the context of exports of Turkish pharmaceutical sector.

CHAPTER 1. PRINCIPLES OF NICHE MARKETING AND IT'S THEORETICAL FRAMEWORK (ORPHAN DRUGS AND TREATMENT OF RARE DISEASES)

1.1 The Concept of Niche Marketing

New demands, changing customer motivations and further individualization (both business to business and business to consumer marketing), have created a multitude of diverse and fractured markets in contrast to what once was a simple mass market.

1.1.1 Definition of Niche Marketing

Niche marketing is a special type of marketing application primarily focused on very small markets. Niche market can be considered a small market consisting of an individual customer or small group of customers with similar characteristics of needs. There are two main approaches which can be addressed with clear distinction;

1. A process of carving out a small part of the market whose needs are not fulfilled. By specialization along market, customer, product, or marketing mix lines, a company can match the unique needs
2. Last stage of segmentation, taking place in the following sequential stages; segmentation, targeting, positioning and niching. Dalgic et al[32]

The distinctive feature of these niche markets is that their size is very small and contains customers with very rare needs compared to the customers of other markets. Kotler et al[3] Niche markets are of a special type of segments which many large firms usually cannot reach. Therefore with the information above we can create a brief definition of niche marketing as follows; " Addressing with adapted and devised products to a small group which has similar characteristics and needs which are not satisfied yet."

Niche marketing has an important standing from the financial profitability and goodwill generation points of view as we are going to observe at the subsequent chapters. Niche markets can be relatively small compared to the conventional markets however they are consisting the potential to grow up and some huge markets in today's world are consisting with the growth of the once niche markets. There is an important point with the "size" and "growth speed" of the niche markets. If the niche markets are growing too fast, this poses a threat to the companies which are operating inside of that market. However with various marketing applications such as the inability of the duplication of existing products in the market or developing strong relationship with the CRM applications, relationship marketing and database marketing in order to deliver a value added product and service to the customers are making the entry to that "niche" market to the outsiders and creates a "wall" for them. Therefore clear distinction and identification of "niche" markets are important.

1.1.2 Evolution of Niche Marketing

After the World War II, with the social changes and technological advancement, mass markets are divided into fragmented markets. In time, those fragmented markets evolve into smaller markets. Therefore it became impossible for the mass marketing applications and their standardized products to meet the different needs and expectations of those small "niche" markets. Niche marketing, taking "unsatisfied needs" as its basis, has more potential at satisfying the needs of these niche markets special needs with its customized products than mass marketing applications.

Increased competition at global markets makes it difficult to survive for the smaller firms against their opponents who are large corporations. Therefore these smaller firms are protecting themselves with targeting niche markets which are not favored by the large corporations and are able to work with large profit margins with the services they provide. However because of these large profit margins, there is always a competition risk related with those small markets. In order to avoid with this risk, companies should establish long term and strong relationships with their customers.

Especially after the World War II, mass marketing applications are evolved into fragmented market applications due to the factors that; increase at the number of families without children and has double income, increase of number of working women and minority markets, changes at lifestyles, increases at the number of hours that individuals spent by themselves, decreasing effect of television advertisements and brand loyalty, and lastly shrinkage of the medium class. In time these fragmented "small" markets are turned into more smaller markets. Then these markets are named as "niche" markets. Rapp et al [34]

Niche marketing are named in foreign literature as "target marketing", "focused marketing", "concentrated marketing", and "micro marketing". But the mostly used named for this application is "niche marketing". In Turkish literature this niche marketing is named as "köşe tutucu pazarlama" or "niş pazarlama".

1.2 Circumstantial Requirements for Identification of the Niche Markets

First of all in order a market to be defined as "niche", identification of the unsatisfied needs inside of the market is required. Then ensuring the product offered to that prospective niche market is differentiated enough in order to initiate the procurement action (which is purchasing) of the prospective customers and as a last step company should inspect that prospective market is suitable for the protection against competition. For the initiation of the procurement action, the product offered should deliver the upmost value to the customers. In order the company is able to protect itself against competition, product should be devised for not to be duplicated easily by the competitors.

Since market segmentation is important both for the identification and devising further niche marketing strategies in accordance with the identification, we now shall discuss the relationship between market segmentation and niche marketing.

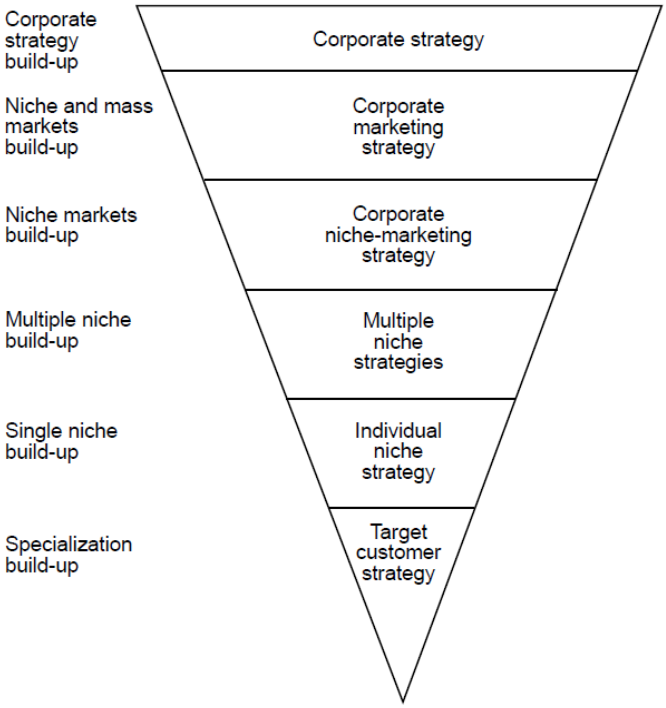
1.3 Relationship Between Market Segmentation and Niche Marketing

The main objective of marketing, is the satisfaction of the needs of the target market better and more efficient than other competitors. In today's world fragmented market environment application of niche marketing is much more suitable than the conventional mass marketing applications. However before the niche marketing applications are preferred, the company should be very careful about identifying its target markets segmentation. This is possible with the market segmentation approach. It is often assumed that segmentation is a starting point in niche marketing however since niche marketing has distinctive features such as market size and differential needs, niche marketing market segmentation should be evaluated differently. Since conventional segmentation is process of breaking a large market into smaller pieces and this is a top-down approach however niche marketing should be a bottom up approach where the marketer starts from the needs of a few customers and gradually builds up a larger customer base.

This in contrast with breaking up a market into smaller markets. This view opposes the concept which perceives niche marketing as the last or final stage of segmentation. With this respect let us emphasize the niche markets distinctive characteristic features once again; Dalgic et al [32]

- A niche is usually smaller in size compared with the size of segment.
- A niche focuses on individuals – in a segment we focus on a so – called homogenous group.
- A niche fulfills a specific need in contrast to a segment where emphasis is on being a manageable part of the market.

Here is a schematic from Dalgic et al [32] about the bottom up approach of niche marketing with a schematic.



Kotler et al[33] suggest that the key idea in niche marketing is specialization and he provides the following ways to specialize;

- End User Specialization.
- Vertical Level Specialization.
- Customer Size Specialization.
- Geographic Specialization.
- Product or Product Line Specialization.
- Product – Feature Specialization.
- Job – Shop Specialization.
- Quality / Price Specialization.
- Service Specialization.
- Channel Specialization. Kotler et al[33]

Another brief information about the distinctive differences between niche marketing and market segmentation practices as given below; Albayrak[31]

Market Segmentation	Niche Marketing
Top down approach.	Bottom up approach.
Takes differences as its basis.	Takes similarities as its basis.
All market segments assumed to be similar.	Even a single customer can be the primary objective.
Relatively big.	Relatively small.
Takes existing products as its basis.	Takes unsatisfied demands as its basis.
Focuses on homogenous groups.	Focuses on individuals or small groups.
Objective: Manageable small parts.	Objective: Satisfaction of the small needs.

We may conclude that niche marketing could be defined as positioning into small, profitable, homogenous market segments which have been ignored or neglected by others. This positioning is based on the integrated marketing concept and the distinctive competences the company possesses.

The previous definition addresses five essential elements of niche marketing;

1. Positioning.
2. Profitability.
3. Distinctive Competences.
4. Small Market Segments.
5. Adherence to the Marketing Concept.

Other essential elements not mentioned explicitly are long term relationships and company reputation. Within the context of this research study, as going to be emphasized in the subsequent chapters especially at "Chapter 6", generation of the goodwill of a pharmaceutical company can increase its profits and therefore long term sustainable growth and presence both at the target niche market and other bigger markets in which it operates. In niche marketing, long term and strong relationships are of key importance. In order to develop them the marketer should practice relationship marketing and database marketing.

1.4 Relationship and Database Marketing in Relation with Niche Marketing

In order to success at niche marketing, it is important to maintain and establish strong and long termed relationship between the company and its customers. Through only this way customer retention is possible.

1.4.1 Relationship Marketing

Relationship marketing is used by a company which establishes, sustains and expands the coverage with the enrichment of the relationship between customers and other business partners. Relationship marketing enables of establishment of long term, strong economic, technical and social bonds.

These established bonds enables the marketer company to adapt itself to be customer oriented. Therefore company evolves itself to be able to adapt itself to the changing market environments and quickly response to the customer needs and observe the "gaps" in the market. From this perspective applications of relationship marketing is important for the niche marketing. Within the context of this research study we have applied to the relationship marketing applications under the title and name of niche marketing with getting the company to know the customers well and acting against the certain demand occurs in future quickly. Further discussion can be found in "Chapter 6". To look a little more detail to the relationship marketing we are continuing with the different levels of relationship marketing.

1.4.1.1 Different Levels of Relationship Marketing

Relationship marketing can be applied at three different levels.

1. At this first level, "price motive" is used to initiate the trade between prospective customers.
2. Second level, price motive is still used but company seeks different ways to communicate with the customer and establish relationships. Company therefore is able to understand the needs of the customer and devise its products and service in accordance with that.
3. At the third level, company continues to use financial and social relationships with the customer but this time in addition with these current relationships, company now tries to add "structural" relationships.

These structural relationships are established with the value added services which are devised for not to be duplicated by the rival companies.

Therefore company should main the current and establish new strong relationships with both the prospective and current customers at its target niche market with engaging social and financial activities.

1.4.2 Database Marketing

In order to apply the relationship marketing companies should satisfy also from the database marketing. Database marketing is used to establish connection with the prospective and current customers, to make process with them and to retain them. At the same time database marketing emphasizes the importance of usage of database systems in order to reduce the costs of the overall marketing expenses. With using database systems a company can divide the existing markets with more accuracy, reduce the market research costs and increase efficiency when evaluating the inventory.

Database marketing enables the company not only reduce the market research costs but also detecting customers with high and low profit margins, therefore focusing on only customer who has high profit margins. With this way, devising new products and services which are suitable to the needs of the customers are possible.

In this research study database marketing is used under the name of niche marketing such as developing statistical database about the prevalence and indices of rare diseases which are very important for the management of the marketing operations and therefore new product development. Statistical information and data about location, density of diseases, and information about medicines are very useful for the market analysis and calculations.

Simultaneous usage of relationship marketing and database marketing enables the company to build protective walls against the rival companies within the niche market is one of the advantages of the niche marketing.

The other concept of major importance to niche marketers is reputation. In niche marketing marketer do not only market the product, he or she market the business; reputation is key. Solid reputation in the minds of the customers is essential to be successful niche marketer.

1.5 Niche Marketing Practices at Large Corporations

Niche marketing for larger firms could be;

- New opportunities for healthy profits in smaller markets.
- A new approach to the market from uniform to fractured.
- Smaller profits per market, but more market.
- An easier defense against potential competitors, by creating safe heavens.
- Structural internal organizational adaptation which due to inherent cultural changes, could be lengthy process.

Most of the large organizations such as Johnson and Johnson which affiliates 170 small business units focused on pursuing niche markets, are abandoning traditional mass marketing techniques and are steadily switching over towards niche marketing. Niche marketing, from the viewpoint of the larger firm, may be seen as selling big by selling small, meaning selling to as many niches as possible, where each niche is a small market aggregating into a large one.

Customer focus helps companies to respond faster to the dynamic changes in customer demand but it takes more than customer focus to become successful niche marketer because an essential requirement for approaching markets however is for the company to focus on the fragmented, ever evolving customer base as if it were part of the own organization. It is about focus on the customer, specializing on the customers' unique needs, finding better ways of doing what the customer values, educating, and informing the customer, commitment and care.

The product should not be just a "thing" but should include added values like service, good, customer perception, quality, company image and etc… In niche marketing marketer do not only market the product, marketer also market the business.

1.6 Comparison of Niche Marketing with Conventional Mass Marketing

As the marketing concept holds "that the key to achieving organizational goals consists in determining the needs and wants of target markets and delivering the desired satisfaction more effectively and efficiently than the competitors". This concept is better suited to the niche marketing in today's world fragmented markets, because niche marketing functions closer to the customer. Niche marketing has recently become a trend as a result of severe competition in mature markets. Standardized mass production and trying to sell the same product to masses of customers seems to become less profitable in these mature markets.

At past, there is a certain understanding that mass production and mass marketing were the most advanced and efficient methods to produce and market products. Today most of the marketing experts are making the debate of whether focusing on standardization of mass marketing or focusing on customization or tailored products of niche marketing.

We can give a brief information about the certain differences of mass marketing and niche marketing; Albayrak[31]

Mass Marketing	**Niche Marketing**
Production approach	Modern marketing approach
High production amount	High profit margin
Standard product	Differentiated product
Intense competition	Competition is very few or none
Central and bureaucratic organization	Flexible and centrifugal organization
Target: Entire Market	Target: Small group whose needs are not satisfied.

In mass marketing (undifferentiated marketing) a company attempts to reach buyers with one product with one marketing mix. In the product oriented era of marketing so called mass marketing strategy was pursued by many companies. Coca Cola for example which was only available in one flavor and in one type of bottle. In this era entrepreneurs perceived the market as one aggregated market, predominantly focusing on the common needs of the customers instead of focusing on differences. Mass marketing is still used at undifferentiated products such as sugar, salt and milk. But even these are becoming more and more differentiated. The most important aspect of the mass marketing is that marketers can attain the over cost leadership by making units of a fairly standardized product and “underpricing” everybody else.

The difference between mass marketing and niche marketing can be characterized by differences in organizations. A mass marketing company can be characterized as being centrally led and bureaucratic which may led to inflexibility. Niche marketing organizations can be characterized as being decentralized, with several strategic business units if the company is large, if the company is small it can be characterized as being concentrated on one part of the market.

Financially profitability of Niche Marketing – The main reason is that the niche marketer ends up knowing the target customer well that he meets better than other firms that are casually selling to this niche. As a result, the niche marketer can charge a substantial markup over costs because of the added value. The niche marketer achieves high profit margin whereas, the mass marketer achieves high volume.

1.7 Product Classification and Niche Marketing

Companies can choose whether to focus on mass marketing or niche marketing with also looking at this contributive factor which is the product classification. Whether the product classification is a commodity product or a specialty product. If the company chooses to serve commodity markets must be low cost producer. Specialty manufacturers are less concerned with cost; they must isolate the customer segments they wish to serve and develop a superior product at an appropriate price. But the important point is; even when a product can be classified as a commodity a niche marketing approach can be successful. For example with the Coca – Cola's Diet Coke. Diet Coke contributes only %4 of Coca Cola's sales volume and might be considered as a narrow segment or niche however it contributes more net profit from in home sales than the main product.

As of niche marketer characteristics we can count the, ability to segment the market creatively, focusing activities only on areas where company has particular strengths that are especially valued, efficient use of R&D resources, using them where they can be most effective and thinking small; adopting a "Small is beautiful approach".

Also as of niche marketing company characteristics, we can count the offering high value, charging a medium price, creating a new experience curves and shaping a strong corporate culture and vision.

1.8 Financial Viability of Niche Marketing (Return on Investment Comparison)

According to the Linneman and Stanton based on their reported study, carried by "Strategic Planning Institute" named "Profit Impact of Marketing Strategy" which investigated hundreds of business units from different types of businesses. It was reported that the return on investment from larger markets averaged %11. By contrast, the return on investment from smaller markets(niche) was %27. This supports the niche marketing approach. Rapp et al [34]

1.9 Relationship of Niche Marketing and Product Life Cycle Model

Most companies start as niche marketers and evolve into mass marketers as their product life cycles tend to develop into maturity and once maturity is reached and saturation starts, innovation occurs and former mass markets tend to return to niche markets. A similarity which can be notified between a large niche marketer however controls aggregated linked niche markets in contrast to just one large market. A combination of mass marketing and niche marketing approach can be found in mass customization. Technological advances such as CAD/CAM made it possible for marketers to customize their offerings for individual buyers. Some car manufacturers, for example, like BMW and GM, offer their customers, within some constraints, the opportunity to custom design their cars. Rapp et al [34]

1.10 Selection of Niche Strategies

When a company should choose a niche strategy?

- If the company concerned has the ability to approach a niche in a specific manner, better and different than others.
- If the company is able to create a considerable amount of goodwill in a relatively short period of time in order to deter potential competitors.

Niche marketing strategy can be employed also for;

- To avoid competition/confrontation with larger competitors and to devote its energy to serving a unique market.
- To enhance an opportunity.
- Survival.

Niche marketing applications can also be used to penetrate large markets or existing segments, as was done with ORAL-B, the children's toothpaste: a weak spot discovered in the toothpaste market and was subsequently filled by positioning ORAL-B as a niche brand.

1.11 Phenomena of Hyperniching

Company should be very careful when exercising the niche marketing about the inherent of hyper – segmentation which is selecting niches which are too small. This can be countered with contra-segmentation which is joining several niches. Within the context of this research study, a pharmaceutical company cannot avoid or ignore the niches which are too small because as the human life matters, the pharmaceutical company should combine the existing niches as much as possible to deliver the upmost utility to the patient and receive the most profit out of the niche marketing applications. See "Chapter 6" for the detailed discussion.

A marketer should take into account the following points before identifying and selecting a niche strategy;

- Realizing a sustainable competitive advantages with products in specific markets.
- Advantages must be based on long term interests of customers.
- Long term interests can be transformed into long lasting relationships with different interest groups.
- Taking initiatives to sustain relationships.

1.12 Niche Marketing and It's Role In Pharmaceutical Sector

Niche markets are of a special type of segments which many large firms usually cannot reach. Niche marketing has an important standing from the financial profitability and goodwill generation points of view. As we are going to see in the subsequent chapters, a company who would like to participate at pharmaceutical sector with niche marketing can generate goodwill at that country while abdicating its profits to a reasonable level.

Within the context of the pharmaceutical sector, niche marketing can be applied on the orphan drugs and rare diseases. Since the primary focus point of this application is human health, niche marketing application is of crucial importance. The limitation within the context of this research comes with a surprising fact that many countries who are having difficulties with rare diseases and orphan drugs are not calculating the total size of their rare diseases market and most of them are not aware with the existence of the current niche markets of rare diseases. Since every citizen living in those countries has the same right to be cured, unawareness at public institutions are making the situation more difficult.

We have to emphasize the philanthropic side of this issue with supporting that fact with goodwill returns for the company because many companies and governments are sharing the idea that excessive amount of costs burden with the company are not subsidized financially because of the very small size of the market. However this is a wrong approach to the issue even within the marketing point view of business and administration since every life of human being matters.

1.13 A Detailed Look to the Niche Markets at Pharmaceutical Sector

We have look at the niche markets at pharmaceutical sector at three different pillars;

1. Niche market products on account of the techniques and methods of medicine production(Biotechnological Products).
2. Niche market products on account of the indications and number of patients (Orphan Drugs and/or Rare Diseases)
3. Niche market products on account of the personally customized pharmaceutical treatment products and methods.

1.13.1 Biotechnological Products

Oncology, blood products, insulin products and vaccine products are niche markets that comes forth compared to the other fields with their increasing volume at the world pharmaceutical market.

At the same time, the size of the biotechnological products market is enlarging. In today's world, %20 of the world pharmaceutical market is consisting of biotechnological products and it is forecasted that this market size will be larger in the future.

As calculated in 2011, the bioequivalent medicines which consists of the %1.1 of the biological pharmaceutical sector is expected to enlarge 10 times within the 10 years period.

As started in Europe, the bioequivalent medicine production are concentrated at developing countries (such as China, India, South Korea) and countries such as Brazil and Mexico are creating funds for the biotechnological products.[5][6]

1.13.2 Orphan Drugs / Rare Diseases

There are known approximately 5000 to 8000 different rare diseases worldwide, only %1 of them has an approved orphan drugs for treatment. These rare diseases are usually threatening the life, chronic, devastating diseases which their underlying cause is still unknown and usually with diagnosis, the latency and errors are observed. % 6 - 8 of the entire public is affected and their prevalence are very rare.[7]

In 1983 at USA, and at EU in 2000, the first regulations are legislated, countries are giving incentives for the R&D projects of these orphan drugs. Especially, recently the research projects are accelerated and 12 orphan drugs are being approved by FDA (Food and Drug Administration) in USA. According to the report published by the Oprhanet, there are 72 orphan drugs in the EU member states, and 11 of them are considered as ultra rare. [5][6]

1.13.3 Personally Customized Pharmaceutical Treatment Products and Methods

Personally customized treatments are gaining importance at worldwide. Two different patients with same diagnosis can respond differently to a treatment. Personally customized treatments are important and has a potential in pharmaceutical market because of the factors of minimizing the side effects, more secure, patient benefit improvement and more efficient. [5][6]

CHAPTER 2. AN EXAMPLE OF NICHE MARKETING APPLICATION IN PHARMACEUTICAL SECTOR

2.1 Orphan Drugs/ Treatment of Rare Diseases (Access of Government and Patients to Medicines) Supply

2.1.1 What is Orphan Drug?

Orphan drugs is the definition given to the drugs which are specialized to alleviate and cure the rare diseases. The term of orphan is used because usually these drugs are not in the payment list of many countries because of the very small size of its market and its high costs. As we have emphasized above that many countries public institutions are not calculating the actual size of the rare diseases and therefore the orphan drugs.

