RECALL AND REJECT MEDICATION MINIMIZATION DEVELOPMENT SYSTEM FOR PHARMACEUTICAL INDUSTRY

by

DİLEK DUYGU

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ABSTRACT

Medications have a crucial importance on the successful medical treatment. The advanced medical science and medications are indispensable elements of our modern lives. However, inaccurate use of medications causes some social, economic and environmental problems. Deficient management of medications leads to the emergence of recalled and rejected medications, which is called Recalled and Reject (R2). Since R2 medicines alter the ecosystem on which all living organisms depend, taking a medication is not simply a personal decision that affects only the users' health.

In this study, the formative conditions of R2 (Recalled and Reject) medicines, R2's role on the environmental pollution, collecting, sorting, transporting, minimization and disposal methods of R2 will be discussed. By the improper management of medications, medical wastes are come into existence which is also the issue of governments. For this reason, the politics of the management of waste is discussed in our study.

For an elaborative understanding, the chosen pharmaceutical companies' R2 (Recalled and Reject) management strategies will be compared. A statistical analysis is done for the purpose. Sustainable development is one of the most crucial issues in the governments' agenda regarding our social and personal lives. In order to protect the environment in ongoing sustainable development process, minimization methods of bin wastes have become more important than disposal methods. Therefore, health sector staffs, pharmaceutical companies, pharmacies, consumers, media and the governments have some responsibilities to reduce R2 (Recalled and Reject) medication in order to minimize the risks for the well-being of the all living organisms.

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ÖZET

İlaçlar başarılı bir tedavinin en önemli bir unsurudur. Gelişmiş ilaç bilimi ve ilaçlar günümüz modern yaşamın vazgeçilmes unsurlarıdır. Bununla birlikte, ilaçların yanlış, uygun olmayan şekilde kullanılması bazı sosyal, ekonomik ve çevresel sorunlara neden olmaktadır. İlaçların uygun olmayacak şekilde kullanım ve bertaraf edilmesi R2 olarak adlandırılan ialçalrın iade, pazardan geri çekilmesine neden olmaktadır. İade edilen veya toplatılan ilaçlar canlı organizmaların yaşadığı ekosistemi değiştirmektedir. Ilaç alma sadece kullanıcının sağlığını etkileyen basit bir karar değildir.

Çalışma kapsamında, özellikle iade ve pazardan geri çekilen, toplatılan ilaçların oluşmasına neden olan durumlar, R2 ilaçların çevre kirliliği üzerine rolü, toplatılması, ayrıştırılması, ulaşımı, bertaraf edilmesi ile ilgili konular ayrıntılı bir şelikde incelenmiştir. Uygun olmayan şekilde ilaç yönetimi, hükümetinde sorunu olan ilaç atıklarının çöplerinin oluşmasına neden olmaktadır. Bu nedenle bu çalışma kapsamında ilaç yönetim politikaları tartışılmaktadır.

Ayrıntılı bir şekilde anlamak için seçilen ilaç firmalarının R2 stratejileri karşılaştırılmıştır. Bu nedenle kapsamlı istatiksel analizler yapılmıştır. Sürdürülebilir kalkınma, hükümetin ajandasında yer alan, bizlerin kişisel ve sosyal yaşamları ile ilgili en önemli konulardan biridir. Çevreyi koruyabilmek için devam eden sürdürülebilir kalkınma süreci, çöp atıklarının azaltılması yöntemleri çöplerin bertaraf edilmesinden çok daha önemli olmuştur. Bu nedenle tüm canlı organizmaların iyi olması için risklerin aza indirilmesi ve dolasıyla R2 ilaçların azaltılabilmesi için sağlık sektöründe çalışanlar, ilaç firmaları, eczacılar, tüketiciler (hastalar), medya ve hükümet'in bazı sorumluluklara sahip olması gerekmektedir.

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AIFD	Association of Researched Based Pharmaceutical Companies
CEDER	Center for Drug Evaluations and Research
CDC	U.S. Centers for Disease Control and Prevention
DTC	Direct-to-consumer
EU	European Union
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GNP	Gross National Product
GSL	General Sale License
OECD	Organization for Economic Co-operation and Development
OTC	Over the Counter
MOA	Molecular Actions
NSAID	Non-steroidal Anti-inflammatory Drugs
PHR	Personal Health Record
POM	Prescription only Medicines
PPP	Purchasing Power Parity
USGS	U.S. Geological Survey
USDA	U.S. Department of Agriculture

1. INTRODUCTION

Today, the most important problem the world face to is environmental pollution. This problem both has some negative impacts for our lives and for the future generations. Increasing environmental pollution leads resources to decrease. The wrong usage of medications and their hazardous disposal are one of the important reasons for the environmental pollution. Hence, in the near future people may face with lack of resources as a result of the changes in ecological equilibrium, thus have a problem with fulfilling their fundamental needs. This dissertation aims to present problems about usage of medications and firstly avoid the creation of pollutants and then try to manage them after they have been created. In terms of medications, some applications are ignored by everyone, including firms, patients, government, warehouse and pharmacy. One of those applications is issue of Recall and Reject (herein it is referred to "R2"). It is unknown R2 medicines' negative effects on environment. Taking a drug is not simply a personal decision that affects only individual's health. It is indeed a more global challenge. Drugs alter the ecosystem on which all living things depend. Besides, far from vanishing into the environment after use, these substances may travel full circle into lakes and streams, and back into our bodies, via the water we drink and the food we eat.

Within the circle of this dissertation, it is proposed that the sustainable development issue will be handled successfully by giving priority to environmental concerns. Firstly, people should be made conscious not to use medications excessively and dispose them unconsciously. Just by cutting inappropriate use and disposal of medications, creation of pollutant and improper consumption of natural resources may be avoided, and thus environmental pollution may be prevented at most extent. Their disposal affects ecological system, and disrupts the circle. As a result of inappropriate disposal, medications made up with harmful chemical are absorbed by land, surface water and ground water, and air. Besides its environmental effects, R2 medicines cause some social and economic problems. Excessive use of medications by some people causes other people who really need them not to be able to use those vitally important medications. Regarding R2 activities within the frame of environmental concerns of pharmaceutical industry, a

systematic procedure is aimed to develop as an integrated methodology for R2 Reduction Assessment Implementation. The sustainable development issue will be handled from this aspect successfully by giving priority to environmental concerns. Regarding the waste minimization; the decrease in the amount of R2 medicine transported to centers where R2 medicines are collected will decrease the potential environmental impact considering waste and emissions generated from hazardous waste incineration plant and disposal of its residue. As it is known many companies send their waste materials to those centers for disposal. Instead of destruction of medications by users, providing collection points for users and pharmacies prevent destruction of the medication and harm to the environment. Besides, this has many economic advantages: re-production is eliminated as these medications are re-used. As pharmaceutical companies are financially responsible for the R2 medicine transportation after being collected from the end user and retailer, those are carried to the manufacturer and then collection centers, which doubles the cost of transportation.