EU has funded with the cooperation of different countries from its union members that an organization named Orphanet. This organization has gathered many countries rare diseases and orphan drugs statistics with their prevalence data sets, medicines with trade names corresponding to those rare diseases and their substances are given as a list. Unfortunately that system does not have any price or availability information regarding to the orphan drugs.

In Turkey a system named Rx is used to monitor the price, availability and all relevant information about any drug which are sold within the Turkish pharmaceutical sector. However solely based on orphan drug versions of this system is not available in many countries.

2.1.2 Supply of Orphan Drugs

Orphan drug policy of government should cover the upcoming supply system and the role of government at this point is important. Among different options, the choice should be made according to the factors of existing public structures, the balance and relationship between public sector and private sector and other factors.

We have two different options;

1. **Direct Distribution Systems;** the prices of orphan drugs are adjusted with offers but the medicine itself is supplied directly with taking into account the existing conditions.
2. **Main Distribution Systems;** contracts are negotiated with one main supplier who supplied the to the regions and to the facilities of distribution.

With a good coordinated supply system, reduces the waste and increases the benefits of orphan drug manufacturers from the public funds that are allocated to that orphan drug. And also this will increase the trust to the public healthcare services offered and contribution of patients to the system.

Government should analyze the options carefully and take decisions with taking into consideration of long term investments before establishing field warehouses.

2.1.3 Basic Procurement of Orphan Drugs

Procurement of medicines and healthcare services are consisting a huge amount of over the total of expenditures therefore expenses for health are playing a deterministic role at this point. Procurement of medicines are playing an important role on over the total of health expenditures also. Therefore governments should establish a system of procurement for efficiency. The very same policies can be used by the private sector also.

WHO, UNICEF, UNFPA and World Bank has gathered 12 principles for good procurement practices for medicines which are can be gathered under 4 different titles; [9]

1. Procure the medicines at right amounts and with upmost expense efficiency.

2. Licensing the trustable suppliers for high quality products.

3. Ensuring the distribution is made on time.

4. Making possible with the very least expense.

2.1.4 Application Principles of Good Procurement of Orphan Drugs

Efficient and Transparent Method

1. Different procurement and procedures processes should be handled separately and be conducted through separate offices and committees.
2. Procurement procedures should be transparent in accordance with the legal legislations.
3. Procurement process should be pre planned, its performance monitored, and supervised periodically.

Choosing the Medicine and its Amount

4. Public procurement of medicines extent should be limited with the list of national basic medicines.
5. Procurement documents should be categorized with the medicines generic names.
6. Ordering amounts should be adjusted in accordance with the realistic forecast of demands.

Financing and Competition

7. Mechanisms ensuring the secure financing for procurement the medicines should be established.
8. Maximum amount of medicines should be procured if possible.
9. Public supply should be based on competitive procurement methods.
10. Members of the sales group should comply with the supply contracts.

Choice of Supplier and its Quality Assurance

11. A supervisory system for supplier licensing should be established.
12. Procurement should be conducted in accordance with the international quality

2.1.5 Guide for Orphan Medicine Donation

WHO is making cooperation with the local NGO's for maximum benefit from the orphan medicine donations. This cooperation has created a guide both for donators and patient who are receiving them. The total content of this guide has 12 guidelines and can be gathered under 4 different titles.

1. Orphan medicine donations should provide the maximum benefit for the patients in need and satisfy their needs totally.

2. Orphan medicine donators should respect to the countries legislations and legal authority.

3. There should be no double quality principle at the orphan medicines.

4. Maximum contact between donators and patients who are receiving them is important.

2.1.6 Emergency Kit for Orphan Medicines

Huge amount of people's requirements or a sudden move of refugees can generate a large amount of emergency medical needs therefore the emergency kit of orphan medicines is of critical importance.

2.2 Public Awareness About Orphan Drugs and Rare Diseases

2.2.1 Medicine Information Centers

As expressed before that the very reason behind of the inappropriate usage of medicines is the lack of information. The only information that can be gained from public about the medicine product is its prospectus therefore medicine information centers plays an important role for satisfying the need of independent medicine information.

Rare Diseases / Orphan Drugs Information Centers can be established by local government and conducted and/or it can work under the roof of an educational hospital. However working under the roof of an educational hospital is a more reasonable choice because the information that is given from these centers are needed 24 hours a day.

Also if these centers operations can be conducted in cooperation with the supplying information based NGO's, these centers can be more effective. Some information centers has started operating with a single manual and enlarged itself as an information resource and requires licensing now. These kind of information centers are experiencing difficulties through bureaucracy because of trying to do many things in small time.

2.2.2 Medicine Bulletins

Medicine Bulletins are very helpful about supplying unbiased information to the prescribers and patients. When these bulletins are published by the regulatory institutions their content tend to be more medicine focused, on the other hand when they are published by the educational institutions and NGO's their content tend to be more disease focused.

2.2.3 Patient Knowledge and Education

Patient knowledge is an omitted but an important subject especially at developing countries. Most of the medicine programs tend to give more education to prescribers about effective prescribing techniques which aims the patients to use more rational medicine usage and stocking the most required medicines.

According to the analysis made, most of the people are using medicines without consulting to a physician and they provide the medicines from different sources including the unofficial sources. At this point patient knowledge about drug usage has an important point.

Patients require the education about the rational medicine usage. This is important for increasing the patients commitment to treatment, and maximizing the benefit of those from the treatment.

Public education about this issue at a broad perspective is important, for the patients individual decision whether to take the medicine or not and to understand the potential benefits and risks of medicines taken.

Direct interventions to patients about this issue is effective only if they are focused on the irrational medicine usage. The criteria's to prioritize the issue's should take into consideration the magnitude of the issue, health issue's seriousness and its costs.

Public Education Principles Which Leads The Rational Medicine Usage

1. Public education of rational medicine usage should be added to the national medicine policy.

2. Public education should be aimed for the most important subjects and the primary focus should be the information of the patients itself.

3. Public education should support rational decision making and should cover the basic concepts of medicine action. Example of these actions are deciding whether to treat on his/her own, deciding whether to have a professional help, which situations does not require medicine treatment, and how to read a medicine tag, or patient information.

4. Cultural differences and social factors should be taken into consideration.

5. NGO's, educators, professional organizations, communities play important role at public education and should participate at planning, development and conducting processes.

6. Education programs should have open and measurable objectives. At this point the difficulty of changing the rooted beliefs and applications should be accepted. Creating awareness and therefore create a change in behavior requires a multiple step approach.

2.2.4 Rational Medicine Usage

Educational programs should be long and sustainable. Short campaigns especially with the usage of media can increase the short term awareness but has a little effect on changing behavior of public. The most effective of these educations is to add them on the school curriculum at the early age of the public. Another model is to educate the matures like the literacy education.

CHAPTER 3. MARKET COMPONENTS OF PHARMACEUTICAL INDUSTRY

3.1 Manufacturers

In general there are approximately 300 pharmaceutical companies both importers and manufacturers are currently operating in Turkey's domestic pharmaceutical market.

3.1.1 Situation In Turkey's Domestic Manufacturers

Turkish pharmaceutical sector consist of approximately 67 manufacturing companies in total. Among those 67 manufacturing facilities there are 12 foreign companies facilities and 55 domestic companies facilities. There are 7 domestic companies which have entered among the top 20 pharmaceutical companies operating in Turkey on sales growth basis[11]. According to the IEIS those 7 domestic firms can be given as follows Abdi İbrahim, Bilim, Ulagay, Ali Raif, Nobel, Santa Farma, Mustafa Nevzat[1].

3.1.2 Global Manufacturers in Turkey

Some of the global pharmaceutical companies have their own manufacturing facilities in Turkey, among those firms some of them can be given as follows; Pfizer, GlaxoSmithKline, Zentiva and other firms which hold the majority in number are only in the market, selling with their product via importing to the domestic market such as Abbot, Boehringer Ingelheim, Merck Sharp Dohme[11].

3.2 Pharmaceutical Import Companies

According to the Ministry of Health of Turkish Republic statistics there are approximately 34 import companies operating in Turkish pharmaceutical market.[11][12] These companies' primary focus of pharmaceutical product groups can be exampled as follows; Proprietary medicinal product, blood medicines, some medicines which has controlled discharged ability, insulin and cancer medicines[10][13].

Import companies are helping the domestic market to reach the medicines that manufacturing companies are unable to manufacture because of it high technology manufacturing requirements and low demand from its patient[13].

As we are going to see in later sections of this study, some orphan medicines has a quite high costs because of the reasons given previously and some come companies are even unable to import these medicines and therefore this inability of import of those orphan drugs stimulates the situation rare diseases into a common public health issue. However import companies activities are crucial due to its role of increasing the product range of manufacturing companies which is important for the ease of purchase made both from government and the public.

3.3 Government Medicines Production

As well as the both foreign and domestic manufacturing companies are operation, Turkish Republic government are also produces medicines. There are only 2 facilities they have, which are SGK Pharmaceutical Products and Medical Devices Manufacturing Institution and Ministry of National Defense Army Pharmaceutical Manufacturing Facility.[14]

3.3.1 SGK Pharmaceutical Products and Medical Devices Manufacturing Institution

In general SGK manufacturing institution has a 28 product range. Some of these medicines are pain reliever, some of them are the combinations of antibiotics and vitamins and the remaining part is the combination of serum and antibiotic liquids. These product groups are chosen on purpose, in order to support the SGK hospitals and clinical facilities with other medicines than inject able vaccines[14].

3.3.2 Ministry of National Defense Army Pharmaceutical Manufacturing Facility

Within the production capacity of Army Manufacturing Facility there are 5 product groups which are;[15] [16]

1. Ampoule drugs

2. Tablets, capsules and blistering section

3. Bandage and dressings section

4. Medical solutions

5. Ointment and Sachet sections

In addition to these there are also diagnosis and control division and also the quality control section. We can give examples of the main objectives of this institution as; [15][16]

1. Satisfying the pharmaceutical products and medical tools needs during the times of massive mobilization and daily usage of the TSK with reducing its foreign dependence on this subject.

2. Conducting R&D in coordination with the universities, ministry of health and department of sanitation to produce the medicines with upmost quality.

3.4 Public Institutions (Public Hospitals and SGK) Procuration System

Here the procuration system is used to describe the public institutions pharmaceutical buying processes. According to the public bidding law and corresponding circular letters; government is purchasing and acquiring medicines through 4 different types of acquisition and bidding methods. These are;[18]Semerci[19][20]Akyürek [21]

1. **Open Bidding Method**; in which all bidders can give bid proposals.[17][18]

2. **Bidding Among Specific Bidders**; bidders can enter and give bid proposals only if they are invited according to the pre evaluation results. This type of bidding is applied when the product and/or service that is planned to be acquired requires high technology and specific expertise for its application. [17][18]

3. **Bidding Through Bargain**; this type of bidding is applied under some strictly pre defined circumstances. These circumstances are defined in the 21. act of 4734 Law of Public Bidding. Akyürek[21] These circumstances are given as follows;

    1. When there are no bids made from the bidders in open bidding method or bidding among specific bidders.

    2. Occurrence of events such as natural disasters, massive epidemic and possibility of loss of life and/or damage to the property which are sudden, unexpected and unforeseeable by the management which forces to make the bidding immediately.

    3. When there are special situations concerning defense and security which forces to make the bidding immediately.

    4. When the bidding requires R&D and not subject to serial production.

    5. When the technical and financial requirements of the product and/or service that is planned to be acquired couldn't being clearly defined because of its genuine and complex nature.

    6. When total cost of the acquisition of product, material and service reaches to 50 billion Turkish liras.

3.4.1 Direct Procurement

The management of the institution can apply direct acquisition without the need of announcing and taking deposit, in accordance with the 4734 Law of Public Bidding in which the terms and conditions that require this application are given as follows;

1. When the requirement of the procurement can only be satisfied with the legal entity or a real person.

2. When the real person or the single real entity has a special right with the requirement of the acquisition.

3. Procurement and lease of the immovable product with respect to the management needs.

4. When it is uneconomic and can be in emergency situations due to its nature and necessity of being used within a certain time, acquisition of the medicines, vaccines, serum, anti - serum, blood and blood products, orthotic, prosthesis in which they can be used with the application can be used in accordance with the patients needs and also the acquisition of medical consumables, test and examination supplies.

This is the article in this regulation that is to primary interest of the pharmaceutical companies. Because of the nature of the health services and products, in order to constant satisfaction of product and services of the management who delivers those health services, a "Regulation Mandatory for Application to Bids of Framework Agreements" enacted.[20]

With this regulation, some differences compared to other managements of public institutions are now in effect with respect to the acquisition circumstances, characteristics of their needs, reducing the costs of stocking, and in order to comply with EU public acquisitions regulations. Within the context of this new regulation, acquisition of pharmaceutical products such as; all kinds of medical consumables, serum, anti serum, vaccines, all kinds of orthotics and prosthesis, medical devices and services such as; services intended for diagnosis and treatment are all included and defined within the context of the "Framework Agreements" which is defined to satisfy the constant need of the management of the institution who delivers healthcare services.[20]

Framework agreements and collective acquisitions are in effect in order to make the acquisitions made by the institutions with circulating capital which are directly responsible to the ministry of health more effectively and efficiently. For the acquisitions made by those institutions at the year of 2010 and after that date which consists of all kinds of medical consumables, serum, anti serum, vaccines, all kinds of orthotics and prosthesis, it has been made mandatory that application of the framework agreements on the city based and in collective form. [20]

Those city based collective acquisitions are being made by central acquisition units. When it is decided that collective acquisitions are to be made in accordance with the regulations mandated by the law of public bidding by the bidding authorities, the necessities that arose until the bidding is closed and signed, are going to be satisfied with the isolated contracts made within the context of framework agreements. [20]

During the acquisitions made through isolated contracts, when there are no valid proposals made, when the given proposals are found economically not viable by the bidding commission, when the bidding decision is rejected by the bidding officials and for other reasons; when isolated contracts are being unable to be made, the necessities in question are going to be satisfied by the institutions in question with other methods defined in the law of public bidding. [20]

For emergency situations satisfaction of the necessities on the institution based is always possible. Isolated contract acquisitions can be made for satisfying the necessities on monthly level and as well as annual level. [20]

3.4.1.1 Stock Management of Public Institutions

During the course of delivering the healthcare service, for the effective and on time satisfaction of the needs with resources, it is important that the economic, efficient and effective usage of scarce resources in spite of the high level of expenditures of health care services. To accomplish this, with making certain adjustments the application of " Maximum Amount of Stock Application" has been initiated. Within the context of this application, turning over the maximum amount of 3 month accumulated inventory to the institution(s) who are in need of that certain inventory has been made mandatory. [20]

And also in order to maintain the efficiency of the city based stock management, "City Stock Coordination Units" has been established. With establishing these units, the institutions needs for certain products are being supplied from the city stock pool of inventory and from the institutions who has the excessive amount of stock and it has been mandated that before purchasing the products from the city stock pool from the pharmaceutical market, it is required to take the permission from the city stock coordination units. [20]

Before the bidding, since the product that is being inquired is made by the institutions through the system, it is not required to take permission for the supply of the products from the city stock coordination units when they are not in the list of excessive stock list. [20]

Stock coordination units which they have been established within the Health Directories, will inspect the current stock levels (entry and exit records) of all institutions, and from those who work with excessive amount of stock, certain amount of stock will be transferred with priced and/or free to the institutions which are in need of those certain products. [20]

3.5 SGK and Third Party Financer Reimbursement Systems

Reimbursement system is the mechanism that regulates the financer institution(s) payments made to healthcare providers for costs of the health services they provide to the patients on what basis. Previously this organization are only focused to the hospitals but now its coverage has expanded to the hospital groups, monitoring centers, home care service centers and other healthcare services.

Previously this reimbursement system is made up of 3 different pillars which are SSK, E.K. and Bağ-Kur;[25]

S.S.K.: The plan covered almost all privately employed workers and blue collar public sector workers, retirees and their dependants. The SSK was mainly financed through mandatory contributions from employers and employees. Additional income was obtained from fees paid by non - members using SSK services (e.g. members of Bağ Kur) and from co - payments. [25]

E.S. : The plan provided healthcare benefits to currently employed and retired white collar public sector employees and their dependants (active civil servants are separately insured by the Ministry of Finance). Insurance premiums are collected from income and the plan is subsidized from the government budget for pension and health care benefits. [25]

Bağ-Kur: The scheme provided insurance for independent traders and the self employed. A reimbursement system was established and fees are determined independently by the institution. Co - payments of %20 from active members and %10 from retired members are required for the purchase of drugs, as in the case of SSK. [25]

These three different systems are combined into SGK "Social Security Institution" because it was unclear and causing difficulties for the contributors of these systems about where contributors are going to acquire their medicine under what conditions and according to which pharmacists. In 2011 they are merged under the title of SGK and these difficulties are resolved.

SGK: The new plan combines all there that were defined previously and including the green card system for the contributors with poor financial conditions. This new system is a part of the Turkey' s ongoing healthcare reforms and aims to solve many problems of the Turkish health system over years, including low population coverage, reliance on out of pocket payments and uneven distribution of facilities and personnel.[25]

3.5.1 Main Principles of Reimbursement System

3.5.1.1 Covering the Expenses of the Healthcare Services

Due to its nature, the healthcare services are usually get its payment after it has been provided. Despite the other sectors in which they before pay the prices and/or get certain finances before having the service and/or the product, in healthcare business, the patients leave hospitals or any other healthcare facilities with already taken the healthcare service or treatment and mostly without paying initially. Doctors and hospitals are always after the return of the toil they did on patients and service they had provided to them. Akyürek[21]

3.5.1.2 Third Party Financer

Third party financer(s) are the institutions that regulates and supplies the payments made to the healthcare providers. In other terms third party financers are the healthcare service(s) and/or product(s) provider for a certain population. Their fundamental role is to ensure that healthcare service is being provided to the population who are under their jurisdiction. To do this, they have to be sure that whether that certain population has the services matching their needs and satisfying them with cost efficient actions and within the quality standards defined previously. Akyürek[21]

3.5.1.2.1 Who are the sides of these financing transactions?

Within the context of these financial transactions the first part are the patients and the patients relatives who are actually the responsible of the cost of healthcare service provided to that patient. Second part is the healthcare provider which consists of doctor, clinic, hospital, nursing home or other healthcare institutions. The second part is generally defined as the healthcare provider because they are the ones who provide that healthcare service. The ones who receive the healthcare service makes the payment to the second part. This is the simplest form of transactions both includes providing the healthcare service and financing the cost. The other type of transaction which is defined as the " complicated transaction" is including a third part which makes payments for the healthcare products and/or services they have provided for the first part. Here within the context of this, the third part consists of insurance companies and health institutions both can be private or public who are making payments to the doctors, clinics or other healthcare service providers for their healthcare service they had provided to the patients (literally the first part in our discussion). Organizations in the third part can be in the form of volunteer institutions, commercial or social security programs and national or local leveled government institutions.

The reason behind developing the third party financing is with the effect of the uncertainty of morbidity of population, to share the financial risks faced by the patients and redistribute among them.

3.5.1.3 Health Insurance

Having a health insurance is an important factor for shaping the demand of the healthcare services. It is known that owning a health insurance by the patients is a factor that increases the demand for the healthcare services. In parallel to this, decision whether to apply the reimbursement system or not, having possession of health insurance is an important factor to consider. As we know that insurance is used to compensate and lower the risks by another part (such as insurance institutions) that people may encounter during the course of their life's. Akyürek[21]

Morbidity risk, uncertainty of occurrence, high costs of healthcare services when it is required forces individuals to have a health insurance. Fundamental aim of insurance is to compensate and support for the possible harms that individuals or groups may encounter through their life's with distributing the risks, in other words distributing the risks associated with an individual or a group among all participants of that insurance policy. This system of distribution is also named as "Risk Pooling". Akyürek[21]

Insurance institution collects a certain amount of payment called "premium" for the compensation of risks it undertakes. When calculating these premium payments, insurance institution based its calculations on actuarial data's. All premiums collected from the contributors are then totaled in pool. With making this, pool size made enough to compensate all the losses of the contributors. Akyürek[21]

This application contributors who are financially in better condition are able to compensate the financially poorer ones, healthy ones are able to help to the sick ones, young people can substantiate the elder people which is important to maintain the justice among the system. Akyürek[21]

3.5.2 Reimbursement Methods at Healthcare Services

The institution which finances the healthcare service should make payments to the healthcare service provider for health insurance (financer of the healthcare service) contributors for their patronage of services of the healthcare service provider. Payment mechanisms explains the relationship between the healthcare service provider and healthcare financer. See diagram no.1 (in Appendix A1) for a simpler depiction.

The fundamental characteristic features used to classify the reimbursement systems of the healthcare services are payment unit, orientation of time, financial risk levels for the parts of the transaction. Payment unit types changes from payments made for each diagnosis to the payments for a certain amount of population based on a certain amount of time just like the transfer of government budgets to the corresponding government organizations. At orientation of time there are two options which are prudential or retroactive. This feature is based on the healthcare service provider's revenue and costs incurred during the generation of that revenue. This feature gives us information about the generosity of the system to the healthcare service providers as well as variability/stability of the healthcare service providers which enables us to understand their behavior in the system, that is going to be expressed in subsequent chapters.

In a retroactive system payments are made for the healthcare services to the provider only after the costs incurred by the provider, totally or in half. In a prudential system, the budget of the payments which are going to be made to the healthcare service provider and rates are defined at the beginning. Unlike the retroactive system, in prudential system there is no connection between healthcare service providers own expenses. Akyürek[21]

Under the title of financial risk, we evaluate the risks undertaken by the third party financer of the healthcare service because of learning the costs after that service had been provided. Healthcare service provider is also undertaking risk when it has to forecast the possible healthcare costs of patients and providing the total healthcare service to them within the limits of those costs.

Another distinction point when evaluating the reimbursement systems is stability and variability. A reimbursement system is considered as stable when the amount reimbursement is fixed in spite of the increase and decrease of the healthcare activities. When those increases and decreases of activities affect the reimbursement payment amounts than that system is considered as variable. Both the variable and the stable systems can be separated on macro and micro levels. Micro levels consists only the healthcare service provider. At this level, behavior of the healthcare service provider to the financial incentives has been inspected. At macro level, all of the healthcare service provider or a certain group is considered. In the end, the third party financer is responsible from the macro level. Akyürek[21]

There are two kinds of reimbursement systems; Reimbursement Made on Service Basis and Reimbursement Made on Treatment Period. Akyürek[21]

3.5.2.1 Reimbursement Made on Service Basis

In this type reimbursement, payment is made on the basis of each unit of service that is being provided by the healthcare service provider. It is a usually resorted method for making reimbursement payments. There is always a certain price for each item of service provided. Healthcare service providers bills its service on the basis of those certain prices. With taking basis of those bills, health insurance institution makes necessary payments to the healthcare service provider for the services that are in the payment list.

The items basis of healthcare services are which in the bills of healthcare service provider. With making appropriate inspections and mandatory reductions, health insurance institution makes the necessary payments.

Participants (Patients) in the health insurance institution which has service basis reimbursement has an advantage of maneuver at every stage of decision process because It creates a possibility for the patients to decide which doctor shall make their diagnosis and receive treatment under which conditions.

However, from the patients point of view the disadvantage of the system is that there are more mandatory reductions and complementary payments compared to other systems. And from the healthcare insurance institutions point of view, the upmost disadvantage of this system is its uncertainty. The costs of the payments made to the healthcare service providers for the services they provide is uncertain to the insurance institutions. Because it is not possible to foreseen which patients are going to receive which services. Additionally, it is possible that raising the cost of each services by the healthcare providers, patients receive more costly treatment services than their expectations and choosing more expensive treatments compared to the cheaper ones. Akyürek[21]

There are two types of reimbursements made on service basis;

3.5.2.1.1 Payments Made Individually in Cash

Payments made individually in cash is a form of payment made on service basis. Cash payments for the purpose of health consists of payments made to the healthcare services by the patients directly or by patients relatives. Later if those patients are contributor to healthcare insure institution then they may ask payback for the prices of the services they had taken. In some cases they have undertake all the costs of the services they had. Akyürek[21]

3.5.2.1.2 Conventional Retroactive Reimbursement Payments

Service costs are being paid to the healthcare service provider after those services has been provided. Retroactive reimbursement payments are also a kind of payments made on service basis because for the each unit of service they had provided, the healthcare service provider receives a payment. Third party financers makes payment for the costs incurred or generated bills previously. Retroactive reimbursement payments generates a chance for the healthcare service providers to receive a payback of the costs they had incurred however this method has been question for its ability to incent to act cost efficient. Akyürek[21]

3.5.2.2 Reimbursement Made on Treatment Period

Treatment period defines the healthcare service that has been provided from a healthcare service provider that has been taken by a patient because of his or her health condition or illness. Reimbursement made on treatment period is reimbursement method that healthcare service provider receives payment in lump sums due to the conditions and illness of its patients. In this type of reimbursement, the important factor is the period itself not the unit of service. If one looks at the starting point of this method, it has devised in order to cover the failures of method of reimbursements made on service basis. Primary aim of this method is to manage the expenses with systematic and large scale. Akyürek[21]

There are three types of reimbursement made on treatment period;

3.5.2.2.1 Individual Reimbursement

In this type of reimbursement, third party financers are making payments to the health care service providers based on fixed charges per individuals within a certain period of time. These payments amounts are determined in order to meet with all the healthcare service that a patient receive within a certain period of time. In this method, volume or density of the service that each patient receives has no effect on the payments. As increases in the amount of service provided doesn't have any effect on payments, also decreases in the amount of service provided doesn't have any effect on payments. If third party financer and healthcare service provider reaches an agreement on providing a service to a certain group based on individual reimbursement, healthcare service receives the payments no matter if patients (contributors) in that group satisfy from services or not. In this method there is no regulation for the complexity or the coverage of the healthcare services. Akyürek[21]

Main advantages of this method are, the non existence of ambiguities for the third party financers and their help for creating a solid customer group for the healthcare service provider. Third party financer is aware of the total costs of the healthcare services within the coverage.

On the other hand, healthcare service provider has a solid customer base. However it is ambiguous for the healthcare service provider that amount of service which patients may receive, complexity of those services and their costs. Akyürek[21]

3.5.2.2.2 Budgeting

Prudential budgeting is used both in tax systems and in payments to the hospitals which are in the coverage of social insurance. Simultaneously and additionally reimbursement per case method initiates with budgeting. Reimbursement per case hospital has been guaranteed and paid with a pre determined amount for a certain service package or treatment period.

With budgeting payments, third party financer pays a block of payment for group of service providers who provides the same service within a certain period of time. Here block of payment refers to the money that is allocated to whole of the program. Payment amount are depending on the previous payments which all can be adjusted according to inflation rates. Hospitals are expected to keep up with the rest of this budget to conduct the program. Budget allocation which is made in accordance with the expense items can categorized as salary, medicine, equipment, maintenance and repair, investment, transportation. In this method, allocation for each type of service and expense group has its own predefined allowances and healthcare service providers are not allowed to make transfers between the expense items. Akyürek[21]

3.5.2.2.3 Prudential Reimbursement Methods

In this type of method payments are made with rates which are adjusted in accordance with the levels of healthcare expenditure resources for a certain amount of time period. Healthcare providers are being paid with pre determined rates without taking the costs into account. Therefore this is an another method in which the predetermined payments are not affected by the number of patients and amount of services provided. Since the future limits of expenses has been drawn from the past, this methods primary objective is to reduce the probability of increases in costs and expenses.

There are two types of prudential reimbursement methods;

1) Reimbursement Made on Daily Basis

In this method, third party financer makes payment on daily basis to the service provider for each patient who receives treatment. This method is used for reimbursement of the inpatients at hospitals mostly. Payment amounts are determined according to the past data.

However there's a certain disadvantage with the system that has been controversial for a long time that is the method creates tendency to exaggerate the number of days that the patients received inpatient treatments or the number of their total staying at the facility in order to receive more money from the third party financer. This strategy in turn increases the reimbursement cost for the third party financer. Akyürek[21]

The other prudential reimbursement method is reimbursement based on cases. The method of reimbursement based on cases is devised to cover the failures of the reimbursement based on daily basis. Akyürek[21]

2) Reimbursement Made on Cases

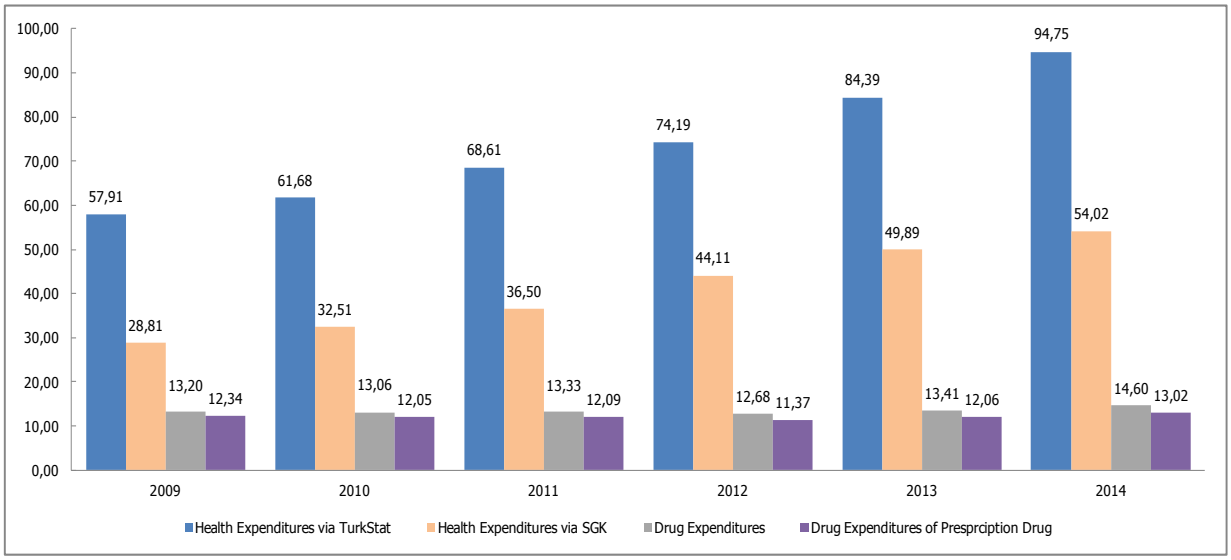
In this reimbursement method predetermined and fixed amount of reimbursement payments made for each case to the healthcare service providers. Here case means the patients who are receiving due to a certain illness or condition. Reimbursements made on cases can be done with a certain price, or rates based on case groups. With this pricing application, patients who are in the same group can receive the same diagnosis, treatment, has the same resource expenses and treatment intervals. The rates are adjusted with respect to different weights which are determined according to the density of the care and treatment a patient group requires. The higher the density of the requirement that group receives more weight in the calculation. Akyürek[21]

Increased amount of resource usage is about the density of the health services provided which are provided with the services which require treatment and cures with expensive medical equipment or is about the frequency of the disease. Akyürek[21]

3.5.3 Healthcare Expenditures

After the discussion made on the purchasing, acquisition and reimbursement methods of both public institutions and SGK, an important highlight which shows the health expenditures can help to understand better the public institutions with a graph below;[2]

Graph No.1: Health Expenditures Statistics[1]



3.5.4 Reflection of Reimbursement Systems on Pricing (From the Company's Point of View)

Since the reimbursement applications has an effect on prices of medicines which also affect to the warehouses and end users indirectly, a pharmaceutical company who would like to sell its medicines or make direct investment into Turkish pharmaceutical should take into consideration thoroughly. Table 1 (in Appendix A1) gives summary about the reflection of reimbursements on pricing.

3.6 Representative and Distribution/Sales Medical Warehouses

According to the Turkish pharmaceutical sector applications there are two types of warehouses used within the supply chain of the pharmaceutical sector. First one is the "representative medical warehouses"[22][23].

3.6.1 What is the aim of these warehouses in pharmaceutical industry?

Both representative and/or sales/distribution medical and pharmaceutical warehouses are used to deliver and supply to the pharmacies with the upmost product security and on time delivery which is crucial both treatment and cure of public health. Warehouses used to deliver the medical and pharmaceutical products which are used both on humans and animals (known as the veterinarian products) such as; medical pharmaceutical products, preparations used at immunology, blood pharmaceuticals, magisterial medicines and substances and supplies used at the beginning of the officinal medicines, cosmeceuticals, sanitary - hygienic medical substances and ingredients, diagnostic products, herbal medicines and other preparations[23].

Officinal and magisterial medicines are the medicines that are being prepared at the pharmacy. Magisterial medicines are the combinations that are being prepared at the pharmacy by the pharmacists according to the directives given by the doctor's prescription which is being prepared both with medical substances and existing medicines on market. Officinal medicines are actually substances that are used directly at treatments or cures of illnesses which is also prepared by pharmacists at the pharmacy according to the Turkish Pharmaceutical Preparation Manual.

Examples to the officinal medicines such as; lime juice, citric acid syrup, mint syrup[23]. Medical and pharmaceutical warehouses are used also to withdraw the defective, fake or expired medicines and other pharmaceuticals from the market. This process has three stages[24];

Phase A ; This first level of withdrawal, goes down to the final consumer level, announcements to the final consumers made in order to make them to turn in their products on their hand in order to reduce the consumption gradually and reaches to halt[24].

Phase B; Second level of withdrawal goes down to the retailer level (Retailers are pharmacy, hospitals and etc…)[24]

Phase C; Third and final level of withdrawal goes down to the warehouse level and prevents the medicines with problems as defined above to reach to the pharmacy and hospitals and therefore to the final consumers.[24]

3.6.2 Representative Medical and Pharmaceutical Warehouses

Representative medical warehouses are establishments used to store and packaging the medicines which are licensed by the ministry of health and in addition; adding prospectus, labeling, price tagging and other relevant packaging procedures can be done also. If it has store qualification applications of "good storing/distribution" and if it has manufacturing qualification applications of "good manufacturing practices (also known as the GMP)" are mandatory for its operation.[22] [23]

3.6.3 Distribution/Sales Medical and Pharmaceutical Warehouses

Distribution/sales medical warehouses are establishments which are licensed from ministry of health that can trade the medical devices and pharmaceutical products also importing pharmaceutical products from abroad. These establishments belong to the real and commercial persons.[22][23]

3.7 Pharmacies

Within the context of the pharmaceutical industry market components one can think pharmacies as the last before the final ring which is customers . Pharmacies as in many other countries are the only place that final customers can acquire their medicines and other pharmaceutical products. Since there are different types of medicines that are in the market we can divide the medicines that are being sold in the pharmacies under two different groups;

3.7.1 Behind The Counter Medicines (BTC)

These medicines are only sold at pharmacies and by only consulting with pharmacists and id identification made of the patient. This status aimed to reduce the reach of patients to these medicines without prescriptions and also the misuses of these medicines by pharmacists. American Food and Drug Administration has enacted this application at August 2006, especially covers the children and young people under the application's jurisdiction. In England, Canada and Australia same application used as a legal limitation for the medicines that can only be acquired through pharmacists consent. In England some medicines that are sold without prescription are also within the context of this application.[13][14]

3.7.2 Over the Counter Medicines (OTC)

OTC medicines can be acquired through medicines and other selling platforms, without the necessity of the prescription or doctors' diagnosis. OTC medicines are used to alleviate and cure health problems that are faced in the course of our daily life's without the help of doctors' diagnosis and if necessary usage of those medicines with the pharmacists consultation and for a very short period of time and also for certain indications are proved to be safe.[13][14]

3.7.3 Prescription Types at Medicines Acquisition

In order to promote the rational usage of medicines and to maintain the efficient usage of medicine resources both at government and private sector many countries in the world including Turkey are using a special system of prescription. This system consists of 5 types prescriptions for special conditions apart from normal prescriptions written for other situations (except the following) are given as follows; [24]

3.7.3.1 Red Prescriptions

Red colored prescriptions are used for the acquisition of the narcotic substances and medicines that contains them. Since these kind of medicines should be used with extreme caution and with a doctor's consent these medicines are sold with red prescriptions. Red prescriptions has their own legal numeric system which means they are traceable and recorded at the ministry of health. These procedures are important because medicines within the context of these prescriptions are subject to exploitation and can create a physical addiction by the patient. [24]

3.7.3.2 Green Prescriptions

Green prescriptions has the same working principle with the red prescriptions and they are used only at psychotropic substances and medicines which contain those substances. Psychotropic substances are used as anesthesia purpose, pain reliever and medicines of psychiatric. Just like the medicines of the red prescription, these medicines are also subject to exploitation, that is because these medicines are acquired with green prescriptions and with respect to the same procedures of the red prescriptions.[24]

3.7.3.3 Orange Prescriptions

With orange prescriptions, patients who are suffering from hemophilia, can acquire their medicines. It is mandatory that orange prescriptions can only be prescribed by practitioners of hematology or pediatrics. [24]

3.7.3.4 Purple Prescriptions

Patients can acquire the medicines used as the blood products with purple prescriptions. Patients who would like to acquire medicines which are in the list of those prescriptions, should also enter their personal such as id number, name and surname and his or her doctor's information's as these information's can be found on each of those prescriptions to a special ledger sent by the city health administration in order to record the acquisition and track the consumption of these medicines as much as possible.

As mentioned before these medicines especially the ones with red and green prescriptions, are all subject to exploitation, so usage of them should be monitored both by the ministry of health, doctor and pharmacists themselves. [24]

3.7.3.5 e - Prescriptions (via MEDULA)

There is a special system which makes the connection between patients, pharmacists and ministry of health electronically named MEDULA. Doctors who are working at healthcare service can enter the very same prescriptions which are defined above including the normal prescriptions electronically which can be seen simultaneously by the pharmacists within the system. [24]

However there are some legal restrictions within this system such as; when "colored prescriptions" are prepared with the system they should be also prepared with handwritten, stamped and signed at the same time but these manually written copies are not going to be sent to city health administration. e - Prescriptions cannot be used for; magisterial products, import medicines which are imported by the real and commercial persons, and for the ones who; are foreigners that come from the countries that Turkey has bilateral contracts of "Social Security Contracts", and for the patients who receive healthcare service from the healthcare service providers which doesn't receive financial provisions but defined in the corresponding legislations. For those people hand written, manually prepared prescriptions are going to be used.

3.8 Patients and Their Relatives

Supply chain of pharmaceutical industry market ends with patients and their relatives. All of the demand forecasts, production adjustments, legal entities, social security contracts' articles, and also government health policies are created and devised in accordance with the number of patients for each illness groups. Therefore gaining information about the health conditions of millions of patients both foreign and domestic market is important both for the private sector and public institutions.

For example these data are important for private sector because decisions of entering to a market, merge of markets if possible, to be efficient on solving public health problems for the goodness of public are made in accordance with these important contributing factors. Same data is important for the government and public institutions for budgeting of the public health projects, forecasts of possible epidemic conditions and being prepared for the possible natural disasters or wars which can create huge amount of demand within a very short period of time.

Within the context of theoretical thinking about people's health, their relatives are should also be taken into consideration. When devising a health plan which it can be forecast of possible medicine consumption, inpatient staying periods length or financial budgeting of a future health service it is important to take into account both patient's relatives and if exists their companions because they also would like to assist to both the patient and their family. Because especially at the patient's relatives, according to different scientific research made, many diseases are found to be hereditary and both to the public institutions and private sector these relatives are prospective patients of them. Resource planning, and expansions of the current facilities can be forecasted according to the number of these patients in order to make future actions devised thoroughly before. Massive scaled diagnosis programs for the people who actually cannot afford to go doctor and make his or her own diagnosis and prognosis application are of key importance here for the early detection of diseases and therefore acting early against them.

Knowledge is crucial in many fields of science however especially at the subject of public health, knowledge is of golden essence therefore education of the patients relatives about the illness of their patient can increase the life quality and/or survival chance of that patient and at the same time increases the chance of avoiding that illness by those relatives.

CHAPTER 4. FUNDAMENTAL FEATURES OF SERVICES AND PRODUCTS OF PHARMACEUTICAL MARKET

As in other sectors in pharmaceutical industry's services and products has certain characteristics which can be grouped and expressed as follows;

4.1 Pharmaceuticals are Public Services

Since any health conditions are important for a nation's well being; delivery, supply, satisfaction and promotion of healthcare services and products are of golden importance. As of government's primary function in a country, is to protect its citizens for any harm and secure their well being, providing and ensuring the healthcare services and products especially for the people who cannot afford without the financial and physical help of the government is one of the main purpose of government's and public institutions. Government's controls and direct these healthcare promotion acts and special programs with the help of the public institutions and governmental bodies such as SGK and ministry of health in Turkey.

The utilitarian principle which means promotion of the upmost utilization for the most of the people in a community, many public healthcare programs calculations, resource planning, and budgeting are made with this way of thinking. It is because developing and brining the pharmaceutical healthcare service and products to the public are one most basic and fundamental service for every human being of the despite demographic factors such as age, gender and income. One cannot diverge the healthcare services from other infrastructure based and other public services such as police force and fire fighters of a city. One of the most basic principle of being a civilized nation is to have a public service satisfaction level which reaches and stays at the top at all time, and at all places.

However nations such as underdeveloped and emerging countries are having difficulties about fulfilling such kind of public services as many witnessed with such unfortunate events especially at delivery and constant supply of healthcare services. These countries are located mostly in Africa which suffers from massive plagues and diseases such HIV/AIDS, diarrheal diseases, malaria, ischemic heart disease, meningitis, tuberculosis, diabetes mellitus.

Such diseases and plagues are problems that are not special to a single country but numerous neighbor countries who are living with the same region and their poverty makes this situation even more difficult. Therefore the last fact given emphasizes the need and importance of delivery for healthcare services and should foster the works done both by the pharmaceutical industry of private sector and public institutions.

4.2 Uncertain Demand of Pharmaceutical Industry

As mentioned before at the previous sections, occurrence of natural disasters, initial start and accumulated growth of massive plagues and diseases especially at countries which has low infrastructure and low quality statistical data collection systems makes it difficult for the expert to analyze the current situations and forecast the possible events in the future.

Uncertain demand of medical services and products makes the job of manufacturers and public institutions more difficult because both at the production phase of products and medical supplies and delivery of those products and supplies to the people who in need of them are all devised from past statistical data and adjusted in accordance with the recent events and data.

With adding the uncertain occurrence of nature of health problems, these makes it difficult for the officials to act fast. The issue of uncertainty of occurrence has another problem; its location. Many countries like Turkey has developed special teams and governmental bodies such as SGK and ministry of health and special teams such as AFAD and UMKE has developed special tactics to reach even the farthest location in Turkey with on time and fast response of actions. These public institutions has established forward bases and monitoring stations as well in order to satisfy the demand at the right place and a the right time.

In order to reduce this uncertainty, as mentioned before at the previous sections, scientific studies conducted on the hereditary of the diseases and its corresponding effects on the accumulated growth of the plagues. Because as well as acting fast on the existing patients at the right place at the right time is important, it is also important that early detection of the prospective patients both for the public institutions and private sector is important for the planning, budgeting and devise of the actions to be made during the conduct of the healthcare services and delivery of medical products.