However, instead, if they are submitted to some centers by users as donation or recalled as practiced in electronically appliances such as batteries, the cost of transportation and disposal of the medication is consequently eliminated. Another issue, the market research for the R2 medicine yields that the Medicine Faculties of Universities are highly interested in the purchase of these R2 at a lower price as a reuse possibility. Instead, if those were collected by universities, this would recycle medication and cut the cost training material of medical schools. Moreover, there is the possibility of distributing the R2 medicine to related research institutes, aids, disaster, third world countries like Africa as a social improvement on local and regional basis. For the success of this study, the developed methodology is formulated based on data obtained from the global pharmaceutical company in Turkey. In this methodology, organizational, administrative and planning activities are comprised. So far, R2 effects on environment have been pointed out. Those effects we mentioned show importance of minimization of unconscious disposal of medications. R2 Medicine Minimization Method will contribute to prevention of environmental harms of destroyed medications.

Today, pharmaceutical market has drawn attention as an important part of health sector. The intervention of government into pharmaceutical sector is related with both health and economical policies (İnan et al., 2006). Now, the pharmaceutical industry is the fifth largest industrial sector in Europe. According to the declaration made by IMS (International Medical Statistics), the global pharmaceutical market is expected to grow by 5-6% and reach to $ 665-685 million in 2007. During the last decade, pharmaceutical industry has got an important role to decrease mortality and morbidity rates.

2. RETURNED AND RECALLED MEDICATIONS (R2)

Medicine has played a central role in health care and therapeutic practice since the earliest times. Medicine has been divided into two groups: over-the-counter (OTC) medications, which are available without special restrictions, and prescription only medicines (POM), which must be prescribed by a physician. Most OTC medication is generally considered safe enough that most persons will not hurt themselves accidentally by taking it as instructed. OTC medicines can be sold without a prescription, while a POM is required a visit to a doctor first; OTC can be purchased just like other goods. Some medicines considered safe in general terms like painkillers and anti-fungal may be available in general stores, supermarkets, gas stations etc. The rules can be different from country to country. Many countries, such as the UK comprises a third category of pharmacy medicines which can only be sold in registered pharmacies by or under the supervision of a pharmacist. It reguires General Sale Licence (GSL) and these kind of medicines are very safe for patients if they take them properly.

2.1. Definition of Returned and Recalled (R2) Medications

R2 is one of the main problems of Pharmaceutical companies which show a continuous increase with the increasing market development. R2 concept can be divided into two distinct type;

i) Permanent removal
ii) Temporary removal

R2 can be defined as permanent removal of medicines from supply or use for reasons relating to deficiencies in the quality, safety or efficacy of the goods. It includes requests to pharmacists, hospitals, pathology laboratories, fractionators, operating and research facilities, biomedical engineers or others to check and return goods found to be defective; and removal from supply or use of goods with inherent design or manufacturing defects R2 medicines include prescriptions or over-the-counter drugs that are outdated, not preferred, or no longer needed.

R2 medicine waste is also included as any drug product either dispensed or purchased over-the-counter (OTC), prescription that is never fully consumed. Medication waste may be due to poor compliance of patients, excessive and irrational prescribing, or the lack of control of the sales of prescription medications in the community pharmacy. The problem of waste is universal among developed countries. For example, In UK, the incidence of medication waste is exceeding. In a survey of 111 British household, the quantity and types of medicines were studied to estimate the frequency of therapeutic duplication medication wastes, and unnecessary hoarding of medications. The study found that 51 % of medicines in the household were not in current use. Of these, 40 % were expired. A separate survey reported that each year approximately 33% of the population in England failed to complete the full course of a prescribed drug regimen. In some study, nearly 25% of adults surveyed admitted to having unused medicine in their homes (Bound and Kitsou, 2005).

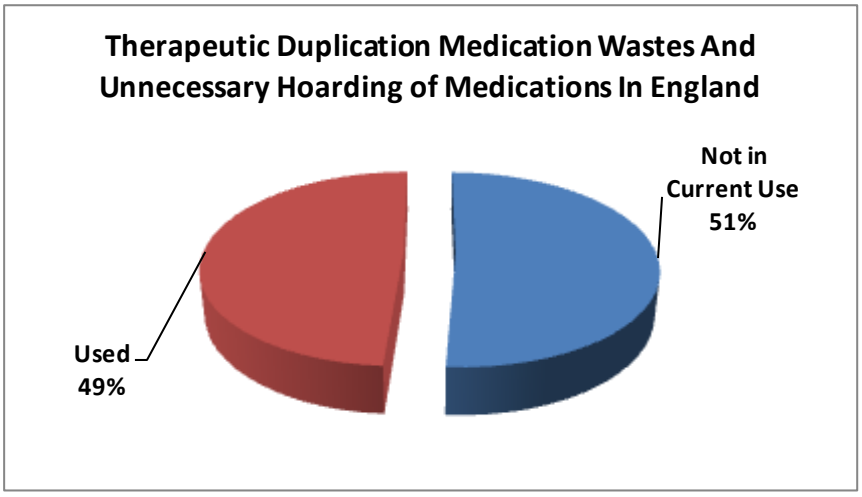


Figure 2.1. Therapeutic duplication medication wastes and unnecessary hoarding of medications in England.

The data included 392 people interviewed (54 % female, 45.2 % male). And also people age ranges and family types took into consideration. (98%) had some type of pharmaceutical in their house; most (60.2%) had a mixture of over-the-counter (OTC) and prescription medicines, whereas 30.7% had only OTC medicines and 9.1% had only prescription medicines. Responses indicate that just more than half (52.8%) finish their

medication and hence have none to dispose of. Around a third (30.7%) keep them until the expiration date, and 12.2% dispose of them when the treatment has been completed. Figure 2.2 describes the disposal of unwanted pharmaceuticals. Two-thirds (63.2%) discard them in household waste, with the remainder returning them to a pharmacist (21.8%) or emptying them into the sink or toilet (11.5%). A small number took them to municipal waste sites that sometimes have special waste facilities.