4.3 Impossibility of Substitution and Delays

Ever since the very existence of humankind is depending on their health condition, it should be expressed that it is impossible for the medicines and healthcare services to substitute or delay them. Unfortunately people who cannot afford medicines and healthcare services are resorting to other means of cures or remedies such as herbal homemade medicines, religious rituals and especially can be encountered in Africa the witchdoctors who try to seek remedy for the ones who consult to him. People who are in need and cannot afford the healthcare services can do anything to cure themselves and become healthy again however both private sector companies and public institutions should run and develop promotional campaign and try to convince local people not to resort other means of cures and remedies rather than using the necessary medicines and other pharmaceutical products. Not using the required medicines and trying different means of cures will not also a waste of time for the people who are in need of a treatment, it also delays the actual treatment that the sick people require. Any professional working at the pharmaceutical industry and practitioner who is also using their products should always keep in mind that any treatment at any diseases or illness cannot be delayed. Many campaigns and large amount of diagnosis programs made previously both by the private sector and public institutions in many countries are aimed to detect and act early at illnesses especially for the ones which early actions can benefit more, for the promotion of the public health.

4.4 Aimed for the Social Health Purpose

As mentioned previously, the existence of the societies at different countries are depending on a single factor; the public health. Among different cultures, it is easy to see that among different subjects which concerns people in their daily life's, health comes at top priority. Especially at the emergency health problems when a single help could deliver the upmost utility and relief for the people who are in need of help. As with the world famous pharmaceutical industrial examples such as Johnson & Johnson's cope with the Tylenol capsule problem and especially the Merck Sharp's River Blindness course of actions are clearly emphasizing the fact that operating in a pharmaceutical industry is not about selling medicines and providing healthcare supplies to the ones in need but its about the survival of people and especially the ones who cannot afford. The reason of the existence of pharmaceutical industry companies is philanthropy of helping the people apart from being profitable and stay in the market. Many companies are also satisfying from the financial returns from those humanitarian and philanthropic actions in many different countries as an increased brand value and well known reputation which cannot be neglected.

4.5 Lack of Knowledge of Those Who Demand

Lack of knowledge about both the symptoms and the course of diseases hinders the usage of medicines, pharmaceutical products and healthcare services. Lack of knowledge about the symptoms makes it difficult for the practitioners and other officials both to apply treatment and cure the patients and at the same time reduces the chance of collecting relevant and satisfying statistical results. This lack of knowledge also effects the way the patient describes his or her own illness that may cause misunderstand the illness which causes misdiagnosis. Uneducated communities are ones with this kind of problem is most experienced.

Promotional campaigns can be used to reduce this rate in order to prevent the deaths because inability of diagnose and/or misdiagnosis.

Also lack of knowledge about the course of the illness also creates another problem for the healthcare service providers, pharmacists and doctors, because this lack of knowledge leads to the misuse and/or irrelevant applications of medical products and medicines. This may lead to fatal consequences which is an undesired one.

Especially for the uneducated communities, assembled teams of practitioners and pharmacist may reach to uneducated patients in far reach places and help them with making prognosis and consult them on the course of the treatment they will receive.

CHAPTER 5. MEDICINE AND PHARMACEUTICAL PRODUCT COMPONENTS OF TURKISH PHARMACEUTICAL INDUSTRY

5.1 Definition of Turkish Pharmaceutical Sector and its Development

The operational experience of the Turkish pharmaceutical manufacturer includes decades of history which has given way to an industry strongly committed to upholding international quality standards. On par with products produced in developed markets, owing to the quality of the country's human capital and state-of-the-art technology, the footprint of Turkish pharmaceuticals now extends to 160 countries, among which include member nations of the European Union (EU), the Commonwealth of Independent States (CIS), North Africa and the Middle East. The Good Manufacturing (GMP) practices, which is a set of rules that ensures the production and control of pharmaceuticals in line with quality standards, was passed in our country in 1984 and accredits pharmaceutical facilities both by the Ministry of Health and by the authorities of countries such as the United States, Germany, Denmark, England, Japan and the Gulf countries.

The Turkish pharmaceutical industry provides more than 11 thousand products to the service of our people produced at 67 facilities at international standards by approximately 300 organizations and 31 thousand employees. [1]

For more brief information about the historical development of Turkish pharmaceutical industry see Table 2 in Appendix A1.

5.2 Definitions of Original and Equivalent Medicines

Within the context of the Turkish pharmaceutical industry there are two types of products that are being manufactured and sold, these are; original medicines and equivalent medicines.

5.2.1 Original Medicines

Original medicines which are proven to have the acceptable efficiency, quality and security in terms of active ingredients; are the pharmaceutical products licensed in order to be presented in to market for the first time. Since before original medicines are to presented in to market, long lasting and expensive clinical tests should be done in order to accurately calculate the efficiency of medicines on humans as a procedure these tests applied on animals first (if they are human medicines) and animals (if they are animal medicines). However these long lasting period of those tests delays the initial launch of the medicines and therefore returns and extra cost caused by this delay. And also expensive costs of efficiency tests conducted by the firm adds extra burden to the company and as a results prices of original medicines are higher than equivalent medicines. Although these negativities occur both before and after an original medicine launched and actively used in the market, there are benefits of original medicines which are enjoyed by the owner company such as patents, rights and data protection.

These are the factors that delay and make the things more difficult for the equivalent medicine manufacturers. Because the time period of delay is approximately 6 - 20 years.

5.2.2 Equivalent Medicines

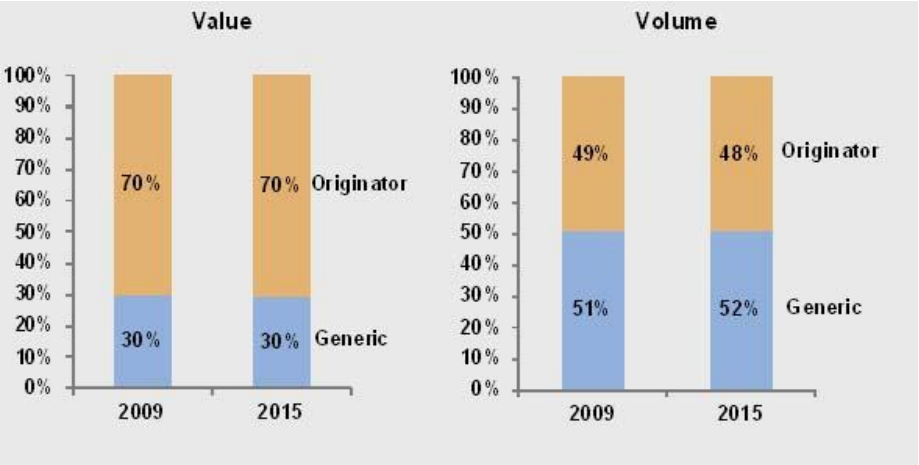
Equivalent medicines are the medicines which has the same active ingredient, at the same amount and in the same pharmaceutical method with the original medicine. Since the R&D processes and clinical trials are not conducted at the development phases of equivalent medicines these medicines are quite cheaper compared to the original ones. The clinical trials conducted at first on animals and then on humans during the developmental phase of original products, repeating these tests are not found to be appropriate in terms of ethics and human health around the world. However before manufacturing equivalent products, there are two important factors to consider;

1. **Patents;** The manufacturer of original medicines since it is the innovator of that medicine, are being protected by patents for approximately 20 years starting from the date of first admission to manufacturing license. In addition there is a also a data (exclusivity) protection which gives to the innovator manufacturing company exclusive rights to hold and not to share the bioequivalence results with the rest of the world. This data exclusivity right has a 6 year length and is within the 20 years of patent protection time period. So a manufacturer who would like to manufacture an equivalent of an original medicine, should look at the first admission date of the original medicines manufacturing license and wait approximately 6 years for equivalent production as long as it can go around the patent protection.

2. **Bioequivalence;** The manufacturer of equivalent medicines should also look at the results of the bioequivalence tests conducted by the independent laboratories. Since that company should send these results to the ministry of health and the existence of mandatory rule which requires the equivalent product should result at least %80 bioequivalence compatibility with the original products which should be proven with the bioequivalence tests. However satisfying this condition is a difficult with reaching to the %80 of bioequivalence, the equivalent medicine manufacturer's should make thorough analysis and R&D applications if necessary to reach to the bioequivalence limit.

Equivalent products are important for the Turkish pharmaceutical sector because most of the Turkish pharmaceutical industrial companies are manufacturing equivalent products mostly, and with this data, overall consumption choice is made from generic medicines. (See Graph no.2 for a summary)

Graph No.2; Consumption Comparison Data of Original and Bioequivalent (Generic) Products [1][4]



5.3 Information About the Market of BTC(Behind the Counter) and OTC(Over the Counter)

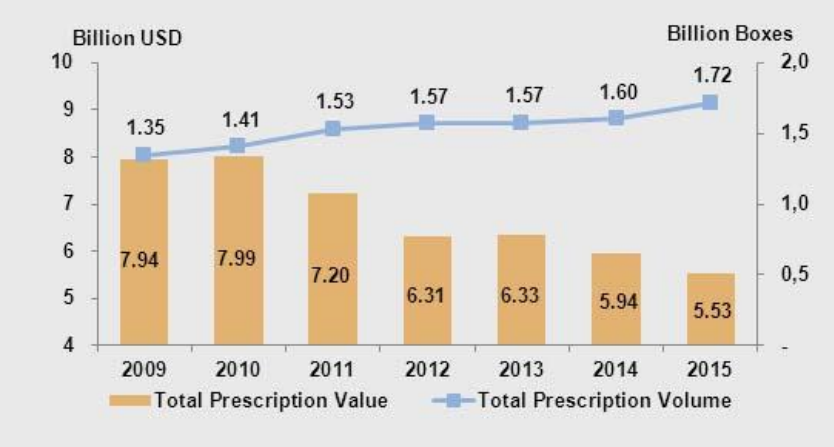
For the ease of the analyze English translations of the terms of BTC and OTC are given below;

BTC (Behind the Counter); Reçeteli İlaç.

OTC (Over the Counter); Reçetesiz İlaç.

Prescription drugs constituted 89.2% of the total pharmaceutical products in market in value terms. In 2015 the prescription market rose by %15.7 in value and %6.9 in volume terms.

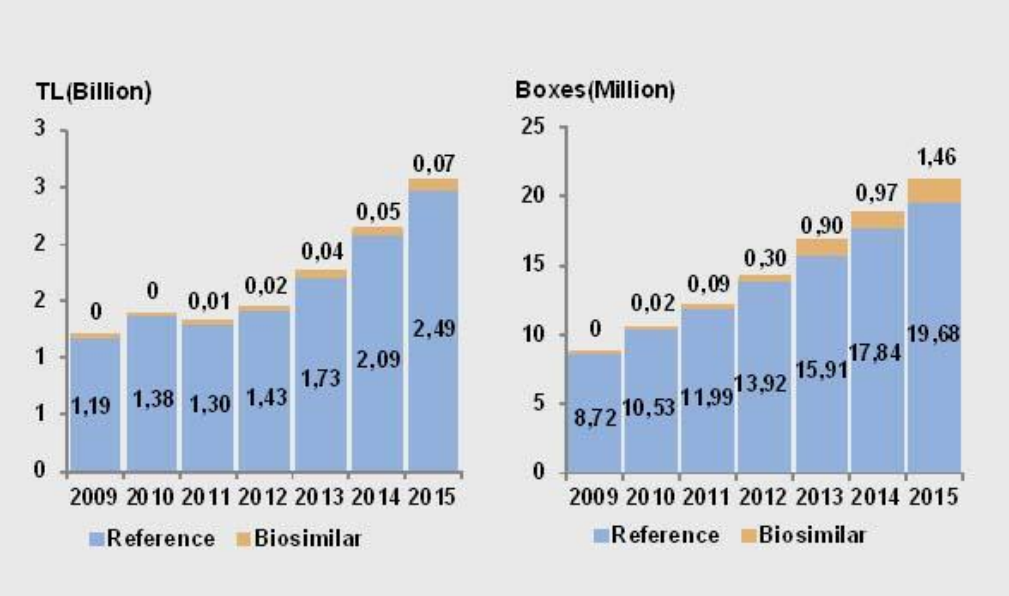
Graph No.3: Current situation (with data from 2015) at Turkey prescription drug market can be seen as follows; [1][4]



For detailed market distributions with reimbursement rates of BTC and OTC medicines see Table No.3 (in Appendix A1) [1][4]

And Graph No.4 shows the total revenue and box sold comparison of original with equivalent products.

Graph No. 4: Total Revenue and Box Comparisons of Original(Reference) and Bioequivalent or Generic Products (Biosimilar) [1][4]



The Turkish market for biotechnological products reached a size of approximately 2.57 billion Turkish lira in 2015, constituting 17% of prescription market.

5.4 Turkish Pharmaceutical Market with Numbers

If we would like to summarize based on production companies operating with Turkish pharmaceutical sector see Table No.4 in Appendix A1.

The products of our pharmaceutical industry which shows the potential to compete with the developed countries by its high quality human factor and high technology, are being exported to 160 countries. According to Turkish Exporters Assembly (TIM), the export goal of industry for 2023 has been set as 3.3 billion $.

This number is valid only when the sector has no strategic planning. The export of the pharmaceutical industry pertains a potential of increasing over 16 billion $ in 2023 if the sufficient conditions are supplied. If this could be succeeded, the trade deficit for pharmaceuticals will be reduced and import will increase to nearly around 80% ratio levels.[1]

The Turkish pharmaceutical industry can develop based on four main building blocks.

- **First;** value creation with R&D and skilled human resources.
- **Second;** competitive cost structure and efficiency,
- **Third;** geographic focus
- **Fourth;** sustainable domestic market which is the main source of the problems that our industry is experiencing today.

In order for the pharmaceutical industry to become one of the key exporter countries, the formation of the Turkish Pharmaceutical Exporters Platform has been initiated with the attendance of the 30 Union and non-Union export companies and with the coordination by our Association. The platform works heavily on advertising and improving the competitiveness of our powerful and developed pharmaceutical industry. Summary as the building blocks with a schematic in Appendix A1.

5.4.1 Turkish Pharmaceutical Market Growth[1]

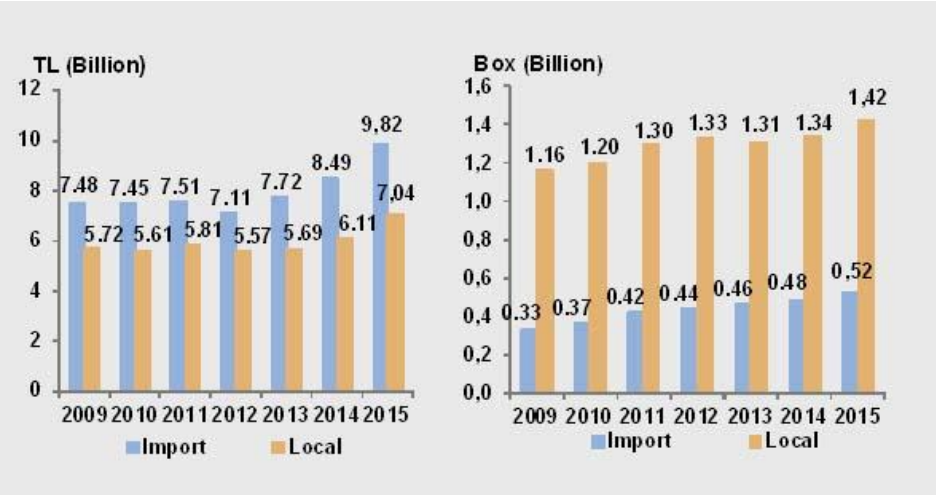
In 2015 the market grew 6.7% in units and 15.15% in value terms, despite the %24 rise in the currency.

Graph No.5 : Total Market Growth [1]

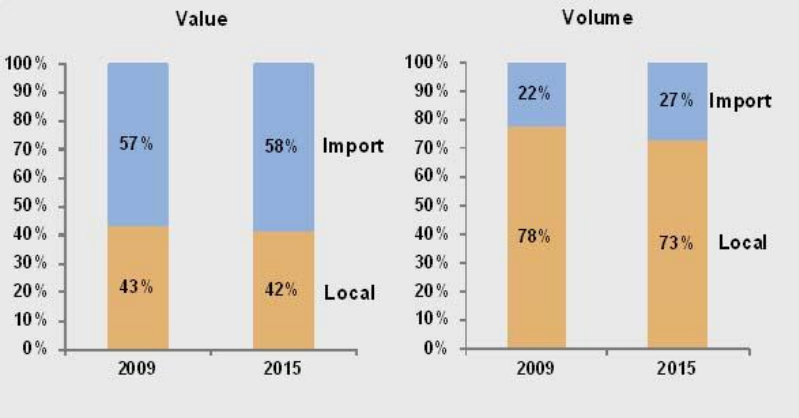
5.4.2 Foreign Trade (Imports vs. Exports)

In 2015, pharmaceutical exports rose %9.8, reaching to $939 million, while imports decreased %2.6, totaling of $4.6 billion. Therefore the export to import ratio increased to %20.3 from %18[1]. Here below there are three different table's which summarizes with making comparisons of import and export highlights. [1]

Graph No.6: Comparison of Local Production and Import Products[1]



Graph No.7: Comparison of Market Share Between Local vs. Imports[1]



Graph No.8: Foreign Trade[1]

Turkish pharmaceutical sector's first 10 biggest export markets are;

1) USA

2) South Korea

3) Azerbaijan

4) Germany

5) Switzerland

6) Turkish Republic of North Cyprus

7) United Kingdom

8) Russia

9) Iran

10) Iraq

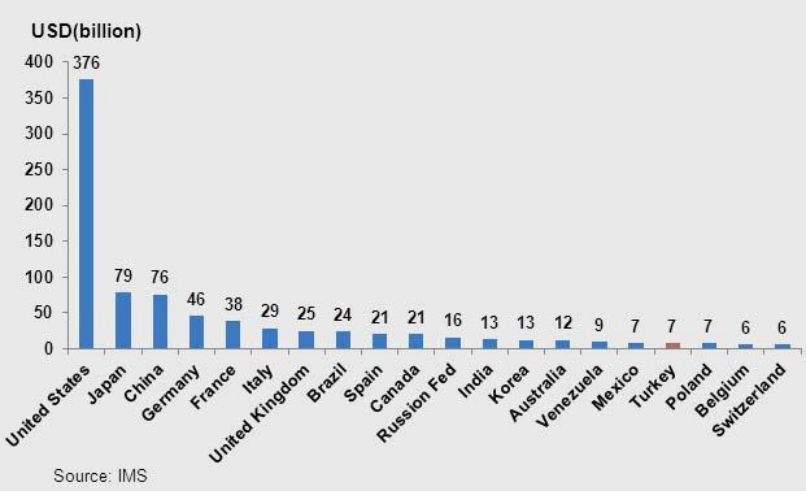
5.4.3 Pricing System

Prices are being regulated by the Turkish Drug and Medical Device Institution which is a part of the Ministry of Health. To determine the price of the pharmaceuticals sold in the market, Turkey operates an external reference pricing system: the lowest ex factory price of the products from the among five EU members (France, Spain, Italy, Portugal and Greece) and the country of origin, from which the drug is procured, is then reduced by %11. The reference price level can mean the price is reduced by %60 by the comparable product in the EU states. In addition a public discount of %28 (for generics) and %41 (for innovative products without generic equivalent) is then applied to the prices. Final retail prices have predetermined wholesale and pharmacy margins, plus a VAT of %8. However if the countries in which the relevant pharmaceuticals are being manufactured and imported are outside of the mentioned reference countries and have warehouse sales prices that are lower than the reference country price, the price in the country with the lowest warehouse sales price is accepted as reference price. Table 6 (in Appendix A1) shows us the comprehensive summary of this complex pricing system.[25]

5.5 World Pharmaceutical Manufacturers and Turkey

According to the IEIS statistics collected in 2014 the world pharmaceutical market reached 934,4 billion USD. Turkey ranked 17th in 2014. Here is the table for the comparison of Turkey with the rest of the world;[1]

Graph No.9: Manufacturers from Other Countries and Their Ranks[1]



Due to the demographic changes, increases in the average life expectancy, changes in disease patterns, social globalization, significant increases at accessibility at healthcare services and rise of the social government management systems has played an important role in the advancement of world pharmaceutical sector. According to Statista, %95 of the world pharmaceutical sector is owned by worldwide manufacturers. Demand in developing and third world countries are being satisfied with the developed countries. According to the EFPIA, world pharmaceutical sales' %41 comes from north America (USA and Canada) and %27,4 comes from Europe. In global market, oncology, pain, diabetes, hypertension are the leading areas of sales. Companies of Novartis, Pfizer, Roche, Sanofi and Merck & Co are leading ones in medicines with prescription sales. Pharmaceutical sector has the leading position with the share of %14.4 in global R&D expenditures with its long duration of patents and high costs of R&D processes. [1]

In global pharmaceutical market, among the fast growing markets, the oncology, blood products, insulin products and vitamin products are the most significant niche markets. Also in global pharmaceutical market, the rise of the biotechnological products are significant. In 2011, the market share of biotechnological product's %1.1 is expected to rise 10 times in 10 years period. Biotechnological products manufacture has started in Europe and it is now focused in developing countries such as China, India and South Korea, also Brazil and Mexico are also making budgeting for the production of the biotechnological products.

5.6 Position of Pharmaceutical Sector in Turkish Economy

According to the "Council of Turkish Pharmaceutical Industry Sector" and IEIS, important contributions made to the Turkish pharmaceutical sector with the healthcare transformation program in 2003. With the help of the advancements and upgrades in health indicators, life expectancy rose to the age of 74 and important declines achieved in mortality rates of mother and children. With making important changes in pharmaceutical sector, facilitation for public to access healthcare services is made. In 2011 %95 of public reached to the social security, the ratio of receiving inpatient service rose from 2.46 to 2.71 per 1000 patients.

Number of patients who are going to the hospital has doubled past 10 years. Total number of patients in hospitals has reached 295 million. With the newly developed, "family practitioner system" the number of patients who are resorting to the first grade healthcare institutions has become more than triple of the previous amount past 10 years. Total number of these patients has become 198 million. According to these health statistics, total number of prescriptions prepared has increased by %4.

Positive results achieved from health indicators are possible only with sustainable healthcare system. Pharmaceutical industry has an important place at this healthcare system. Pharmaceutical sector is creating added value for the economy with employing qualified senior workers and experts. Pharmaceutical industry maintains its strategic position in Turkish economy. Within the pharmaceutical sector there are approximately 300 companies, with 67 of them has production facilities which are both domestic companies and foreign investments. There are approximately 11 thousand products ready to serve to the Turkish medicine. In total there are approximately 31 thousand employees with the Turkish pharmaceutical sector. Pharmaceutical sector has a state of art technology and conducts its operations compatible with the world manufacturing standards. Requirement of compatibility to the international standards at technology and quality standards, aids the efforts to comply with the EU standards, increasing the added value brought to the Turkish economy and strengthens its position with investments and with its high potential of foreign exports. [1][5][11]

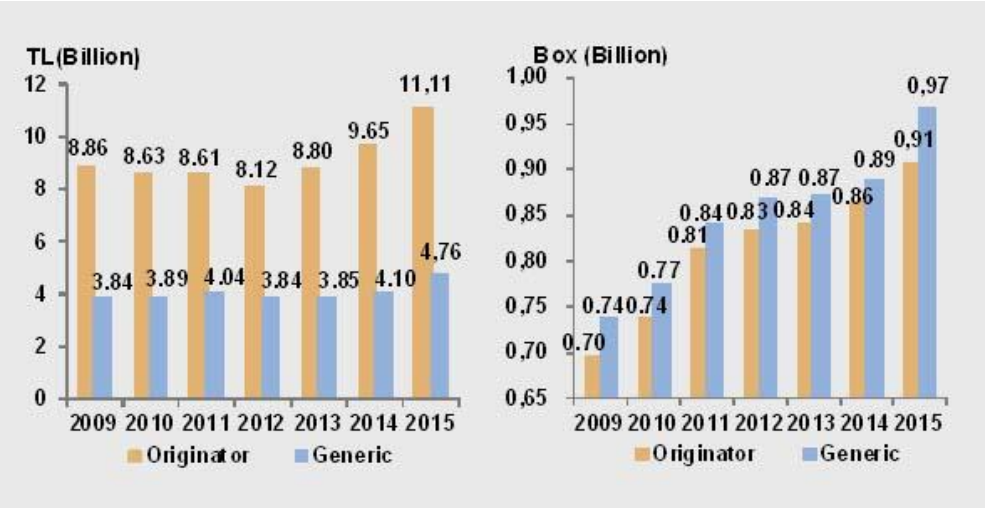
5.7 About Turkish Pharmaceutical Manufacturers

At Turkish pharmaceutical sector mostly production with license, contract manufacturing, generic/equivalent medicine production, antibiotics and many medicine raw materials which analgesics comes first. As of 2014, medicines used in Turkey of %73.5 on box basis and of %41.9 value basis are manufactured in Turkey. According to the data of ministry of health, there 18.981 number of medicine types and total sales revenue is 1.871.469.389 TL. SGK has 8.619 number of medicines in its reimbursement list. In Turkish pharmaceutical market, Novartis has the leading position with the 1.095 billion TL sales revenue which is followed by Sanofi, Abdi İbrahim, Pfizer, Roche, Bayer, GlaxoSmithKline, Bilim İlaç, Merck & Co. and Astrazeneca.[5]

However some medicines which requires high technology can be manufactured only in certain countries around the world. Also, in Turkey medicines which consumed so few and manufacture of them are not financially feasible are not manufactured in Turkey. To these medicines we can also give examples of orphan medicines and medicines used in the treatment of rare diseases. In addition to this, there is a tendency of manufacturing choices to biotechnological products around the world and products which are produced with synthesis chemistry are decreasing more and more. Therefore Turkish pharmaceutical manufacturers should also comply with this trend and answer its demand in order to sustain its position both in foreign and in domestic markets. [5] Because some %20 of the medicines that are being sold in the market are biotechnological products. %14 of the global pharmaceutical market is biotechnological products. In Turkish pharmaceutical market within the market of pharmaceuticals with prescriptions, biotechnological products has a market share of %14.5 and the share bioequivalent products in the same market is %0.3. [5]

Here is the comparison of original medicines and generic medicines of Turkey

Graph 10: Originator vs. Generic Medicines in Turkey.[1]



5.8 About Foreign Pharmaceutical Manufacturers

There are many multinational companies operating in Turkish pharmaceutical market which include Sanofi, Baxter, Bayer, GSK, Novartis, Pfizer, Eastpharma and Roche. Leading multinational companies such as Pfizer, Novartis, Bayer and Roche command market shares of %4 - %6 each. Baxter runs 50:50 joint venture with Eczacıbaşı (Eczacıbaşı - Baxter Hospital Supply Inc.) . Their products and services cover nephrology, hematology, oncology, surgery, anesthesia, and intensive care departments in hospitals, as well as in blood banks and private hemodialysis centers. [25]

International firms are represented by the Pharmaceutical Manufacturers Association of Turkey (IEIS) which mostly includes domestic firms. But mostly multinational firms are represented by AFID in Turkey. The association's membership of IEIS stands at 60 with leadership coming from leading domestic player Eczacıbaşı. Pharmaceutical production is the primary activity of IEIS's local and multinational members. [25]

5.8.1 Closer Look on Major Multinational Players in Turkish Pharmaceutical Market

GSK: GSK is global pharmaceutical company operating across 40 countries with 102 production facilities and 42000 employees. GSK announced sales of GBP 28.4 billion in 2010. GSK has been operating in Turkey for over 50 years and has 10 offices across the country. GSK has made Turkey its regional base and Istanbul its headquarters for the MEA region. [25]

Novartis: Novartis is a global pharmaceutical company based in Switzerland. Novartis Turkey began operating in Turkey in 1997. It bought a production from Roche facility in Gebze in 2007. Now company plans to open a production facility in Turkey so they could sell their products in the Middle East, Central Asia and Africa. [25]

Pfizer : Pfizer is a global pharmaceutical company based in the USA. Pfizer Turkey began operating in Turkey in 2006. Turkey became the regional leader for the Caucasus and Central Asia region in 2008. Pfizer Turkey opened its R&D center in Hacettepe Teknokent in 2010. In 2012, Pfizer opened a production facility in Pendik that has a production capacity of 75M boxes. [25]

Bayer : Bayer is a German pharmaceutical company based in Germany. Bayer Turkey has been operating in Turkey for more than 60 years and employs 1300 people. Bayer Turkey has 18 offices across Turkey with its headquarters located in Ümraniye, İstanbul. The company has invested more than 75M EUR in Turkey since 2000. [5]

5.9 About Pharmaceutical Imports Made To Turkey

Pharmaceuticals which are under protection, products which require high technology and products which has low demand and production of them are not financially feasible are mostly imported. At most, in Turkey the product types of preparations, some vaccines, blood products, medicines which has changed dissolve systems, insulin, and cancer medicines are being imported. Turkish pharmaceutical industry imports different kinds of raw materials used in their production and finished pharmaceuticals from many countries including the developed countries.

The important fact about Turkish pharmaceutical companies is not the amount of imports made however the lagging of number of exports compared to number of imports made. According to TurkStat, our top 5 import countries are Germany, USA, France, Switzerland and Italy. However Turkey has a large amount of imports made. The short list below which shows total import groups can be found in Appendix A1, Table No.7 ; [5]

5.10 R&D Structure of Turkish Pharmaceutical Sector

R&D in pharmaceutical industry includes works of research made on discovering new molecules, making able that new molecule into an efficient and useful medicine after a series of processes which can be used and satisfied by the public, development of new value added products which can be based on generation of new formulations and combinations from the existing medicines. Pharmaceutical industries R&D processes has a distinctive feature from other industries is that it includes human contributions. Generally in Turkish pharmaceutical sector covers the title's as of fundamental research part; R&D processes, discovery of new molecules, finding new application fields to the existing molecules and reassessment of medicines with side effects and as of clinical research part which includes clinical trials which both of them are long and costly processes.

Discovery of a new molecule is actually consists as a starting point for both the innovator/reference and the equivalent/generic medicine manufacturers. Discovered molecule can be upgraded by the patent holder for a considerable amount of time, and after the patent expired, can be manufactured by the generic manufacturer companies. Discovery of molecule can help to both sides both in the long and in the short run. Additionally, pharmaceutical research is focused on making double or triple combinations of existing molecules or different dosage forms or developing equivalent/generic medicines rather than discovering a new molecule or developing a new medicine. Turkey does not have a discovered molecule yet. [5]

Pharmaceutical sector has R&D expenditures reached at 137 billion USD by the end of 2013 and it is expected to reach 162 billion USD by the end of 2020. Additionally, by the end of 2013, according to TurkStat, R&D expenditures at the sector of "Consumables Related to pharmacy and pharmaceutical products" has reached to 210 million TL which has increased by %9.82 compared with the previous year. On the basis of R&D expenditures pharmaceutical sector has a share of %5.82 compared to the rest of the manufacturing sector. Competitiveness and production of medicines and services is only possible with increasing the R&D processes which is one of the fundamental principles among the development of the Turkish pharmaceutical sector. In Turkey, both domestic and foreign pharmaceutical firms are conducting clinical researches. By the February 2015, Turkey has number of 1750 clinical trials which has a rank of 31st in global and 17th in EU. Its share in global clinical researches is %0.95 since the total amount of clinical trials are 184.187. [5]

%14.4 of the total global R&D expenditure is of pharmaceutical sector's. Pharmaceutical's R&D expenditures requires long time and high cost. Approximately a molecule that becomes into a commercial product takes 10 - 15 years and requires high investment costs. [5]

With the contribution of the R&D incentive project's conducted by the BMT Technology and Process Development Ltd.Co. the companies of Abdi İbrahim, Bilim İlaç, Zentiva, Mustafa Nevzat, Koçak Farma, Sanovel İlaç, Nobel İlaç, Pharmactive İlaç has been approved by the ministry of science, industry and technology to establish their own R&D centers. By the October 2014, the share of pharmaceutical R&D centers among the total R&D centers globally (number of 165) is %6.06.

5.11 Patent Protection and Data Exclusivity

5.11.1 Patent Protection

Turkey complies with international treaties in the field of intellectual property and complies with the European Union Standards. By adopting patent protection into national legislation for pharmaceuticals, the transformation period right allowed by the WTO's TRIPS agreement was waived and as of January 1, 1999, all applications that had been accepted since 1995 were given patent protection. As expressed previously total length of the patent protection is 20 years. After the patent is acquired none of the firms except the reference medicine owner company can manufacture the equivalent medicine within this 20 years protection period. However with taking into consideration of 6 years data exclusivity protection which is going to be expressed in the next section, other companies can produce equivalent medicines with "going around" the patent protection itself within this 20 year period.

Companies should keep in mind that equivalent products should have the upmost closer effect as reference medicine however since the patent protection prevents the generic manufacturers from accessing the full list of ingredients and process method of manufacturing, generic manufacturers has a long way up to manufacture the medicine that is alike the reference medicine. This long way consists of expensive R&D expenditures, clinical trials for the effectiveness and side effects and marketing of the reference medicine into order to sustain its standing which is done by promotion to the doctors and pharmacy warehouses…etc. [25][27]

5.11.2 Data Exclusivity

The data protection liability under TRIPS entered into effect in Turkey in March of 1995. In this context, all of the confidential information submitted for the purpose of obtaining a license is protected. Within the context of this subject, the data means that effectiveness of the active ingredient and secondary ingredients inside of a medicine which is planned to be launched into market. These important information's about the medicines can only obtained by conducting clinical trials and researches on animals and humans. For the generic manufacturers conducting clinical trials are very expensive and time consuming, also conducting researches on animals and humans are found inappropriate by the public when already those tests has made by the reference medicine manufacturer.

There was a controversial debate about the length of this data exclusivity. According to the TOBB and IEIS which are supporting the domestic firms the total length of the data exclusivity right should remain with 6 years however AFID which is the supporter of the importers and foreign manufacturers in Turkey supports to extend (with the addition of the SPC; used as exclusive right to market of the product) that period to 11 year which is complying with the EU conformity rules. Since from the domestic manufacturers point of view this length should stay at 6 years because since the 20 years of patent is long enough to protect a medicine and if within the same period of this 20 years length, there comes another protection of 11 years which makes the results of the efficiency of the medicines and clinical tests are confidential would make the job for the domestic manufacturers more harder than ever since as expressed before most of the domestic production is depending on generic medicines. [10][11][25]Güneş[30]

While assessing this situation one should keep in mind that, the license required to manufacture and market the product in discussion takes approximately 3 to 4 years which is in the 6 years of data exclusivity right. This possess problems to the foreign companies because they are complaining about that they are not satisfied fully from the 6 year length of data exclusivity right.

Because with excluding this approximately 4 years from the 6 years of data exclusivity there are only 2 years which they have the upper hand within the context of this situation. However this situation creates an environment for the generic manufacturers to speed up their generic medicine license efforts and therefore manufacturing the generic medicine. So as expressing our ideas about this debate the length of the data exclusivity should stay as 6 years. [10][25]

5.12 Medicine Licensing Process

In Turkey, real persons and legal entities are required to present an application to the ministry of health in order to receive a license for their products. To make procedures more efficient and less time consuming, different committees operate simultaneously. The related committees are as follows;[25]

1. **Advisory Committee for the Licensing of Pharmaceuticals:** Issues an opinion for the product that will be licensed.

2. **Pharmaeconomic Advisory Committee:** Reviews the pharmaceuticals in terms of effectiveness and cost - benefit as well as performing a cost minimization analysis.

3. **Technology - Pharmacology Advisory Committee:** Examines the product pharmacologically.

The licensing process in Turkey carried out according to the provisions of the Human Medical Products Licensing Regulation, which has prepared under the scope of Law No. 1262 named the Pharmaceutical and Medical Preparations Act and in compliance with European Union legislation. The Human Medical Products Licensing Regulation came in to effect on January 19, 2005. The application files are presented in CTD format in accordance with the regulations. CTD format, which is an international standard, was established to present applications in an organized manner and standardized with the procedures of pharmaceutical licensing authorities in Europe, the USA and in Japan. CTD comprises five modules which are; [25]

Module 1 : Administrative Information

Module 2 : Quality Information Outside of Clinic and Clinical Summaries

Module 3 : Chemical, Pharmaceutical and Biological Information

Module 4 : Outside of Clinic Reports

Module 5 : Clinical Study

Licensing procedures are different for generic and reference medicines. Differences are given with a table in Appendix A1, Table No.8.

5.12.1 Types of Products Within The Context of Licensing and Pharmaceutical Market

Reference pharmaceutical is a product that has been developed by an innovating company and offered to the market under patent protection. After the patent period has been expired, these products are used as reference products in order to produce generic pharmaceuticals.

Generic pharmaceuticals are medications that have been scientifically proven to have the same properties as the reference pharmaceutical and therefore, provide the same therapeutic results on the patient. They are presented for sale after the patent period expired. A generic pharmaceutical must have the most of the same effectiveness, quality and reliability as its reference pharmaceutical.

All of the phases that generic pharmaceuticals go through from production until it is put on shelf for sale, are the same ones that reference pharmaceuticals go through as seen with the "Diagram No.2 Summary of the Licensing Procedures". Only the clinical studies that are performed on living organisms by reference pharmaceutical producers are not done. Therefore, the R&D costs are significantly reduced. [25]

Overall licensing procedures of Turkish pharmaceutical sector can be summarized as Diagram No.2 Summary of the Licensing Procedures [25] in Appendix A1.

5.13 Steps of Patients Access to Pharmaceutical Products and Healthcare Services

This chapter consists of overall summary of steps explained so far from manufacturer or healthcare service provider to the patients.

5.13.1 Manufacture, Marketing, Sales and Distribution

Initial phase starts with the manufacture of pharmaceutical products and supplies from pharmaceutical companies which can be both private or public sector institutions. However there is a clear distinction between public and private sector manufacturers, which is public manufacturing institutions are manufacturing pharmaceutical products in order to satisfy the consumption demand of patients and usage demand in healthcare services delivered by the public healthcare service institutions. SGK Manufacturing Institution and Military Pharmaceutical Manufacturing Institution can be exampled for the public manufacturing institutions. Private sector manufacturing companies are consisting of both foreign and domestic companies which operates in Turkey. These companies with their numeric values are given at the previous sections. Apart from manufacturers there are also import companies which are imports certain pharmaceutical products which are crucial both for the consumption by the patients and for the usage during the healthcare services. Information about these importer companies are also given at the previous sections.

Marketing of products are being conducted by the companies which manufactures them and also by the independent companies which services for marketing of those products. Marketing of these products are being considered both as the domestic consumption of medicines both on the value and box basis as given at the previous sections. Marketing of products are being done to the doctors and to the healthcare service providers for the ones used in the healthcare services. Doctors within the context of this subject are very important because as long as the doctors prescribe those medicines manufactured by a pharmaceutical company, that company's product will be sold through the pharmacies and may be listed in the reimbursement list of the SGK.

If doctors will continue to prescribe (for BTC) and advise (for OTC) of usage of the medicines at the center of our discussion, delivery of healthcare services to the public will be sustainably continue and company can maintain its financially viable position to continue its operation.

Sales and distribution of the drugs is another important subject because it constitutes the bridge between pharmaceutical companies and the pharmaceutical warehouses and healthcare service providers. Because pharmacies can only have the medicines from pharmaceutical warehouses and therefore the patients because they are also procure their medicines from both the pharmacies located throughout country and in healthcare service providers. This system can be considered as a supply chain of medicines starts from the pharmaceutical manufacturers and ends at the hand of patients. Relevant pricing systems and reimbursements are explained at the corresponding previous sections.

5.13.2 Representative and Sales/Distribution Medical Warehouses

Medical warehouses of those two types are located actually right between the pharmacies and the company itself. Because of the mandatory applications by the ministry of health, pharmacies can have their medicines only through those warehouses. Pharmaceutical company can choose whether to distribute their medicines with sales/distribution medical warehouses in end product form or can hand over the packaging or prospectus addition process to representative warehouses and after then distribute the medicines to the pharmacies. These choices are made in accordance with the companies cost benefit analysis and legal restrictions imposed. Applications of pricing, VAT and reimbursement rates are explained thoroughly at the relevant previous sections.

5.13.3 Pharmaceuticals Reimbursement System

The existence of the reimbursement in public healthcare service especially under developed and developing countries is a must. Because reimbursement system not just lifts some of the cost burden from the pharmacies also from the patients who are merely able to afford the medicines and healthcare services.

Therefore the existence of the reimbursement system creates an economy itself and attracts many pharmaceutical companies which has a target markets consisting of low and mid level income patient to produce generic medicines which are in the reimbursement payment list of social security institutions. In Turkey the reimbursement system is used the same way as it is around the world.

The reimbursement system consists of two types; first one is the payment made to the pharmacies for the medicines sold within the context of the social security system to the participators of that system who are the patients. These payments made are used to lower or totally diminish the costs of medicines in order to help the patient to acquire those medicines in a decreases cost or totally free under certain circumstances.

Second one is made to the hospitals or to certain kind of healthcare service providers which works in the same way, in order to reduce the prices paid to the healthcare service providers by the contributors of that system.

Reimbursement system is important for the pharmaceutical companies because medicines that are in the reimbursement list means that patients with low and mid level income which consists most of the entire pharmaceutical market are eligible to access the medicines. This creates a huge opportunity of making profit and alleviating the public health problems especially for the generic companies because of their low prices. Financial detail and information about the reimbursement types are given at the relevant section previously.

5.14 Medicine Tracking System

The Pharmaceutical Track and Trace System monitors pharmaceuticals at every stage and was created in order to prevent fraud and maintain patient security. Under this system, all pharmaceuticals are defined with a two dimensional square code system which contains a variety of information. The square code is the pharmaceutical's fingerprint. The square code number, serial number, expiration date and party number are included in the square code. As of January 1, 2010 all license holders are required to place a square code on all products that they produce.

Hospitals, health centers, family physician centers, pharmacies, pharmacy warehouses, manufacturers, importers and reimbursements institutions are all stakeholders under the scope of the Pharmaceutical Tracking System.

Products under the scope of this system are drugs and medical nutrition products.

Drugs: These are the prescription drugs which can be obtained only from the pharmacies with a valid prescription.

Medical Nutrition Products: These products are also known as "food supplements" and those used for medical purposes called "medical nutritional products". As with drugs, medical nutrition products require monitoring and they fall under the scope of the system. [25][28]

Products which are not in the scope of the system are;

Serums, radiopharmaceuticals and drugs manufactured for private use with the exception of medical food and enteral nutrition products lie outside the scope of the system until 01/01/2014. [25] [28]

CHAPTER 6. NICHE MARKETING STRATEGIES

In this chapter different subjects which has direct and/or indirect affect on a pharmaceutical company's niche marketing on orphan drugs and treatment of rare diseases will be explained. Since there are so many different factors contributing, they are explained with grouping under different titles.

All of the marketing application are valid and applied in niche marketing and the only difference from other marketing applications is that small size of the markets. Due to the natural characteristics of the pharmaceutical sector and its market, there are some difference that needs to be considered. One of them is that the pharmaceutical company is unable to advertise its products to the public because of the regulations applied by the ministry of health in Turkey, advertising is forbidden for the pharmaceutical products to the public. Only advertisements in form of promotions and informing the doctors who is going to prescribe that medicine and pharmacists by the sales team are only allowed. The other important factor to consider is that other than the price, the end user does not have any other choice but to buy that medicine in case of if she/he is ill.

Because especially with the treatment of rare diseases, procurement of the orphan medicines is the only option that the end user has, therefore marketing applications should be devised and adjust according to these factors.