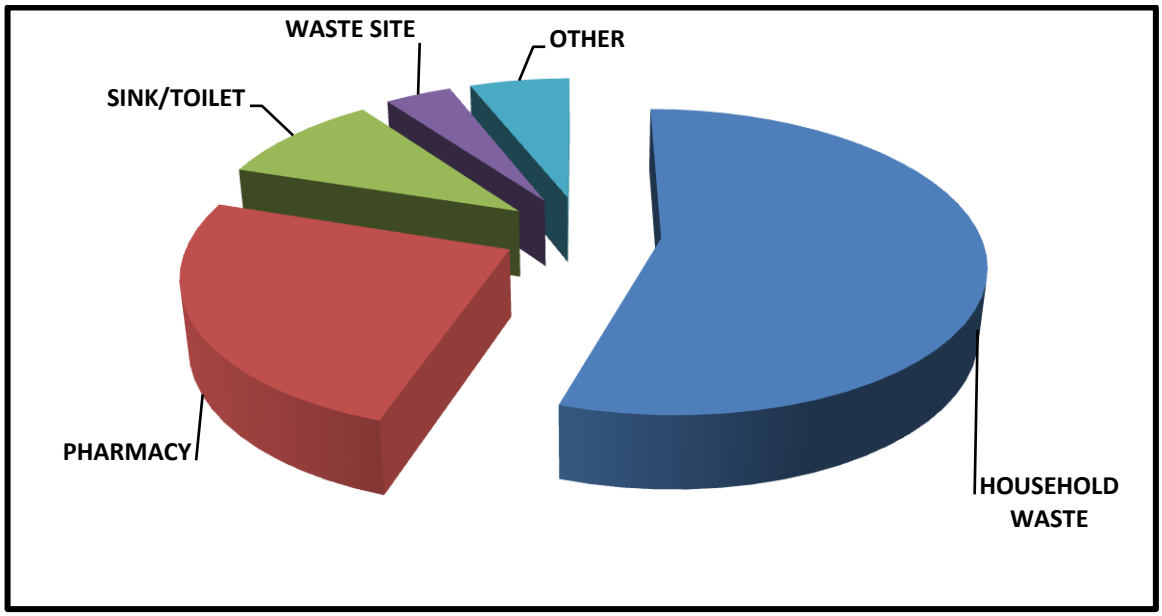


Figure 2.2. Disposal methods of medications in England.

Because of the expense associated with unused medications, policymakers have expressed interest in finding ways to reduce medication waste. It is much more important to address considerations related to the legitimate return and reuse of unused medications as allowed by federal and state laws and regulations, and when reasonable mechanisms are in place to accurately account for medication tracking, billing, and crediting (Bound and Kitsou, 2005).

This study evaluates medication use and waste quantification. Also, it decreases amount of R2 medicine with special emphasize on economic and environmental burden reduction. It has been determined that R2 medicines cause pharmaceutical companies to experience negative impacts in their financial situation as well as their ethical and market

image. For this reason, an appropriate managerial roadmap will be developed to minimize R2 medicine amount and to maximize the social environment and economic advantages from Recycling and Reuse application of the R2 Medicine (CEDER, 1999).

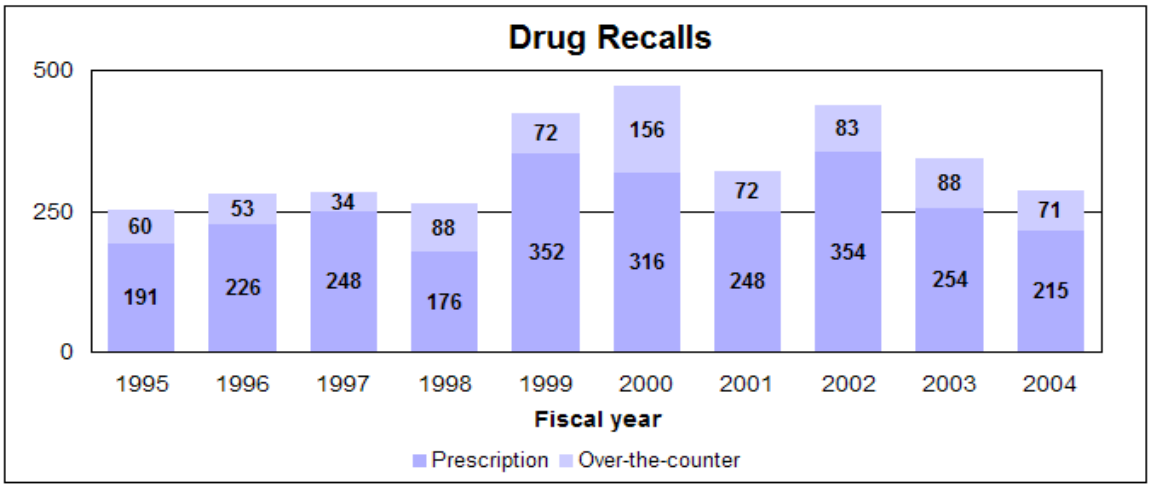


Figure 2.3. Drug Recalls between 1995 and 2004.

As medicines consumption grows, the pharmaceutical industry faces a growing concern of R2 medicines. Figure 2.3 shows that the number of recalls has accelerated rapidly in between 1999 and 2004. Much of this increase is due to recall of cellular blood products, which commenced in 2001. The increase in amount of recall medicines can cause;

i) The increased marketing costs for pharmaceutical firms

ii) The expenses incurred in the development of new drug products

iii) The increased cost of medication wastage

2.2. The Classification of Returned and Recalled (R2) Medications

R2 medicines are classified according to the European classification system taking into account of Class 1, Class 2, and Class 3. Classes I recall occur when products are potentially life-threatening or could cause a serious risk to health.

Examples of Class I ;

i) Wrong product (label and contents are different products)
ii) Correct product but wrong strength, with serious medical consequences
iii) Microbial contamination of sterile inject able or ophthalmic product
iv) Chemical contamination with serious medical consequences
v) Mix up of some products with more than one container involved
vi) Wrong active ingredient in a multi-component product with serious medical consequences.

Class II recalls occurs when product defects could cause illness or mistreatment, but are not Class I. Examples of Class II Defects;

i) Mislabeling , wrong or missing text or figures
ii) Missing or incorrect information on prospectus
iii) Microbial contamination of non- inject able, non-ophthalmic sterile product with medical consequences
iv) Chemical/physical contamination (significant impurities, cross contamination, particulates)
v) Mix up of products in containers
vi) Non-compliance with specification (assay, stability, fill/weight)
vii) Insecure closure with serious medical consequences (catatonics , child resistant containers, potent products)

Class III recalls occur when product defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons. Examples of Class III Defects;

i) Faulty packaging, wrong or missing batch number or expiry date.
ii) Faulty closure
iii) Contamination – microbial spoilage, dirt or detritus, particulate matter

Class I or Class II recalls are considered to be urgent safety-related recalls. A safety related recall is defined under the Trade Practices Act 1974 as the recall of 'goods of a kind which will or may cause injury to any person. Where the recall is safety-related, there is a legal requirement to notify the Minister. Class III recalls is considered to be routine non safety-related recalls.

2.3. Pharmaceutical Industry for Sustainable Production & Consumption

Turkey is a middle-income country on its course towards full EU membership. The most recent and internationally comparable estimates from the National Health Account study indicate that Turkey spent, in 2000, US$ 13.1 billion on healthcare (or US$ 30.4 billion at PPP) corresponding to US$ 194 (or US$ 443 at PPP) per capita. The share of total health expenditures in GDP was estimated at 6.6%. Of the total healthcare spending 63% was made out of public purse (of the total health expenditures of which 37% came from social security organizations). Out-of-pocket expenditures constituted 27.6% of total health expenditures.

Regarding Turkey, there are 134 companies operating in Turkey, 36 of which are international chain companies. As per 2002 data in Turkey, 3316 types of medicines are produced in Turkey and another 6549 types are developed and entered into market. In 2002, the global pharmaceutical market has grown by 8% and reached to 437 billion dollars. European pharmaceutical market accounts for 25.4% of global pharmaceutical market. Turkish pharmaceutical market accounts for 3% of European pharmaceutical market. On the other hand, health expenditures in Turkey rapidly increased especially in 1990s. The share of total health expenditures, which was 3.5% in 1990 in gross national product (GNP), increased up to 4.4% in 1993 and realized as 4% in 1998. The share of public health expenditures was 63.9% out of total health expenditures in 1990 increased up to 63% in 1998. There are, as of May 2005, 1388 active ingredients and 3667 products

with different forms (about 7000) currently available on the Turkish market. The market is exclusively served by either branded original products, or by branded generics. There are 33 multinational companies operating in Turkey some with owned manufacturing capacity while others predominantly utilizing local generic facilities as toll manufacturers. The 167 generic and mostly domestically owned companies focus on the generic market either as manufacturers or importers. Pharmaceutical expenditure in Turkey is lower than that of Western Europe. In 2000, per capita pharmaceutical expenditure (PPP) was $ 110 in Turkey where it ranged from 189 in Ireland to $ 491 in France in Western Europe (WHO, 2005).

3. PHARMACEUTICALS AS THE SOURCES AND CAUSES OF ENVIRONMENTAL POLLUTION

Pharmaceuticals metabolic excretion and direct disposals are released to the environment by two different ways.

3.1. Disposal of R2 medicines

3.1.1 Metabolic Excretion

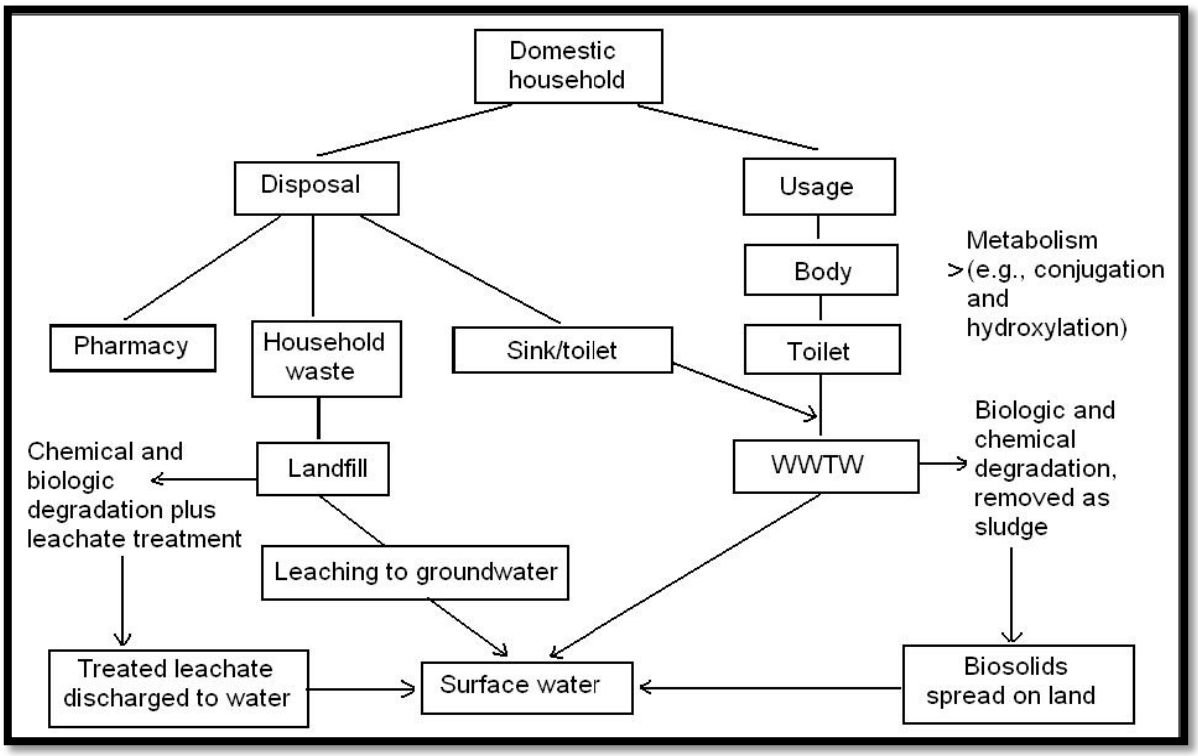


Figure 3.1. Pathways of drugs from households to the environment.

For example, β – blocker nadolol may pass through the human body completely unmodified. In contrast, only 3% of the parent form of the antiepileptic carbamazepine is excreted unchanged in the urine; the rest may be conjugated or hydroxylated and also released in the feces. Release via this pathway is governed by the pharmacology of the

drug and the efficiency of the wastewater treatment works (WWTW). The exact rates also depend on the dosage and the physiology of the individual.

Table 3.1. Urinary excretion rates of unchanged active ingredient for selected pharmaceuticals.

Drug	**Therapeutic class**	**Parent compound excreted (%)**	**Reference**
Ibuprofen	Painkiller	10	Dollery, 1991
Paracetamol	Painkiller	4	Huschek et al., 2004
Amoxicillin	Antibacterial	60	Martindale, 1993
Erythromycin	Antibacterial	25	Huschek et al., 2004
Sulfamethoxazole	Antibacterial	15	Hirsch et al., 1999
Atenolol	β -Blocker	90	Dollery, 1991
Metoprolol	β -Blocker	10	Huschek et al., 2004
Carbamazepine	Antiepileptic	3	Huschek et al., 2004
Felbamate	Antiepileptic	40–50	RxList, 2005c
Cetirizine	Antihistamine	50	RxList, 2005d
Bezafibrate	Lipid regulator	50	Ternes, 1998

Data on waste water treatment works (WWTW) removal efficiencies are largely dependent on the facilities at individual WWTWs and on variables such as local rainfall and temperature (Table 3.1). For example, only 9% of diclofenac was found to be removed by biologic filtration, whereas 75% was removed by activated sludge treatment.