There are two main groups of discussion under the main title of "niche marketing of orphan medicines and treatment of rare diseases." One of them is financial profitability and the other is generation of goodwill through philanthropic applications. During the evaluation of pharmaceutical sector both at Turkey and around the world, financial profitability and generation of goodwill are of equal importance. Financial profitability is important because of the pharmaceutical companies existence and sustaining the ability of creating new medicines and cures for the usage of public health. Also generation of goodwill through philanthropic applications are also important because as expressed in previous sections, not only these the positive goodwill outcomes of these applications are important for alleviation of public health issues which are crucial for the treatment of rare diseases and procurement of orphan medicines, but also these positive goodwill outcomes increases the chance of that pharmaceutical company to remain in those markets longer and stronger with its financial returns.

From the niche marketing point of view supply of orphan medicines by the pharmaceutical company and procurement of orphan medicines by the patients who are the end users are of equal importance with the treatment of rare diseases.

Treatment of rare diseases are a public health concern and should go hand in hand with the supply by the pharmaceutical company and access of patients to the orphan medicines. Treatment of rare diseases and access of patients to the orphan medicines are inseparable and should be dealt consecutively.

In order to observe and evaluate the niche marketing of orphan medicines and treatment at the Turkish pharmaceutical sector, subsequent sections will introduce and analyze different contributing factors and new ideas which might prove to be useful to apply, from the pharmaceutical companies point of view.

6.1 Market Challenges and Substitutions of Products

Large portion of the orphan medicines niche markets are belonging to the foreign firms because international pharmaceutical companies are making exports in order to satisfy the demand of the orphan medicines for the treatment of rare diseases all around the world however domestic companies are less able to access these markets both internationally and domestically. High cost of manufacture and low demand blocks the way of domestic firms to be active and aggressive in this field of market. Also the high technology and educated personnel requirement for the production of orphan medicines and difficult R&D processes are making the product development for the domestic firms more difficult.

According to the analysis conducted among 4 different rare diseases chosen among the OrphaNet database which are assumed to be easily remembered from the everyday life, there are 72 different medicines are currently in the Turkish pharmaceutical market for the needs of the patients suffering from rare diseases. Among these 47 different medicines unfortunately there are only 25 of them has bioequivalent medicine alternatives. And also the major part of both the reference and equivalent medicines are foreign companies products.

According to the price and information Rx System of Turkish pharmaceutical industry, very small portion of equivalent medicines (only 3 of them since their mg levels are; one of them is 20 to 1, the other is 40 to 1.) has quite low prices compared to the original ones however huge portion of them has still very high prices to afford by the patients in Turkey.

In general about substitutions of the orphan medicines rare disease of ovarian cancer has a good performance but still the prices of equivalent medicines are high compared to the prices of the original medicines.

Another issue with the orphan medicines is that the legal restrictions and inspections applied to the orphan medicines by the government. According the Rx, overwhelming portion of the orphan medicines are allowed to be accessed by the patients of the rare diseases on special conditions. These special conditions are defined at SUT rules of SGK.

Special conditions should be satisfied by those patients who would like to access to those medicines and the satisfaction level should be monitored with the health council of the SGK or with proficient medical practitioner. These applications are delaying the time of the patients who are in need of those medicines and sometimes it blocks it with SGK tells to the patients that they are unable to pay some the price of the medicines and they should procure that medicine with paying the total price.

As a conclusion for this section, if a company would like enter to this market with the current given circumstances given above would possibly face with the reimbursement conditions of SGK based on "special conditions." Also since the major part of the both reference and bioequivalent medicines are foreign companies products, possible competitors within the market will be the foreign companies themselves. However if the company will be able to manage its costs and would accept to forego some of its profit for philanthropic reasons company may be able to reduce the price and gain the market share from other foreign companies.

6.2 Profile of Patients and Procurement Approach

Within the context of the orphan medicine and treatment of rare diseases niche markets, there are some differences with other markets of pharmaceutical sector. As a customer (patient) profile also there are some important and different characteristics apart from other pharmaceutical markets such as;

- **Inaccessibility of patients to the orphan medicines and treatment of rare diseases;** patients of rare diseases in Turkey, just like other parts of world are inaccessible to orphan medicines that are used in treatment of rare diseases because of various reasons. Examples for these reasons are; expensive medicine prices, lack of reimbursement support, import regulations, lack of import alternatives, international regulations of WTO, insufficient domestic production, lack of donations of orphan medicines, lack of statistical information and unawareness of rare diseases by the government officials and practitioners.

- **Lack of time;** especially with the niche markets of orphan medicines and treatment of rare diseases this unfortunate aspect is surfacing itself. Availability of orphan medicines is a must however making it possible at the right and at the right place is also a must. So many of the rare diseases, syndromes are making the situations for the patients of rare diseases worse because many of the treatments require on time medicine intake by the patient and due to the lack of available orphan medicines by various reasons most of the patients are out of treatment or receive lack of treatment than as it needs to be. Because of similar reasons patients in this niche market group does not have enough time to wait.

- **Unidentified existence or exact location;** this is also an important characteristic of patients suffering from rare disease and in need of orphan medicines. In most countries especially with the European, middle east and north African countries, they do not have any statistical database about the existence and exact locations of rare diseases and therefore companies are unable to make predictions about possible demands of orphan medicines. Unawareness of both private sector and the government creates an important problem because the government is unable to develop a pharmaceutical policy and develop special reimbursement program in order to alleviate this public health problem and without these actions private sector is experiencing difficulties about entering this market. In order to make certain actions knowing exactly how many of the patients suffering from a certain disease and their exact location is vital.

  According to OrphaNet, these statistical data are given as prevalence and incidences based on the total population of 38 member countries however actual, accurate numbers of patients are still unclear.

As a procurement approach, pharmaceutical companies should cover even the most remote locations in Turkey because of the historical experience shows that many people in villages and even in places which are far from the locations of the villages.

According to the distribution system which is the same for the big cities and metropolises people go to the family practitioner, prescribe their medicines and then go to the pharmacists and procure their medicines. However with the case of orphan medicines and treatment of rare diseases, finding the orphan medicines at those remote locations are nearly impossible and this situation creates and inaccessibility to the medicines. Therefore usage of the procurement channels for the patients should be carefully analyzed both by the company and the government itself.

For the case of procurement of orphan medicines and the treatment of rare diseases, in order to make the process and procedures more easy for the patients because primary focus of the current legislations and legal procedures are reducing the fraud and efficiency at the management of the government resources however certain legislations and bureaucracy of the medicine procurement should be eased for the patients.

6.3 Suppliers and Supply Approach

Profile of suppliers from the end users (patients) point of view consists of two steps; local pharmacists and hospitals. Profile of suppliers from the companies point of view consists of raw material suppliers and pharmaceutical warehouses. Within the context of this research suppliers will be pharmaceutical warehouses and pharmacists. Distribution of the medicines are made through only with the pharmaceutical warehouses and access of medicines are made possible through pharmacists. Activities between pharmaceutical manufacturers, pharmaceutical warehouses and pharmacists are being controlled by the ministry of health and SGK, therefore without the permission of those authorities are nearly impossible because all activities of prescription and access of patients to the medicines are being electronically tracked by the MEDULA system.

However within the context of orphan medicines and treatment of rare diseases, this environment covered by the network of bureaucracy is lagging the time of access of patients to the orphan medicines as mentioned before.

At first sight MEDULA system looks as if it is sufficient enough to reflect the approximate usages of orphan medicines and indirectly shows the number of patients of rare diseases and their locations of.

However this is not the case because especially at remote locations and at small cities, practitioners are unaware of the symptoms of rare diseases even if they had the necessary education at medical faculties. With the addition of the well known lack of diagnosis performance of government hospitals at small cities most of the rare diseases are unknown, therefore not treated and as a result not recorded.

It is easy to make an educated guess from this situation that the orphan medicines are not even prescribed also. Education and increasing the awareness of doctors, healthcare service providers is crucial which in later sections will be emphasized.

As a supply approach, coordination of the private sector with SGK and ministry of health is a must. Just like the emergency services provided to the farthest locations on Turkey, orphan medicines should be delivered directly to the patients themselves whenever it is required because some of the patients are unable to be transferred to the nearest hospital therefore service based on locations is necessity. However to achieve this service quality, necessary amount of statistical data about the locations of diseases, syndromes and their exact number of patient should be gathered, analyzed and actions should be devised in accordance with that.

For a fast pace of system working with providing the treatment of rare diseases and orphan medicines to the patients, both NGO's, ministry of health, SGK and private sector companies should reach to a consensus on philanthropic course because all parties of this will satisfy from the generated goodwill from the alleviation of public health concerns.

Finding a cure to a long lasting public health concern is one of the duties of the government with the combination of its power of making legal legislations and facility of improving the infrastructure level of the country, government should provide the upmost cooperation to the private sector during these operations and when giving incentives and support, domestic companies should be given prioritized.

6.4 Product Standards and Their Range

Orphan medicines product standards are all comply with the GMP applications which is mandatory internationally. Therefore production of medicines has its own and same standards.

In Turkey and especially developing countries around the world, FDA rules and application are strictly followed by the relevant ministries of health. As product specifications and characteristics the following can be given;

- **Raw material costs;** generally at most of the scientific resources which orphan medicine issues covered, it has been expressed that the reason behind the high costs of medicines is that their low demand and therefore low sales rates of pharmaceutical companies because low demand in conjunction with the low sales rates may lead to the companies to avoid those markets because of the cost of generating products. However this is not the only contributing factor to expensive costs, there is also the high raw material costs. Raw material costs of some orphan medicines is high because of their high technology manufacturing requirements. These medicines are addressing to the most fatal and vital diseases, therefore their raw materials are more expensive compared to the ordinary medicines.

- **Low demand and low sales;** as expressed previously, since there are very small amount of patients of rare diseases, there is also low demand of orphan medicines. Therefore new entrants to the market fear that their investment costs will not be subsidized totally in order to make profits from the orphan medicines and treatment of rare diseases.

- **Reimbursement support of the government;** as mentioned at previous sections, reimbursement support is relatively low compared to other medicines by SGK. This situation has a conjunction with the low demand of orphan medicines because as low demand there are low sales which means support of those medicines both not financially viable and contributive to the overall public health concerns.

Since efficient usage of government resources mandates officials that supporting the medicines for diseases which suffered most based on number of patients nationwide. Therefore low reimbursement can be based on this situation.

At the same time this low reimbursement level makes the situation of patients of rare diseases even more difficult because only those who can afford the expenses of treatment of rare diseases and costs of orphan medicines. Since the percentage of the patients who can afford these expenses are quite low, the need for the reimbursement is getting vital day by day.

For the product range, according to the analysis conducted on 4 different rare diseases chosen from the OrphaNet database among those assumed to be familiar with everyone from their daily life. Those diseases with their number of medicines are;

1. **Tumor of Endocrine Glands;** 25 reference medicines, 0 equivalent medicines.
2. **Renal Cell Carcinoma**; 12 reference medicines, 4 equivalents medicines.
3. **Ovarian Cancer;** 6 reference medicines, 20 equivalent medicines.
4. **Uveitis;** 4 reference medicines, 2 equivalent medicines.

It is a fortunate situation to observe the number of equivalent medicines which gives a good opportunity about the procurement of orphan medicines for the patients of rare diseases. However according to the Rx system, when reference and equivalent medicines are benchmarked on the basis of milligrams of active ingredients as given at Table 9, the price reductions observed with equivalent medicines are assumed not enough to be purchased by the patients. Within the context of the pharmaceutical sector of Turkey, there are only 7 domestic companies products against 18 foreign companies product which is low. Also if the prices benchmarked between domestic and foreign companies, domestic companies products' prices are quite low ranging from 45,57 ₺ to 256,20 ₺ which is quite low compared to the expensive prices of foreign companies which reaches 6000€ and 9.863,90 ₺.

Therefore certain investments can be supported by the government to the domestic companies in order to offer cheaper alternatives of expensive foreign medicines. Because of the link between the amount of reimbursement support with the level of prices, reduction in price can increase the chance of being supported by the government and SGK through reimbursement systems. For the detailed pricing information of orphan medicines and rare diseases see Table 9. Price Research of Orphan Medicines at Appendix.

6.5 Analysis Methods

Process research is used to understand the factors that are effective on drug usage and to determine the best method on supply, distribute and usage of orphan medicines. With the outcomes of this research the primary aim is to reach practical and cost efficient decision making on subjects of R&D of medicines, neglected infectious diseases, determination of new dosage levels, process methods, research at chemical and molecular biology, conducting orphan drugs and vaccines clinical and field experiments.

The most important obstacle here is to medical practitioners and policy makers does not have the time to make process research and therefore they are not giving the necessary effort on this subject. Second most important difficulty is that the results of this process research are not used for strategy development and preparing of action plans.

Process research is therefore should be conducted with policy makers contribution and governments should fund these research.

6.6 Process Research

There are different mechanisms developed within the context of national pharmaceutical policy for process research. Examples for these mechanisms as standardized variables to monitor the national policies, application of these variables at the local healthcare facilities and sampling methods. Standardized variables and sampling methods are created a measurements for making comparison among different countries and regions. A multinational cooperative research projects can help to the pharmaceutical development.

6.7 Orphan Medicines and Treatment of Rare Diseases Niche Marketing From 4P's of Marketing Point of View

Since this field of marketing deals with the orphan medicines and rare diseases from a pharmaceutical companies point of view, one should evaluate the situation and circumstances and what can a company do as a course of action from 4P's of marketing point of view. The four pillars of this marketing approach are; product, price, promotion and place.

6.7.1 Product

Product variety; changes depends on the treatment of the rare diseases. Since as of product variety orphan medicines does not have any difference with the normal medicines the following can be given as different product varieties; solid (powder, dragee, capsule, tablet, pill, suppository, and sachet), liquid (solution, suspension, tincture, extract, syrup, potion, lotion, elixir, milk, aerosol), half solid (ointment, transdermal therapeutic system, patches).

Since very small markets has distinctive features such as diseases specialties and treatment differences a pharmaceutical companies which would like to make an investment in orphan medicines production should consider combination of different rare diseases into one single pharmaceutical product which is currently practiced by the international pharmaceutical companies. Combination of different active or secondary substances in order to be able to market them to different marketing segments which are different rare diseases is useful to alleviate the diseases burden of rare diseases patient and therefore help to the public health concern also in order to make the orphan medicine production and marketing more financially viable. According to the analysis conducted through Rx, various differences both between the 4 target rare diseases and also their medicines positive effect on other rare diseases. (For the ease of the analysis it is advised to see Table 10 and Table 11 together) At Table 10 there are also number of approximate populations of other rare diseases which the original diseases medicines are effective and Table 11 their prospective and approximate export volumes of both the target and other rare diseases are given. Target diseases are in italic and in upper side, other diseases are below of them with the thick box. Table 10 and 11 can be found in Appendix A.1.

6.7.2 Price

As explained in Section 2.6.4 "Reflection of Reimbursement Systems on Pricing" and in Section 4.4.3 "Pricing System"; pricing of all pharmaceutical are being regulated by the ministry of health. There are also indirect regulations such as the SGK's reimbursement systems as explained in Section 2.6 "SGK and Third Party Financer Reimbursement Systems." which is of primary importance for the pharmaceutical company. Within the context of this research, different prices of 72 orphan medicines used at the treatment of 4 target rare diseases and other than these 4 different diseases there are also 10 other rare diseases which orphan medicines of 4 target diseases can be used for their treatment.

According to the observations made through Rx orphan medicines prices are so high. Also if the medicine prices even the ones with prices ranging from 150 ₺ to 270 ₺, these prices are also very high to purchase by the patients living in Anatolian regions except the metropolis cities. Since within the context of this work, the primary aim is to make every patient of rare diseases to be able to reach orphan medicines. Thus to achieve this, one of the many difficulties that the patients face is the very price itself. There are two important pillars that can be count as a result of price reductions. One of them is when the prices are lowered, than many patients are able to reach to those medicines and therefore alleviate their health problems caused by the rare diseases. Secondly reduction of prices are philanthropic course of action because so many of the patients of rare diseases are unable to afford the prices of medicines. So reduction of prices are of vital importance.

According to the Rx data of medicine prices and reimbursement information, it can be seen that many of the medicines are reimbursed on "Special Conditions". Therefore it is believed that reduction of prices may help the government to reimburse those orphan medicines on more "procurement of patients based" and more accessible terms. Because it is obvious that for the ones who cannot afford those medicines, the only way to access those medicines is SGK however because of the daunting bureaucratic rules does not permit total access to those medicines, this situation makes the job more difficult for the patients of rare diseases.

6.7.3 Promotion

Since making the promotional advertisements and running promotional campaigns by any means are forbidden in Turkey, pharmaceutical companies can make rare diseases based promotional campaigns which aims to raise the public awareness on certain rare diseases issues. As a result company will be also promoted its own orphan medicines that awaits its patients.

Running promotions also helps to raise awareness on two different sides; on patients who are unaware of their rare disease or haven't heard that there is a cure for it and on government which does not have any statistical database on this orphan medicines and rare diseases issue.

Because of not having a relevant database about orphan medicines, government officials are unable to make any legislation and therefore act to solve this problem. With the sponsorship of the pharmaceutical company certain experts on the rare diseases can make public speeches and travel different parts of the country for the raise of awareness. Distribution of brochures and schematics of rare diseases symptoms and with a content of showing differences between rare diseases symptoms with other diseases.

Also another part of the promotion can be made to the doctors which "reminds" them the symptoms of rare diseases with promoting the orphan diseases in order to increase the number of prescriptions. This part of promotion is important because especially in remote locations and in small cities many practitioners are unaware of the symptoms and therefore the rare diseases themselves. With the addition of unawareness of orphan medicines existence, diagnosis, prognosis, report and record of the cases encountered will be difficult and mostly impossible.

Therefore running promotion can also help to raise awareness on all sides and helps for the recognition of orphan medicines.

6.7.4 Place

As expressed in depth at Section 3.6 "Representative and Distribution/Sales Medical Warehouses", medical products and pharmaceutical medicines are being distributed with medical and pharmaceutical warehouses.

Therefore pharmaceutical company should rely on the supply network of existing warehouses within the pharmaceutical sector. However if government and pharmaceutical company can reach an agreement about certain legislations and cooperation on distribution of orphan medicines especially the ones with urgent by the expecting patients.

In accordance with this cooperation, relevant marketing channels and supply chain management can be adjusted. Within the context of the place, exact location and total number of demand is important since production of orphan medicines are adjusted in accordance with these statistical values therefore this is important.

Direct reach to the patients is a must because most of the low and middle level income patients living in Anatolia except the metropolis cities are living villages and remote locations therefore orphan medicines should be delivered directly to them.

On time and on demand delivery is only possible with the combined effort given both by the pharmaceutical companies and government institutions. MEDULA system can be upgraded to notify the authorities about the certain demand of orphan medicines which may give hint about the possible rare disease patients location. However as statistical information shows its necessity again, all of the supply chain adjustments are based on statistical analysis therefore establishing the relevant statistical database about orphan medicine demand and treatment of rare diseases is a must because predictive statistical information of Orphanet would not be suffice.

6.8 Distinctive Features of Orphan Medicines and Treatment of Rare Diseases

At first sight, it can be seen that both normal and orphan medicines are being treated with the same precaution and applications however there are special contributive factors which analysts and pharmaceutical companies should take into account. This section consists of a summary and emphasizes the special factors related to orphan medicines and treatment of rare diseases.

First of all, orphan medicines have very little demand compared to normal medicines, therefore it is difficult for the pharmaceutical companies to predict the demand, produce the medicines and conduct the marketing operations to the patients rare diseases and practitioners.

Secondly, unawareness by the practitioners, patients and by the government officials makes orphan medicines and treatment of rare diseases job much more difficult than ordinary medicines. Without the statistical information, practitioners are having difficulties to remember the rare diseases which they educated at medical faculties of universities. This situation is important because everything about the public health issue of orphan medicines and treatment of rare diseases starts with the diagnosis of practitioners, since rare diseases are not encountered usually, they are hard to detect by the practitioners.

Without the detection made during the diagnosis process, patients can end up with being diagnosed with different illness and therefore receive different medicine and also their rare diseases are not being recorded which was a vital information also for the policy makers within the government. Government is unable to make certain legislations and mandatory applications in order to solve this problem without the statistical information which consists of the reports being made by the practitioners based on cases encountered. Therefore raising awareness is a philanthropic and a vital course of action aside from generation of profits.

Third, the orphan medicines and rare diseases has limited amount of time and necessary facilities during the procurement of orphan medicines by the patients of the rare diseases. As ordinary illness requires certain medication within a certain amount of time, orphan medicines requires these medication more urgently because as mentioned previously, some practitioners are unable to detect the rare diseases which means many people needs to go to the different practitioners until their rare disease has been detected. Therefore this reduces the time required for the treatment of rare diseases.

Fourth, certain bureaucratic rules and applications does not let the patients to procure the necessary orphan medicines for the treatment of rare diseases.

Since applications of SGK in order to reduce the fraud and therefore are more suitable to apply to ordinary medicines, they cannot be applied to orphan medicines and rare diseases. Reduction of bureaucratic rules and applications should prove to be helpful with the problem access to the orphan medicines.

Fifth, difficulties at reimbursements are making the access and procurement of orphan medicines by the patients of rare diseases more difficult because it should be not only having access to those medicines are not enough but also at affordable prices and if possible for free. At these circumstances government institutions and pharmaceutical companies should reach an agreement and if possible pharmaceutical companies should reduce their profits from the marketing operations as much as possible.

After considering these important feature, one should look at the niche marketing strategic action plan to see what can a pharmaceutical company do to with orphan medicines and treatment of rare diseases from marketing point of view.

6.9 Niche Marketing Strategic Action Plan

Niche marketing strategic action plan consists of course of actions which addresses to two different main subjects;

1. Corporate social responsibility of the pharmaceutical company.

2. Financially viable and profitable marketing application.

These two titles are the outcomes that the pharmaceutical company is going to receive on its way to devise and apply the course of actions against the public health problem of orphan medicines and rare diseases.