3.1.2. Direct Disposal

The second path by which pharmaceuticals can enter the environment is by the disposal of out-of-date or unwanted medicines, which may occur via the sink/toilet or in household waste that is then taken to landfill sites (Figure 3.1). Entry into the environment by this route is dependent on the habits of the patient and the efficiency of prescription practices leading to fewer unfinished prescriptions. In the most countries, few formal guidelines are available for individual consumers on drug disposal, and, consequently, most of their unused pharmaceuticals enter septic tanks, sewers, or landfills. Discarded pharmaceuticals are defined by the Controlled Waste Regulations 1992 (HMSO, 1992) as clinical waste and as such are controlled by the Special Waste Regulations 1996 (HMSO, 1996). According to this legislation, such waste may be disposed of in landfill sites

designed to accommodate hazardous waste, or it may be incinerated. However, once dispensed to or purchased by a member of the public, any unwanted pharmaceutical products are classified as household waste, and their disposal is not subject to any controls. Manufacturer packaging usually recommends disposal by returning to the pharmacist; however, disposal via the sink/toilet or in normal household waste is common. Pharmaceuticals in landfill sites are subject to biologic degradation processes, but some may persist and even leach into surrounding groundwater and rivers (Bound and Kitsou, 2005).

The information on the disposal of two different types of pharmaceuticals, metoprolol and ibuprofen, along with figures on the elimination of the compound in the human body and WWTW removal efficiencies, was used to model the relative importance of the pathways into the environment. Metoprolol succinct is a β-blocker, mainly used in the treatment of high blood pressure. It is available only by prescription. Figure 3.1 is a mass balance flow chart showing the fate of 100 units of the parent compound. Only 46.8% of respondents who had been prescribed β-blockers said that they finished the prescription. Assuming, as previously stated, that those people took half of the medication, then 26.6 units are disposed of and 73.4 units of the active ingredient are consumed. Because 90% of the medication taken is modified by the body, this leaves 7.3 units of active ingredient that are introduced to the wastewater system. When combined with the 4.4 units (16.7%) of drugs that are put down the drain, this results in a total of 11.7 units entering WWTWs. 83% is removed, leaving 2 units to be discharged into surface water. Of the 26.6 units that are unused, 4.4 are returned to the pharmacy whereas 17.7 units, nearly 10 times as much as is released into the environment from WWTWs, are put into household waste that is subsequently taken to a landfill. Once there, some will be removed by biologic and chemical degradation within the landfill, some will be collected at leachate treatment plants and subjected to similar processes as in the WWTWs and then released into surface water, and some may leach directly into the surrounding groundwater and possibly rivers.

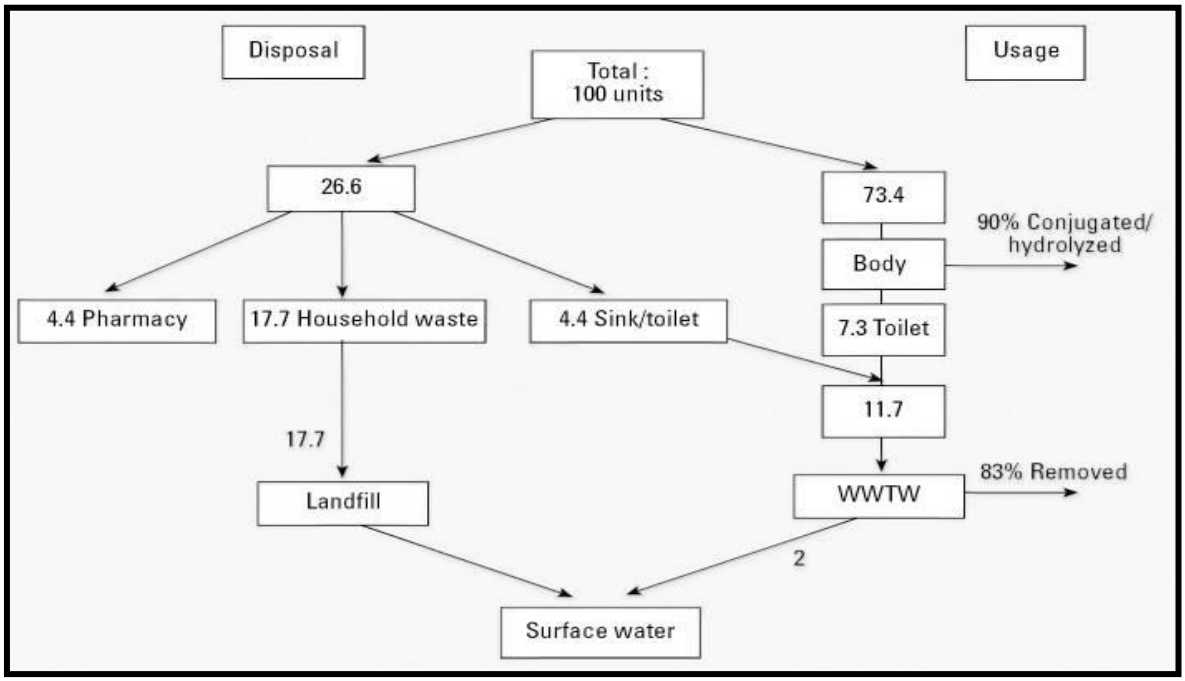


Figure 3.2. Direct disposal of medications (Bound and Kitsou, 2005).

This is because the drug is not removed or modified by the body, nor is it modified by WWTW processes. The literature currently reflects a bias toward research of WWTW treatment rather than landfill leachate that may not fully address the risks of pharmaceuticals to the environment. It is also important to note that the sludge generated during WWTW treatment may be itself land-filled or spread on agricultural land the risk of pharmaceuticals is not necessarily removed, just moved. Millions of tons of sewage sludge are generated in the European Union every year. The proportion of the pharmaceutical load contained within the solid waste products of WWTWs depends largely on the properties of the drug, especially the octanol–water coefficient (KOW), which is an indicator of the likelihood that the compound will be partitioned into the solid phase. Other important interactions are the sorption to organic matter, surface adsorption to mineral constituents, ion exchange, complex formation with metal ions such as Ca^{2+}, Mg^{2+}, Fe^{3+}, or Al^{3+}, and hydrogen bonding. Once these "biosolids" have been spread on agricultural land or landfilled, degradation may continue, but there is also the potential for soil and groundwater contamination, runoff, and even adverse effects on plants or animals reared on the land.

The same model applied to ibuprofen also shows that usage is a more prominent pathway than it is for metoprolol. Results of the survey showed that fewer people (20.8%) had any painkillers to dispose of. Assuming they consumed of these, only 10.4 units require disposal. Therefore, even though from the model the rates of elimination in the body and WWTWs are comparable with those of metoprolol, the ratio of the active ingredient entering landfill sites compared with that entering surface water from WWTWs is 5.5:1 for ibuprofen (the ratio for metoprolol is 8.9:1). Figure 3.2, demonstrates that both human behavior and pharmacologic properties of the active ingredient are important in assessing the significance of the different pathways into the environment.

3.2. Interaction of Pharmaceuticals With Environment

Pharmaceuticals are consumed by human being, and continuously being released into the environment, mainly as a result of excreta, disposal of unused or expired products, and manufacturing processes. Moreover, contamination of the environment by drugs is partly a function of the quantity administered, the excretion efficiency of the parent compound and metabolites, propensity of the drug to adsorb to solids, and the biodegradation in sewage treatments (or in landfill). Recent studies have shown that trace levels of pharmaceuticals detected in environmental samples, including sewage effluent, surface water, groundwater, and even drinking water, mainly in European countries. Thus, the occurrence of drugs in the environment is now a subject of concern.

The usage of pharmaceuticals helps to perceive the environmental effects of those chemicals. Several thousands of active ingredients are used for drugs, which are represented in even more products. The analgesics e.g. paracetamol and acetylsalicylic acid (Aspirin) are the highest consumed drugs. The antibiotics, as amoxicillin and penicillin V, are also highly prescribed. According to recently studies, antibiotics were the most consumed group in human therapy (Haling-Sorensen et al., 1998). Synthetic steroids are frequently prescribed as oral contraceptives; because of their high pharmacological potency, the total amounts annually sold are relatively low.

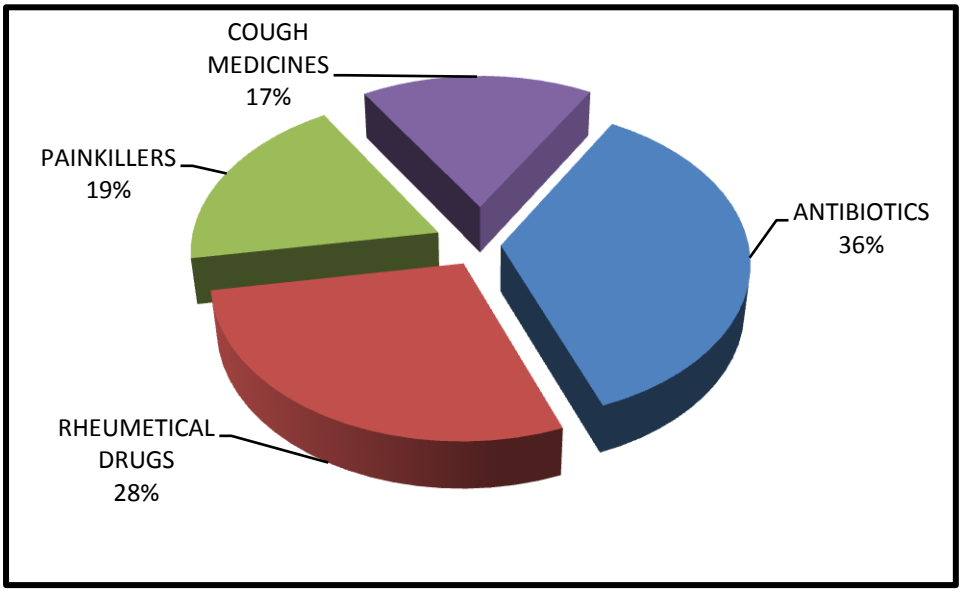


Figure 3.3. Groups of medications consumed in Turkey between January and July 2007.

According to the data obtained from the Pharmaceutical Manufacturers Association of Turkey, among the medicines with the highest consumption rates in the domestic medicine market, in various treatment groups during the period between January and July in 2007, antibiotics hold the first rank with a market share of 16.5 %. The following highest market shares are held by rheumatic drugs by 13%, painkillers by 8.7%, respiratory and cough medicines by 7.9%. While already used in vast quantities, the consumption of drugs is expected to increase for the following reasons: expanding population, increasing age of the population, increased per capita consumption, expiration of patents. Some active ingredients in medications can cause environmental damage.

Pharmaceuticals identified in the environment are generally present in concentrations several orders of magnitude lower than the concentrations those required to exert their known effects on humans. This makes direct human toxicity unlikely but does not rule out the possibility of subtler long-term changes that are harder to detect. The combined effects of medications in the environment are unknown. Some scientists believe that low-level exposures to numerous drugs with the same or similar methods of action may add up to larger effects on aquatic organisms, that certain combinations of drugs may act synergistically to produce disproportionately large effects, or that other unpredictable

interactions between chemicals may occur. Types of human pharmaceuticals that have been identified in water bodies include; Hormones, Antibiotics, Blood lipid regulators, Analgesics and anti-inflammatory, Beta-blockers, Antidepressants, Antiepileptic, Antineoplastics (used in chemotherapy), Tranquilizers, Retinoid, X-ray contrast media 22.

3.3. An EOP (End of Pipe) Facility of Pharmaceutical Wastes

Pharmaceutical substances were detected in hospital and sewage effluents, surface waters and even in ground and drinking waters. Although pharmaceutical chemicals receive considerable pharmacological and clinical testing, information on the ecotoxicity of these biologically active substances is generally limited. Acute toxicity values are in the mg/L range for most of the pharmaceuticals detected in the environment. But, reported levels in surface water are at least three orders of magnitude below the mg/L levels which cause acute toxicity. It is more difficult to assess whether there is any environmental significance with regard to long-term effects as chronic toxicity data are lacking.

Pharmaceuticals have been detected in sewage effluents or surface waters, the levels are in trace amounts at the ng/L or, at most, low μg/L level. The groups of pharmaceuticals detected are broad e.g. contraceptive hormones, lipid regulators, pain killers, antibiotics, anticancer drugs, antiepileptic drugs and those regulating blood pressure.