The pharmaceutical company certain course of actions to gain the results of the main subjects given above such as;

- **Establishment of the JPPI's:** Private pharmaceutical companies can join together with the contribution of the government institutions to form a company named JPPI (Joint Public and Private Initiatives) for the production of the low priced alternative of orphan medicines in order to supply the necessary medicines.

  Therefore company can also use the necessary voluntary and compulsory production licenses which are used to make generic versions of the reference drugs especially for the patient groups who are unable to afford granted by the originator company which is an application of the WTO's TRIPS.

  Some minor issues and setbacks might be resolved about the compulsory and voluntary licenses before the initiation of production with the help of the sanctions power of the government. JPPI's such be based on a private pharmaceutical company and such periodically report to the ministry of health.[29]

- **Protection of the Domestic Manufacturers:** Within the context of the voluntary licensing (VL) and compulsory application(CL); according to the experts companies who are selling with the VL are forcing other firms to lower their prices.

Government at this point, can apply certain measures and mandatory applications there in order to break the certain restrictions and protect the domestic firms.

By enacting certain new taxes on foreign import medicines which does not have any generic equivalent in domestic market to protect domestic manufacturers. Because of the mandatory applications of VL and CL such as restrictions of export or conducting marketing and selling based on the consent of the patent holder, may make the situation for the domestic company difficult. However usages of VL and CL's can speed up the new product development and makes the company do not struggle with clinical studies, patent and manufacture/selling license approval processes.

Therefore for reaching the rare diseases market usages of these licenses by the domestic companies or newly developed ones (such as JPPI's) within the context of the WTO's TRIPS is advised.

- **Construction of the Statistical Database:** As expressed previously non existence of the national statistical database is making market research and therefore investing into the business harder.

  Since OrphaNet is a EU funded and collecting information from approximately 38 countries which are based on "estimations", data collected from that very only source making the market research task more difficult and ambiguous. To solve this problem establishment of "National Database of Orphan Medicines and Rare Diseases" is a must. This could be sponsored by private companies and which could act like TurkStat.

  Organizing "Mobile Diagnosis/Prognosis Reporting Centers" expert practitioners can travel across Turkey both the metropolis cities and to even remote locations to collect relevant data periodically which gives strong and solid information both for the domestic and foreign companies about the existence of patients of rare diseases and for the demand of orphan medicines.

These mobile centers software can be combined with the existing MEDULA medicine tracking system to make prescriptions at the same time when the cases encountered.

After the construction of the database the most important action is to combine the relevant international databases such as WHO, ministries of health of the contributing nations, OrphaNet and Medecins Sans Frontieres (Sınır Tanımayan Doktorlar) which provides 24/7 and free access on both the number of patients of rare diseases and their orphan medicine consumption which is of vital importance both for the government institutions and private pharmaceutical companies.

- **Raising Awareness About the Rare Diseases and Existence of the Orphan Medicines:** As mentioned at previous sections, some practitioners especially at remote locations are unaware of the rare diseases and their symptoms which are assumed to be the lack of cases encountered. Therefore private sector and individual companies can run promotional campaigns and practitioner promotions in order to raise awareness about the existence of the rare diseases. This operation can be based on the existing promotion operations which are made to the practitioners.

  Raising awareness at government institutions is also required because government officials who are unaware about this orphan medicines and rare diseases issue can make enact certain legislations and most importantly include the public health issue of orphan medicines and rare diseases to the "National Health Policy of Turkey" which is assumed to be huge effect both on international and in domestic market about the existence of the patients of rare diseases in Turkey.

Raising awareness on patient is very deep but very important subject at this point which leads to different and a number of positive outcomes at its ends. Patients awareness is important because it leads to the "Rational Usage of Medicines" which is important especially at the scarce amount of orphan medicines provided to them. This is emphasized because it has a direct effect on the course of the treatment of rare diseases which is one of the primary objectives of the entire operation.

To achieve this company can run promotional campaigns to promote the awareness on rare disease by addressing to the symptoms of the rare diseases. Also another outcome of this is to make the patient to consult to the physician with notifying the possible symptoms of rare diseases which is of vital importance both for their treatment and for the public health. Just like the mobile diagnosis/prognosis centers there should be also "Mobile Blood Collecting and Analysis Centers" to diagnosis and run certain blood analysis for more accurate and detailed tests which prove to be useful on gathering statistical information about rare diseases. This information is also useful for the notifications of patient about their rare diseases. These different analysis centers can be combined and act together if possible.

- **Support of The Parallel Import:** If granting processes of VL and CL takes longer than it needs to be then as defined in WTO's TRIPS application support of the "Parallel Import" can be used. In parallel import, individuals or a corporation (which can be as a JPPI) can import certain vital and important orphan medicines directly from abroad to satisfy the needs of the patients of the rare diseases.

  This philanthropic action has a great positive impact both on the government and to the private companies which are contributing to this operation however there is an important factor to consider purchase of every orphan medicine from abroad and directly importing is very expensive and as a result financially not viable. Therefore this operation should be applied to the most vitally and urgently required orphan medicines.

- **Donation of Orphan Medicines;** Just like supporting the parallel import, donation of the orphan medicines can also be applied to the most urgent and vital medicines. This could be applied by the domestic companies after production of orphan medicines are achieved.

  This action's philanthropic side is superior therefore very little or no amount of financial revenue is expected to be generated however as explained previously within the context of this research positive well known and reputational gain could be generated at the end of this operation which is important for the companies retention in the market. Listing application to detect the most important and vitally in need patient should prove to be useful at this point.

- **Rational Medicine Usage;** This subject is important same as the usage of ordinary medicines because pharmaceutical and medical warehouses are holding inventories of medicines as well as government however uncontrolled prescriptions and as a result uncontrolled distribution of medicines are causing stocks to diminish therefore government institutions and pharmaceutical and medical warehouses are unable to supply the necessary medicines. Also without the rational usage of the medicines, uncontrolled usage of orphan medicines which most of them have intense effects on human body may cause the treatment of the rare diseases fail or even worse the death of the patient. Since promotional campaigns can be run about the rational usage of medicines without giving the trade names since it is restricted and directly targeted to the patient of the rare diseases. Companies can also use existing INRUD and WHO's education sets about "Rational Medicine Usage" and also can develop their own version of these educations which are based on orphan medicines. This is important about for the pharmaceutical company's addressing to this public health issues.

- **Combination of Market Segments:** Since within the context of niche markets of orphan medicines and treatment of rare diseases the market volumes are quite low, therefore potential investors, should make the necessary market research to find out whether to combine the existing small markets in order to create a financially feasible investment alternative. According to the Rx medicine information system some orphan medicines have the ability to cure different orphan medicines.
  Therefore instead of developing different medicines for each of the rare diseases, some diseases can be combined into one single orphan medicines as much as the pharmaceutical technologies permits. With this, company will be able to create a low cost alternative of developing generic version of reference orphan drugs which paves the way to the access of patient to the required medicines.
  Also the single combine medicines are much more easy when it comes to the management of supply chain which saves more time both for the pharmaceutical and medical warehouses and the government institutions. Detailed information for the medicines which can be used for the treatment of multiple rare diseases with their estimated number of patients in Turkey at Table 10 in Appendix A1.

- **Decrease of the Raw Material Costs;** Since many of the ingredients including the active ingredient of medicines are currently imported from abroad, if raw material manufacturers of these ingredients can only be included in the course of resolving the orphan medicine development and manufacture issue with their decreasing the price of the raw material costs as much as possible, this assumed to have a reflection on the final price of the medicine. With the support of the government, private companies are able to make certain agreements to reduce the raw material costs.

- **Use of Government Incentives During the Orphan Medicine Development Process;** Small companies which would like to invest on orphan medicines production may experience financial difficulties during the investment and product development phase due to the high cost of clinical trials applied.

  Therefore government has different special incentive programs for these innovative firms to help financially. Pharmaceutical company can satisfy from TEYDEB which offers different steps of support such as;

  1st Phase: Conceptual Design

  - Understanding Demand
  - Ideation of the Product
  - Idea for Process of Manufacturing

  2nd Phase: Technology Development

  - Design of the Product
  - Product Prototype
  - Production System Design
  - Pilot Production

These steps are useful for the issue of orphan medicines development especially for the domestic companies.

The Technology and Innovation Funding Programs Directorate (TEYDEB) supports the R&D activities of private sector organizations. In the pharmaceutical sector, a total of USD 45 million were provided to 172 unique pharmaceutical projects between 2000 and 2012. It constitutes a 3.3% share of total grants within that period.

TEYDEB also covers some operating expenses such as; [25]

- Personnel expenses
- Equipment, hardware, software and purchases of publications
- Consulting services locally and internationally as well other services
- R&D expenditures incurred by universities within the country, R&D centers associated with TÜBİTAK and similar institutions.
- Material and other related expenses
- Travel expenses of project personnel and – if applicable – of consultants
- Project preparation expenses (only for Support Program No. 1507)
- Certified Public Accountant expenses (only for Support Program No. 1507)
- Expenditures regarding patent registration from the Turkish Patent Institute [25]

There are also SAN - TEZ projects which the cooperation of universities and industrial companies also supported by the government institutions. Direct financial support is available for the adaptation of new technology, process development, the improvement of quality and environmental modification projects via university partnerships. Up to 75% of the project budget can be supported by direct grants. [25]

CHAPTER 7. COORDINATION OF PUBLIC INSTITUTIONS TO REACH NICHE MARKETS

7.1 Monitoring and Evaluation

Monitoring and evaluation should be a part of the national pharmaceutical policy. These monitoring instruments should be consisting of necessary personnel and a working budget. Except the time, human resources and budget deficit, there is a resistance, to understand the importance of monitoring the events on time and to evaluate the formulated activities with objectiveness.

7.1.1 Monitoring the National Orphan Drug Policies

It is advised that the orphan drug national pharmaceutical policy should be monitored on the basis of situation at its beginning phase throughout the country. The output of this research can be used as a starting point. The research also helps to detect the issues at pharmaceutical sector. Repeated region and nationwide research provide important information for the decisions made and policy decisions.

7.1.2 Key Policy Subjects

Monitoring and evaluation is a cornerstone of a nationwide orphan drug policy. Key policy subjects are as below;

- Government assurance for the monitoring and evaluation.
- Monitoring the pharmaceutical sector with constant measurements.
- Evaluation of the effect of orphan drug policies on all the sectors of the public and the economy.

7.2 Changing Pharmaceutical Sector Dynamics

7.2.1 Globalization

Globalization is an important factor to consider when assessing the pharmaceutical sector. It is now almost impossible to evaluate the overall performance of domestic companies both in domestic and foreign markets because it is obvious that large portion of both the domestic and foreign markets in pharmaceutical sector has overlaid.

The international regulation standards such as WTO's TRIPS, compulsory licenses, voluntary licenses and SPC, INRUD, WHO, GMP rules, and EU regulations which are mandated to the Turkish domestic pharmaceutical (just like the mandated rules applied to international companies in Turkish domestic market) in order to be able to challenge with the international foreign companies at their home market, should be taken into consideration when making assumptions and plans about pharmaceutical investments. Güneş[30]

Because especially at foreign export based marketing, there are so many applications which are some of them mandatory and some of them are binding with other rules should be reviewed carefully and therefore applied satisfactorily in order to avoid other regulations which may lead to blocking of export and cancellation of license at the relevant country. These international regulations creates both restrictive and value added chain to the international pharmaceutical markets because if both sides of the import and export transaction which can change from raw materials to the end products.

As long as this system works functionally, overall top standards of product quality can be maintained.

Globalization has an important contribution also at niche markets of orphan medicines and treatment of rare diseases. Both at procurement and rational use stages of orphan medicines and their affect on treatment of rare diseases, globalization serves its benefits such as communication and gathering of different patient groups which is important for the market generation and also improving their quality of life. The most important factor at access of patients to the orphan medicines and treatment of rare diseases is communication which can only be achieved and sustained with the globalization. Therefore globalization is an indispensible and inseparable subject of niche marketing of orphan medicines and treatment of rare diseases.

7.2.2 What is Voluntary Licensing?

Typically, a VL is where a pharmaceutical company that holds patents on a product (patentee) offers on his own accord a license to a third party (usually a generic producer) to produce, market and distribute the patented product. In exchange, the patentee will usually request a royalty on the net sales made by the licensee as well as impose other restrictions, such as geographical restrictions on where the licensee can sell the product, restrictions on what price the product may be sold at and any other terms or conditions it might insist on. This type of licensing is also referred to as "outlicensing".[26]Amin[27]

7.2.3 What is Compulsory Licensing?

Compulsory licensing is when a government allows someone else to produce the patented product or process without the consent of the patent owner. It is one of the flexibilities on patent protection included in the WTO's agreement on intellectual property — the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement.[26]Amin[27]

7.2.4 Information Society and Information Technology

In today's world the importance and the affect of information technologies to the pharmaceutical sector is crucial. Information technologies are used starting from the production phase both pharmaceutical products and raw materials and continues at with the usages of patients and the calculation of the expected effects on them. Usage of information technologies not just adds speed of to processes but also increases the accuracy of results of the tests made and reduces the risk of making errors during the tests.

With the help of information technologies and at the same time being information society of members of pharmaceutical market, niche marketing of orphan medicines and treatment of rare diseases are more easier than it used to be because with the information technology systems patients can share their thoughts, feelings and pharmaceutical information with other patients and pharmaceutical companies.

This improves the chance of gathering information about efficacy of orphan medicines on treatment of rare diseases and provides vital data for the development of new drugs in order to use at the treatment of rare diseases. Notification of officials about the prevalence of rare diseases both at metropolitan cities and on remote locations is possible with the information technologies.

Just like the other sections of the world pharmaceutical sector, supply and range of orphan medicines and therefore treatment of rare diseases are racing with time because some rare syndromes and diseases requires efficient and on time procurement of their relevant orphan medicines thus usage of information technology is important.

Number of patients and their specific location is consisting the basis of all research conducted on orphan medicines and treatment of rare diseases. Fast and efficient connection between patients and companies and therefore with the government is important and only possible with the information technology.

7.2.5 The Role of Government

Since the government stands both as a giant buyer and regulator, the role of government in Turkish pharmaceutical sector is important and continuous. Government is a giant buyer because of the medicine procurement made through public hospitals and other public institutions such as SGK as explained in previous sections. Major part of the sales made in Turkish pharmaceutical market is made to government itself, therefore most of the companies operating are adjusting their demand in accordance with the demand created by the governments themselves. Government bids and other procurement incidents are very important for every pharmaceutical company because of the amount of sales made.

Government is also important because of its regulatory role both at administrative and incentive level. Government regulates the pharmaceutical market by applying mandatory rules to all of the operating companies in order to maintain certain production standards and positive contribution to the country's economy. Government also plays the role of indirect connective bridge between foreign markets and domestic companies.

Foreign mandatory applications are inspected and applied via the local government authorities and also international government level communication is established via the local government officials with the domestic companies. Thus administrative role of government is indispensible for the efficiency and sustainability of pharmaceutical sector.

The other regulatory level of the government is incentive level. Since the government is responsible about the management of the ongoing activities and direction of economy, with giving incentives to certain sectors, governments are indirectly supporting them in order to expect positive contribution to the overall economy.

In Turkey some incentives are given as financial exemptions such as;

- Income tax exemption
- Corporate tax exemption
- Income tax exemption for researchers
- Developers and R&D personnel
- Social security premium support and value added tax exemption.

Also government can also apply different incentive and support programs such as;

- TÜBİTAK - TEYDEB program
- TÜBİTAK Industry R&D Projects Support System
- Law No.4691 on Technology Development Zones
- Law No.5746 on Supporting R&D Activities
- Entrepreneur Support (TÜBİTAK / KOSGEB)

7.2.6 Generation of Government Support at Reaching Niche Markets

Within the context of this subject the most important factors to consider are information share, logistics support and convenience at legal legislations and mandatory applications. Information share is important both for identifying the location of patients suffering from rare diseases and unable to access to orphan medicines. Both at financially profitable and philanthropy point of view information exchange with different parties such as NGO's, government institutions, private manufacturing and distribution companies.

Once the information network is established, logistics support of the government is important because no matter how the orphan medicines are manufactured in Turkey or imported from around the world, the logistics management within the borders of Turkey is an important factor to consider. Within the context of the logistics management, reliability of logistics firms and pharmaceutical warehouses are of crucial importance.

Pre made agreements and history of companies compliance with the on time delivery and cold chain transportation standards can give certain indications to the company that is planning to invest.

Convenience at legal legislations and mandatory applications are also important because flexibility at these subjects can buy some time and easiness of work to the company that is planning to invest. As expressed at previous sections, acquiring a manufacturing, sales and marketing licenses has different stages and most of them require in depth understanding therefore helping the companies at this point is important with easing the legislations or at least giving consulting about the procedures are important.

With taking into consideration of the current situation at orphan drug market and the current industrial vision of Turkish Republic, it is forecasted that the government will enhance and support the public health and advancement objectives with the aim of Turkish pharmaceutical sector's sustainable and efficient growth.

As TUBITAK has declared within the context of Medical Biotechnology Road Map, that they are going to generate programs for bioequipment, vaccine and medicine fields (1003 Top Priority R&D Program), 1007 (Program of Supporting Public R&D), and 1511 (Prioritized Fields of R&D and Support of Innovation program).

Especially at 2013, they had opened "Generic production and development of bioequivalent medicines) and " Anti Viral, bacterial pathogen and parasites vaccines programs" and at 2014 "Epidemiologic Works" and at 2015 "Biotechnological / Biosynthetic / Synthetic new candidate molecules for medicine development, its patenting and preclinical works are declared to be funded.[8]

CHAPTER 8. CONCLUSION

This niche marketing approach to orphan medicines and treatment of rare diseases and course of actions listed in the previous section are making a great example of how to gain financial returns from the niche markets of rare diseases and philanthropic gains at the same time. Throughout the context of this research study the necessary titles which a pharmaceutical company can face during the course of the niche marketing application on orphan medicines and treatment of rare diseases has been gathered together as much as possible and explained from a private pharmaceutical company's perspective.

A pharmaceutical company can combine different active substances into single medicine, therefore different rare diseases can be treated with the usage of a single medicine. Within the context of the niche marketing this is the combination of different market segments. Combination of these niche markets into a single and a big market, enables the company to focus on that market with efficiency which leads to the reduction of the prices. Overall price reductions enables patients of the rare diseases to procure the orphan drugs and at the same time enables the government which is also a huge healthcare service provider, to distribute to the patients of rare diseases who are at the same time unable to purchase those medicines through the reimbursement applications of SGK.

With the applications of niche marketing, company can also increase the awareness on the current rare diseases. Raising awareness on rare diseases has multiple positive outcomes, for the company, the patients, the practitioners and for the government institutions. For the company raising awareness was important and effective because advertisement of medicines are prohibited in Turkey. Therefore with raising awareness on rare diseases, company also advertises and markets its own medicines without giving its trade name. With this way, company increases its own sales and create new niche markets for its operations. From the patients point of view, raising awareness was also important because most of the patients of rare diseases are unaware of their rare diseases. Therefore raising awareness within the context of the niche marketing is important for the generation of new niche markets and prospective customers.

From the practitioners' point of view, it is also important because most of the symptoms of rare diseases are hard to be detected by the practitioners due to their small incidence and prevalence numbers. Therefore with the implementation of niche marketing practices, practitioners will have been reminded with the existence of rare diseases which will also increase the rate of prescriptions of orphan drugs. As a result of more prescriptions by practitioners the pharmaceutical company will increase their sales of orphan drugs. Also within the context of niche marketing, establishment of the information network and system of on time delivery of orphan drugs to the patients of rare diseases will lead to the increase of sales and therefore increase of financial returns from the implementation of niche marketing of orphan drugs.

Within the context of the niche marketing, establishment of the JPPI's, protection of the domestic manufacturers, construction of the statistical databases, support of the parallel import, donation of orphan medicines, rational medicine usage, combination of existing niche market segments of orphan medicine, decrease of raw material costs and usages of the government incentives during the orphan medicine development process are all useful practices which will help increase financial return from the niche markets of orphan drugs.

Another important point to be emphasized is that philanthropic gains at the end of this niche marketing application will be great to the pharmaceutical companies because the most important aspect of life is the human health, therefore helping to even a single person and alleviating the burdens of diseases of the patients and helping them to continue to live their daily life's without reducing the overall living quality is of great importance all around the world and at all times. This niche marketing application can be implemented to orphan medicines which could alleviate the pain of thousands which it's a positive return of brand value which can benefit for the company as retention in the market. Generation of new domestic industrial companies also which contributes to the overall Turkish economy and creates new employment opportunities for Turkish young highly educated workforce at the same time.

With this application of niche marketing on orphan drugs, all parties of pharmaceutical market are expected to achieve positive gains, beginning from the company which will have financial gains and advancement of brand value and ends with patients of rare diseases who will gain the opportunity to procure the orphan drugs and alleviate the burden of rare diseases of patients which was an important public health concern.