3.3.1. Pharmaceuticals' Pollutive Effects

Analgesics and Anti-Inflammatory Drugs: As a pro-drug, Aspirin (acetylsalicylic acid) is easily degraded into its more active form salicylic acid. These metabolites are detected in sewage influent, effluent and river samples at concentration up to 54 μg/L. Aspirin was efficiently removed by the municipal STPs. Salicylic acid is biodegradable.

The pain killer paracetamol (acetaminophen) is also easily biodegraded (CDER, 1999), while Paracetamol in less than 24% of all samples at a maximum concentration up to 10 μg/L. Ibuprofen, diclofenac and ketoprofen has been detected in STP influents and effluents and in surface water samples.

Ibuprofen showed high removal rates with biological treatment measured. For diclofenac, a removal rate of between 17% and 75 % in different STPs. In addition, diclofenac was sensitive to photodegradation and ozone. Measured a removal rate of 48% for ketoprofen with an activated sludge treatment.

Several other analgesics such as, for instance, codeine and naproxen, have also been detected in sewage and surface water samples. These drugs were non-biodegradable. Phenazone, diclofenac or ibuprofen, have also been detected in some ground water or drinking water samples.

Antibiotics: Antibiotics have a different effect because bacteria are the target organism of antibiotics. The increased use of antibiotics has caused a genetic selection of more antibiotics resistance is favored by pollution or concentrations of antibiotics in waters or sediments. A high number of antibiotics detected in surface water samples. Ciprofloxacin and norfloxacin in wastewater sample at a maximum concentrations up to 400 ng/L. Ciprofloxacin has been detected at high concentrations (3 to 87 μg/L) in hospital effluents. Ciprofloxacin and norfloxacin in surface water, but less consumed antibiotics as fleroxacin or lomefloxacin were not detected. The occurrence of sulfamethoxazole, dehydroerythromycin and sulfamethazine in groundwater. Most of antibiotics (ciprofloxacin, ofloxacin, metronidazole, erythromycin, tetracycline and sulphamethoxazole) were biodegradable, with the exception of penicillin G.

Antiepileptic drugs, Beta-blockers and Blood Lipid Regulators: The antiepileptic drugs carbamazepine and primidone have frequently been detected in wastewater and surface water samples. Several studies showed that carbamazepine was not significantly removed during sewage treatment and can be detected in groundwater and drinking waters. Several beta-blockers (metoprolol, propanolol and bisprolol) have been found in sewage effluents and in surface waters. Sotalol was detected in three groundwater samples. The detections of clofibric acid, the active metabolite of the blood lipid regulators clofibrate, etofyllin clofibrate and etofibrate, in wastewaters from STPs. This substance was one of the most frequently reported pharmaceuticals. It has been detected in waste, surface, ground and

drinking water samples. Bezafibrate and gemfibrozil have been detected in wastewater and in surface water samples.

Anticancer drugs: Some anticancer drugs like antineoplastics are a class of drugs of potential concern for environmental effects, not only for their acute toxicity but for their ability to effect subtle genetic changes. Indeed such compound often exhibit carcinogenic, mutagenic or embryo toxic properties. Drugs used to treat cancer inhibit the mechanisms of cell proliferation. There are approximately 50 active substances which are classified in several groups depending of their modes of action. For instance, Alkylating agents (e.g. cyclophosphamide, busulfan, carboplatin) add alkyl groups to DNA bases, causing cross-linking of DNA strands, abnormal base pairing, or DNA strand breaks, thus preventing the cell from dividing.

Anticancer drugs which are ifosfamide and cyclophosphamide have been found in sewage samples from hospitals and STPs. 5-Fluorouracil has been detected at high concentration 900 ppm in wastewater from a 5-Fluorouracil plant. On the other hand, cytostatics have not been detected in surface water. Ifosfamide, cyclophosphamide and methotrexate exhibited poor biodegradability.

Oral contraceptives, Endocrine Disruption and Acidic Drugs: NSAIDs and Clofibric Acid: Some of the oral contraceptives that are 17-ethinylestradiol and mestranol were detected at trace-level concentration (<1-3 μg/L) in sewage effluents, surface waters and ground waters measured a removal rate of 85% for 17- ethinylestradiol with an activated sludge treatment. Endocrine disrupters or chemicals which can disturb the normal function of hormones, cause environmental damages even if they are found in very low concentration. For example 17-ethinyloestradiol or tamoxifen show hormonal activities.

Several pharmaceutical substances widely consumed in all over the world. They are not readily biodegradable that are Ibuprofen, Mefenamic acid, Diclofenac and Ketoprofen. They are non-steroidal anti-inflammatory drugs (NSAIDs) and possess analgesic and antipyretic activities. They are used for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis and are indicated for relief of mild to moderate pain. They are

also indicated for treatment of primary dysmenorrhea. The first and highly persistent substance detected in the environment: Clofibric acid. Clofibric acid is an active metabolite of Clofibrate, Etofibrate, Etofyllinclofibrate, which are drugs used as blood lipid regulators. These substances are used to decrease the plasmatic concentration of cholesterol and triglycerides.

Owing to the adverse effects on the environment and the patients caused by the above-mentioned illnesses and the medication required to treat them, new technologies should be introduced in the making of drugs and discovery of treatment methods with minimized adverse effects for patients as well as minimized toxic effects on the environment.

3.3.2. R2 Medicines Toxicological Effects

In order to assess the levels of hazard posed by chemicals in vivo and in vitro, units such as ng/L and μg/L' measuring amounts that are way below the previously anticipated amounts thought to cause environmental harm, are used. Although many of the relevant in vivo and in vitro studies have been conducted under laboratory conditions, various risk assessments related to deleterious effects of pharmaceuticals have shown that measured or predicted environmental concentrations of some compounds are sufficient to pose a threat to some aquatic organisms in their actual environment. The most serious environmental effects have been observed in relation to the impact of endocrine disrupting compounds, such as the synthetic hormone 17α-ethinyl estradiol (EE2), where it has been shown that exposure to wastewater treatment works (WWTW) effluent can cause the feminization of some fish species (Jobling, 1998) at levels as low as 1 ng/L.