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10. APPENDIX

10.1 A1 TABLES AND DIAGRAMS

Diagram No.1

Diagram No.1; Reimbursement Relationship of Institutions

Table No.1: Reflection of Reimbursements on Pricing[25]

Sales Price to Wholesaler (SPW)	Reference Prices		Generics	20 Year of Patent Ends		
SPW ≤ 3.83	0%		0%	0%		
3.84 ≤ SPW ≤ 7.32	Without Generics	With Generics	10%	0%		
	10%	10%				
7.33 ≤ SPW ≤ 11.01	31%	18%	18%	Production	With Ref.	Without Ref.
				10%	10%	10%
11.03 ≤ SPW	41%	28%	28%	28%	28%	40%

Pharmaceutical companies have to apply to the Ministry of Health and SSI in order to include their drugs in the reimbursement program. Reimbursement procedures for different pharmaceutical products and medical devices may differ and are explained in detail in the SSI (SGK) Health Application Registration. Reimbursement is made for the pharmaceuticals that are at most %10 above the determined price of the related pharmaceutical in the generic group. Discounts are applied by pharmaceutical companies and pharmacists to the public for pharmaceutical purchases.[21][25]

Table No.2: Historical Development of the Industry [1]

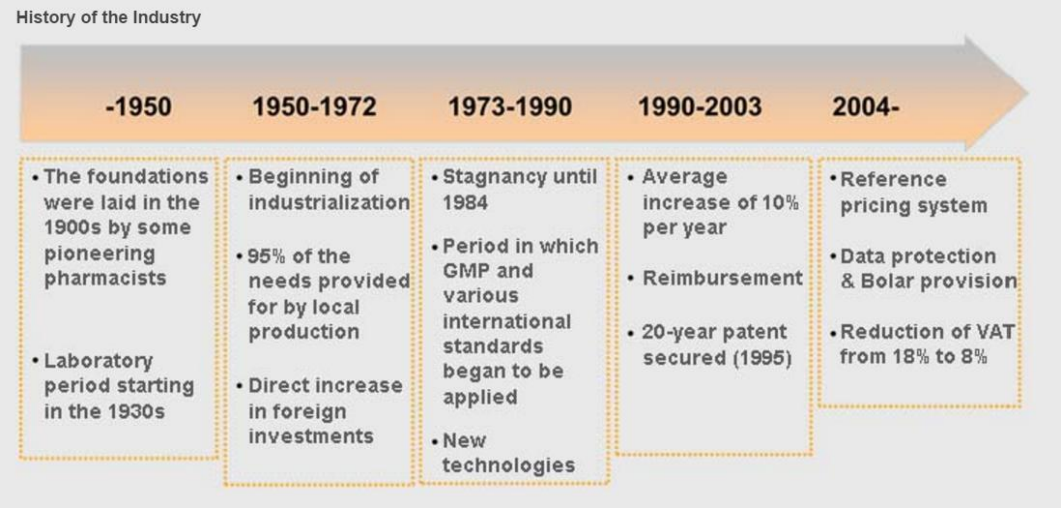


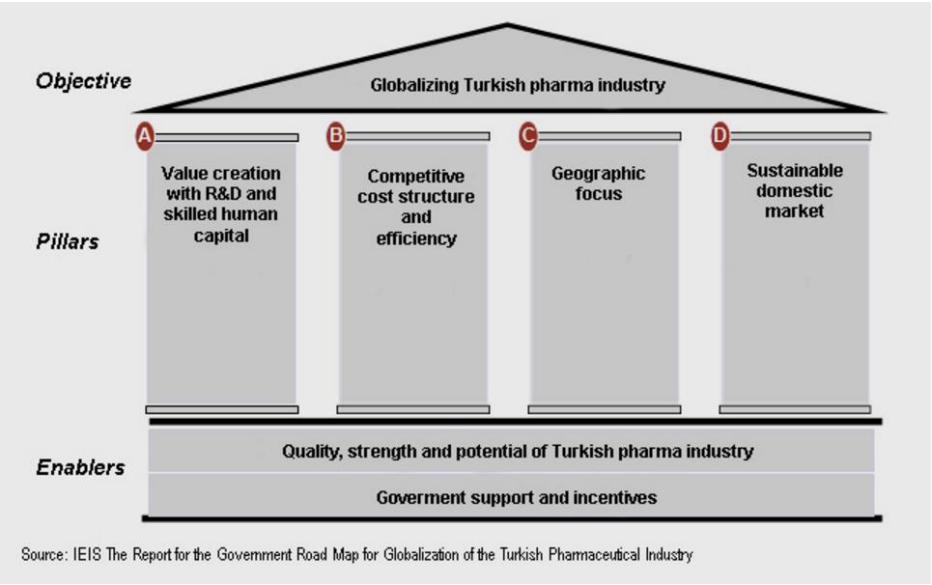
Table No.3 Market Distributions with Reimbursement Rates of BTC and OTC Medicines [1]

	Unit	TL
Overall Market	**100%**	**100%**
Prescription Drugs	**88.1%**	**89.2%**
Prescription Reimbursed	86%	85.6%
Prescription Non-Reimbursed	2%	3.6%
Non-prescription Drugs	**2%**	**0.9%**
Non-prescription Reimbursed	1.7%	0.7%
Non-prescription Non-reimbursed	0.36%	0.2%
Other*	**10%**	**10%**
Other Reimbursed	6%	3.7%
Other Non-reimbursed	3.9%	6.2%

Table No.4 : Number of Companies in Turkish Pharmaceutical Sector[1]

Production Facilities	67	
multinational companies		12
Producing Companies	65	
multinational companies		12
Raw Material Producing Facilities	12	
multinational companies		3
Raw Material Producing Companies	12	
multinational companies		3

Table No.5 : Building Blocks of Turkish Pharmaceutical Sector [1]



Source: IEIS The Report for the Government Road Map for Globalization of the Turkish Pharmaceutical Industry

Table No.6: Pricing System of Pharmaceuticals in Turkey[25]

Reference Pharmaceuticals that Do Not Have Generic Competition	Reference Pharmaceuticals that Have Generic Competition	20 Year Pharmaceuticals (over TL 6.79)
Reference Price + Wholesaler and Pharmacist Profit Margin + 8% VAT	60% of the Reference Price + Wholesaler and Pharmacist Profit Margin + 8% VAT	80% of the Reference Price + Wholesaler and Pharmacist Profit Margin + 8% VAT

Table No.7 : Turkish Pharmaceutical Import List (Most Abundant Ones) [5]

Top Import Products - GTIP No.	Product Name	Import (in USD)
300490000000	Other medicines that are used in treatment and/or prevention - mixed or not mixed - dosaged and packaged.	2.248.869.260
300210980000	Other blood fractions and products that generate immunity*	476.842.956
300220002019	Other vaccines that are used on humans*	243.062.960
300210910013	Serum globins	202.465.681
300431000000	Products that contained insulin (dosaged or packaged for sale) *	196.604.994
300439000000	Products that contain hormons positioned at 29.37 which are not contain antibiotics. (dosage for retail.) *	180.538.504
300210910012	Blood Globins *	172.776.065
300420000000	Medicines that contain other antibiotics (dosaged and packaged for retail sale)	104.945.381
300230000000	Veterinary Purposed Vaccines	57.351.674
294190000059	Other Antibiotics	48.119.052
TOTAL	**3.931.576.527**	

Table No.8: Requirements for Licensing in Generic and Reference Medicines[25]

Licensing Requirements	Generic	Referrence
General Information of Company	✓	✓
Product Properties	✓	✓
Expert Report	✓	✓
Pharmaceutical Compound	✓	✓
Good Manufacturing Practices	✓	✓
Primary Materials Inspection	✓	✓
Stability Test (Active Content and Finished Product)	✓	✓
Comparison of Generic Product with Reference Product	✓	
Pre - Clinical Studies		✓
Clinical Studies		✓
Bio - Equivalence	✓	

Diagram No.2 Summary of the Licensing Procedures [25]

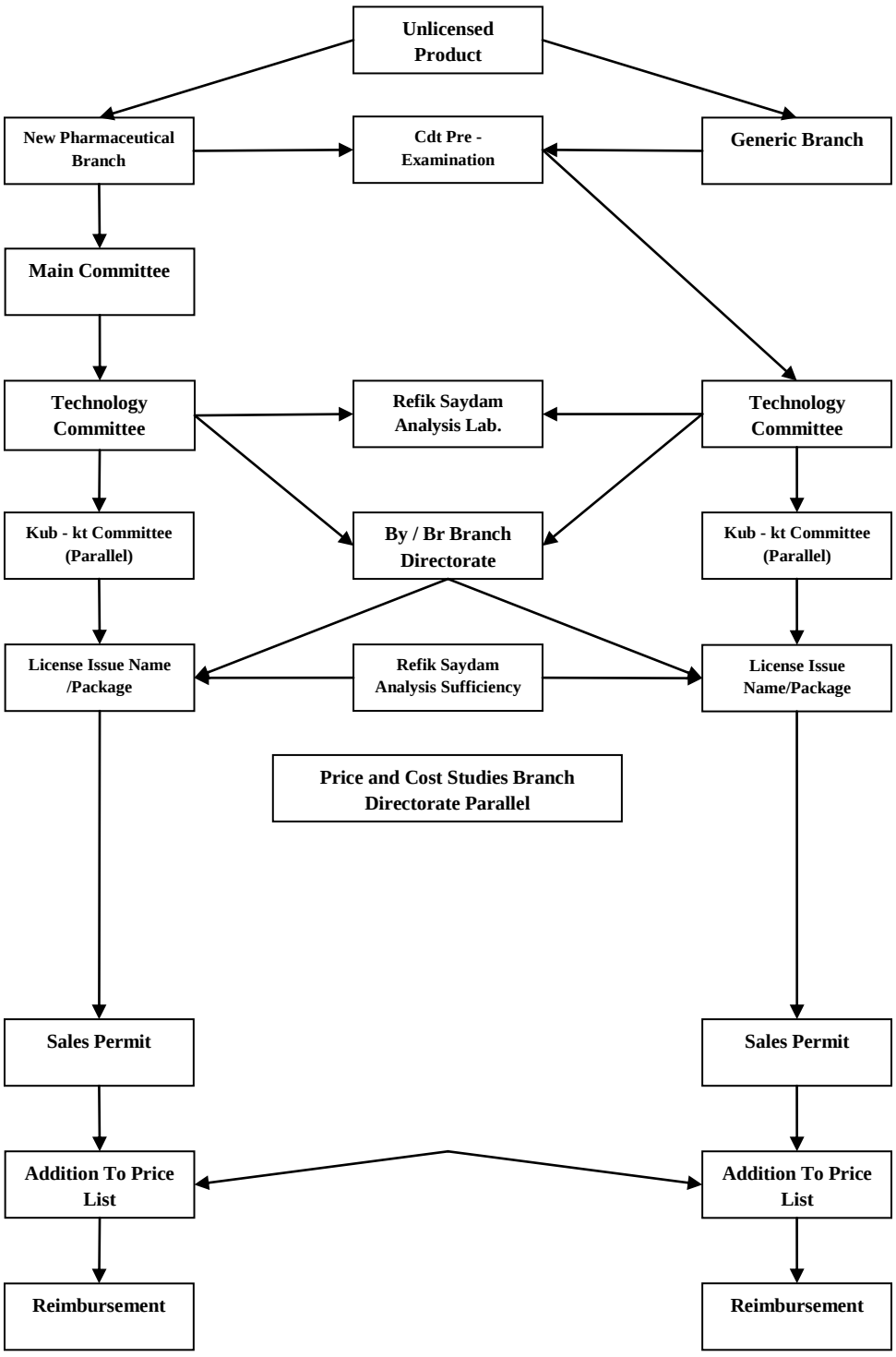


Table No.9 Price Research of Orphan Medicines (PART:1)[13]

PRICE RESEARCH OF ORPHAN MEDICINES							
	ORPHAN MEDICINE NAME	**ORIGINAL PRICE**	**GENERIC AND/ EQUIVALENT VERSION**	**EQUIVALENT**	**DOMESTIC OR FOREIGN EQ.**	**EQUIVALENT PRICE**	**REIMBURSED**
TUMOR OF ENDOCRYNE GLANDS	CAPRELSA 100 mg	1.400 €	N/A	N/A	N/A	N/A	YES
	CAPRELSA 300 mg	4.070 €	N/A	N/A	N/A	N/A	YES
	COMETRIQ 20 + 80 mg	6.000 €	N/A	N/A	N/A	N/A	YES
	LYSODREN 500 mg	400 €	N/A	N/A	N/A	N/A	YES
	NEXAVAR 200 mg	8.732,55 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SANDOSTATINE 0.1 mg/ml	21,61 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SANDOSTATINE 30 mg	2.877,79 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SANDOSTATINE 20 mg	1.928,11 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SANDOSTATINE 10 mg	978.43 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SIGNIFOR 0.3 mg/ml	7.632,72 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SIGNIFOR 0.6 mg/ml	8.788,65 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SIGNIFOR 0.9 mg/ml	9.863,90 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SOMALUTINE 60 mg	1.708,87 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SOMALUTINE 90 mg	2.079,31 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SOMALUTINE 120 mg	2.079,31 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SOMAVERT 10 mg	4.770,48 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SOMAVERT 15 mg	7.123,28 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SOMAVERT 20 mg	9.514,40 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	INTRONA 10M U	112,41 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	INTRONA 18M U	188,90 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	INTRONA 30M U	343,18 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	INTRONA 60M U	622,82 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SUTENT 12.5mg	3.712,57 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SUTENT 25 mg	7.396,40 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SUTENT 50 mg	7.396,40 ₺	N/A	N/A	N/A	N/A	On Special Conditions

Table No.9 Price Research of Orphan Medicines (PART:2)[13]

RENAL CELL CARCINOMA	AFINITOR 5 mg	6.734,32 ₺	YES	CERTIGAN EFER. 0.25 MG	Foreign	278,01 ₺	On Special Conditions
	AFINITOR 10 mg	8.677,82 ₺	YES	VOTUBIA 2.5 MG	Foreign	2.995,00 ₺	On Special Conditions
				CERTIGAN TABLET 0.25 MG	Foreign	278,01 ₺	On Special Conditions
				CERTIGAN TABLET 0.75 MG	Foreign	786,97 ₺	On Special Conditions
	INILYTA 1 mg	1.619,65 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	INILYTA 5 mg	7.983,22 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	NEXAVAR 200 mg	8.732,55 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SUTENT 12.5mg	3.712,57 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SUTENT 25 mg	7.396,40 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	SUTENT 50 mg	7.396,40 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	PROLEUKIN 18m U	325,07 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	TORISEL FLAKON 25mg/ml	1.709,98 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	VOTRIENT 200 mg	1.745,08 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	VOTRIENT 400mg	6.893,99 ₺	N/A	N/A	N/A	N/A	On Special Conditions
OVARIAN CANCER	ALKERAN 50mg	60,80 €	YES	MEGVAL 50mg	Foreign	37 €	YES
				ALKACEL 50mg	Foreign	30 €	YES
	ARIMIDEX 1mg	71,66 ₺	YES	ANAZOL 1mg	Domestic	45,57 ₺	On Special Conditions
				SANTRA 1mg	Foreign	41,44 ₺	On Special Conditions
				ARISTU 1mg	Foreign	47,07 ₺	On Special Conditions
				VERIDEX 1mg	Domestic	46,25 ₺	On Special Conditions
	CAELYX	856,80 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	HYCAMTIN 4mg	379,09 ₺	YES	TEKAN 4mg	Domestic	256,20 ₺	On Special Conditions
				TOPOXIN 4mg	Foreign	272,94 ₺	On Special Conditions
	TAXOL 30mg	76,32 ₺	YES	ATAXIL 30mg	Domestic	46,44 ₺	On Special Conditions
				TAKSEN 30mg	Domestic	50,63 ₺	On Special Conditions
				EBETAXEL 30mg	Foreign	51,11 ₺	On Special Conditions
				VITAX 30mg	Foreign	51,11 ₺	On Special Conditions
				SINDAXEL 30mg	Foreign	53,26 ₺	On Special Conditions
				ANZATAX 30mg	Foreign	55,64 ₺	On Special Conditions
	TAXOL 100mg	232,09 ₺	YES	ATAXIL 100mg	Domestic	139,80 ₺	On Special Conditions
				TAKSEN 100mg	Domestic	152,13 ₺	On Special Conditions
				EBETAXEL 100mg	Foreign	153,63 ₺	On Special Conditions
				VITAX 100mg	Foreign	153,65 ₺	On Special Conditions
				SINDAXEL 100mg	Foreign	159,54 ₺	On Special Conditions
				ANZATAX 100mg	Foreign	153,63 ₺	On Special Conditions

Table No.9 Price Research of Orphan Medicines (PART:3)[13]

UVEITIS	YONDELIS 1mg	4.859,54 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	OZURDEX 0.7mg	2.013,48 ₺	N/A	N/A	N/A	N/A	On Special Conditions
	TEGELINE 100ml	1.628,13 ₺	YES	FLEBOGAMMA 100mg	Foreign	1.471,93 ₺	On Special Conditions
	TEGELINE 200ml	3.227,48 ₺	YES	FLEBOGAMMA 200mg	Foreign	2.915,08 ₺	On Special Conditions

Table No.10 Medicines Which Can Treat Different Diseases [8][9]

MEDICINES WHICH CAN TREAT DIFFERENT DISEASES			
ORIGINAL DISEASE	NAME OF MEDICINE	OTHER DISEASE NAME	NUMBER OF PATIENTS (TURKEY)
Tumor of Endocrine Glands	COMETRIQ	THYROID CARCINOMA	9643
	INTRONA INJECTABLE	RECURRENT HEPATITIS C	5315
	INTRONA INJECTABLE	CHRONIC MYELOID LEUKEMIA	4556
	INTRONA INJECTABLE	MULTIPLE MYELOMA	9036
	INTRONA INJECTABLE	NON HODGKIN LYMPHOMA (incidence data)	8808
	INTRONA INJECTABLE	KAPOSİ SARCOMA (incidence data)	258
	INTRONA INJECTABLE	RENAL CELL CARCINOMA	31892
	NEXAVAR	RENAL CELL CARCINOMA	31892
	SIGNIFOR	CUSHING DISEASE	3037
	SUTENT	TUMOR OF ENDOCRINE GLANDS	48597
Renal Cell Carcinoma	AFINITOR	PANCREATIC ENDOCRINE TUMOR	159
	SUTENT	GASTROINTESTINAL STROMAL TUMOR	759
	SUTENT	PANCREATIC ENDOCRINE TUMOR	159
Ovarian Cancer	CAELYX	KAPOSİ SARCOMA (incidence data)	258
	VITAX		
	SINDAXEL		
	ANZATAX		
	TAXOL		
Uveitis	TEGELINE	GUILLAIN BARRE SYNDROME	2658
	FLEBOGAMMA		

Table No.11 Diseases Prospective Patient Volumes At Export Markets[8]

DISEASES PROSTECTIVE PATIENT VOLUMES AT EXPORT MARKETS										
DIESEASE NAME	RATIOS	GERMANY	LIBYA	TUNISIA	MOROCCO	ALGERIA	S.ARABIA	QATAR	UAE	TOTAL
TUMOR OF ENDOCRINE GLANDS	0,00064	51769	4006	7038	21710	24918	19767	1390	5815	136413
RENAL CELL CARINOMA	0,00042	33974	2629	4619	14247	16352	12972	912	3816	89521
OVERIAN CANCER	0,0003	24267	1878	3299	10176	11680	9266	652	2726	63944
UVEITIS	0,00038	30738	2378	4179	12890	14795	11737	825	3453	80995
THYROID CARCINOMA	0,000127	10273	795	1397	4308	4945	3923	276	1154	27069
RECURRENT HEPATITIS C	0,00007	5662	438	770	2374	2725	2162	152	636	14920
CHRONIC MYELOID LEUKEMIA	0,00006	4853	376	660	2035	2336	1853	130	545	12789
MULTIPLE MYELOMA	0,000119	9626	745	1309	4037	4633	3675	258	1081	25364
NON HODGKIN LYMPHOMA (incidence data)	0,000116	9383	726	1276	3935	4516	3583	252	1054	24725
KAPOSİ SARCOMA (incidence data)	0,0000034	275	21	37	115	132	105	7	31	725
CUSHING DISEASE	0,00004	3236	250	440	1357	1557	1235	87	363	8526
PANCREATIC ENDOCRINE TUMOR	0,0000021	170	13	23	71	82	65	5	19	448
GASTROINTESTINAL STROMAL TUMOR	0,00001	809	63	110	339	389	309	22	91	2131
GUILLAIN BARRE SYNDROME	0,000035	2831	219	385	1187	1363	1081	76	318	7460
DIESEASE NAME	RATIOS	AZERBAIJAN	BELGIUM	FRANCE	UK	ITALY	CANADA	UKRAINE	TURKEY	TOTAL
TUMOR OF ENDOCRINE GLANDS	0,00064	6104	7184	42372	41287	39255	22746	29032	48597	236578
RENAL CELL CARINOMA	0,00042	4006	4715	27807	27094	25761	14927	19052	31892	155254
OVERIAN CANCER	0,0003	2861	3368	19862	19353	18401	10662	13609	22780	110896
UVEITIS	0,00038	3624	4266	25159	24514	23308	13505	17238	28854	140468
THYROID CARCINOMA	0,000127	1211	1426	8408	8193	7790	4514	5761	9643	46946
RECURRENT HEPATITIS C	0,00007	668	786	4634	4516	4294	2488	3175	5315	25876
CHRONIC MYELOID LEUKEMIA	0,00006	572	674	3972	3871	3680	2132	2722	4556	22179
MULTIPLE MYELOMA	0,000119	1135	1336	7879	7677	7299	4229	5398	9036	43989
NON HODGKIN LYMPHOMA (incidence data)	0,000116	1106	1302	7680	7483	7115	4123	5262	8808	42880
KAPOSİ SARCOMA (incidence data)	0,0000034	32	38	225	219	209	121	154	258	1257
CUSHING DISEASE	0,00004	382	449	2648	2580	2453	1422	1815	3037	14786
PANCREATIC ENDOCRINE TUMOR	0,0000021	20	24	139	135	129	75	95	159	776
GASTROINTESTINAL STROMAL TUMOR	0,00001	95	112	662	645	613	355	454	759	3697
GUILLAIN BARRE SYNDROME	0,000035	334	393	2317	2258	2147	1244	1588	2658	12938

CURRICULUM VITAE

Ali Tolga Taştekin was born on January 1st, 1990 in Istanbul. He has received his B.S. degree on Industrial Engineering in 2013 from Işık University. He is currently working at BMT Technology and Process Development Limited Company located at TUBITAK MAM Gebze, Kocaeli as process development engineer since 2013.