Another concern is that of drug resistance, especially the potential to create antibiotic resistant strains of pathogens. This may occur in WWTW or receiving waters or in the environment where antibiotics are released directly such as in fish farms or other forms of agriculture. For instance, when a fish farm used the manure from chickens administered with antibiotics as growth promoters, it was substantially discovered that resistance to sulfamethoxazole was present in 100% of the fish samples in the WWTW (Hirsch et al, 1999). A consequence of the presence of antibiotics in WWTW influent is the possibility

that they could disrupt the treatment processes that are driven by bacterial degradation (Cooke et al., 2002). This property may result in incomplete degradation of other classes of chemicals and pathogenic organisms (FDA, 1998). The science of mixture toxicity is a complex issue. Organisms in the environment are continuously exposed to a broad spectrum of contaminants not limited to pharmaceuticals. Pesticides, industrial by-products such as heavy metals and even naturally occurring toxins are among many types of pollutants that may be present in the aquatic environment, acting against flora and fauna. While each component of the mixture individually may be innocuous, together they have the potential to cause harm. Certain combinations of chemicals could interact and produce toxic effects different from those attributable to concentration addition. These interactions may be synergistic (greater than expected) or antagonistic (less than expected). Alternatively, these types of toxicity are uncommon and difficult to predict. One study into the effects of a variety of organic chemical mixtures found that synergism was rare and that concentration addition was the more likely outcome, followed by antagonism (Huschek et al., 2004). But an investigation into the testing of WWTW effluent found that synergistic behavior was common in mixtures of antifouling paints. This, however, calls into question the ability to predict the effects of the release of an individual pharmaceutical based on its no observable effect concentration (NOEC), as increasing the total environmental load may be sufficient to lead to harmful effects in the environment. Whatever the possible risks, it would seem judicious to employ the precautionary principle and minimize the amounts of medicines that are released into the environment (Länge, 2001).

Table 3.4. Toxicological effects of some pharmaceuticals.

Pharmaceuticals	**Toxicological Effects**
Estrogen – female sex hormone	- Feminization effect on male fish and decrease the reproductive capacity of affected species
Anti-depressants/Obsessive-Compulsive Regulators	- The spawning behavior of shellfish and delay fish and frog development - Slower heart rates for the water flea *Daphnia* - Physiological effects (Daughton, 1999)
Antibiotics	- Antibacterial resistance - Reduce the growth of aquatic plants (Brain et al., 2004)

4. RECALLED AND REJECTED (R2) MEDICATIONS MINIMIZATION METHODS

Pharmaceuticals are present in water bodies on all over the world. Certain drugs cause ecological harm. When unused and disposed directly to waste bin, having various chemical elements, those medications lead to various risks for environment. Pharmaceuticals In 2002, the U.S. Geological Survey (USGS) released a nationwide reconnaissance of the occurrence of pharmaceuticals, hormones, and other organic wastewater contaminants in surface waters. The USGS study revealed that pharmaceuticals and other personal care products are commonly found in the nation's surface waters. In the USGS study, nonprescription drugs were detected in more than 80% of tested streams; prescription antibiotics were found in nearly half of tested streams. Worldwide, dozens of pharmaceuticals have been detected in surface waters, wastewater treatment plant effluent, and sewage sludge (Heberer, 2002).

R2 medicines as mentioned above are taken part in pharmaceutical wastes which are also classified as risky and hazardous wastes. These wastes threaten the human health and cause a danger for the environment. The minimization methods for the wastes have much more importance today than their ultimate disposal. Since, without the waste minimization methods in 20 years period, it is expected that the amount of wastes doubles itself. For 2002 OECD statistics between the years 1980-2000 the municipal wastes increased 54%. This trend will have a gradual increase up to 2020 (Harjula, 2004). As a result, the augmented amount of waste will be a serious problem for human being as far as it is prevented. Prevention of wastes is included in waste management strategies and it is widened to the concept of waste minimization.

Owing to the above-mentioned negative environmental, social and economic effects of pharmaceuticals, a substantial decrease in the amount of R2 medicines is an absolute necessity. There are some minimization methods that are suited to this purpose.

4.1. Improving Government's Responsibilities

Government should ensure that health services are organized, funded and delivered in an effective, efficient and equitable way. It is necessary to draw attention to all subjects as follows:

i) restructuring of the Ministry of Health to enhance its core functions of setting priorities,
ii) ensuring quality and managing public health processes, including preventive services;
iii) introducing compulsory statutory health insurance for the whole population, with the possibility of supplementary voluntary health insurance operated by private insurers;
iv) increasing access to health care by making use of private facilities where necessary, strengthening primary care, improving the referral system and giving institutions more administrative and financial autonomy;
v) improved and more appropriate training for doctors, nurses and administrators and better incentives to encourage a more even distribution of personnel across the country;
vi) establishing a school of public health and a national quality and accreditation agency;
vii) supporting more rational use of drugs and medical devices through the establishment of a national drug agency and a medical device agency;
viii) improving health information systems.

As a result, the Turkish health care system is undergoing significant change at this juncture. The changes are driven by a strengthened national commitment to deliver healthcare in a fair and equitable manner to all citizens. An unbalanced social structure and a significant gap in income distribution, mean that the needs of urban and rural areas are vastly different in Turkey. Recently, some of the practices such as dose-limitation have been prescribed by Social Securities Institutions. As an example, unused medications (except for syrups and anti-biotic) are being submitted to Haseki Hospital in order for them to be prescribed to patients who have insufficient economic power.

While in Europe doctors write active ingredient of the medication, in Turkey doctors write specific name of the medication on prescription. This attitude in Turkey increases the rate of consumption. Moreover, instead of using medications prescribed by a physician, people tend to use what their intimate ones recommend. Therefore, a structural change, managed by the government, is necessary to ensure that patients seek professional help from doctors, and that excessive amount of medication is hindered.

4.1.1. Training of Health care Practitioners and Patients

Hand-in-hand with education of the public is education of those working in the health care industry–not just pharmacists, but all health professionals and technicians, federal and state policy makers and regulators, organization managers, and governing boards. A good way to teach the importance of dose minimization and proper disposal could be achieved through formal, continuing education courses, where the interface between medicine and environmental is made explicit to the participants.

Patients frequently fail to finish their courses of medication for a wide variety of reasons. This problem not only increases health care costs and can jeopardize patient health but also leads to unnecessary accumulation of unused drugs, which then require disposal (this is a major problem at long-term care facilities). Further education of patients might reduce patient noncompliance.

Additional patient education regarding appropriate drug use and drug abuse (consumption of more frequent or higher doses than prescribed, or use of illicit drugs) could reduce unnecessary excretion or disposal. By showing the linkages between human and ecologic health benefits, perhaps more progress can be made in minimizing overuse or misuse of legal drugs (e.g., antibiotics) and illicit drugs.

4.1.2. Drug Packaging and Dispensing

Consumer-oriented packaging for OTC and prescribed drugs in the most countries lacks guidance for disposition of unused medication contents. Standardized nationwide guidance regarding recommended routes for responsible disposal could be easily added to package labeling/inserts. The use of consumer guidance on labeling for protecting the environment is necessary throughout the world. Standards that cover the entire packaging system are developed and promulgated. Consumer warning and use information regarding drugs is conveyed not just on affixed labels but also on attendant documents such as prescription leaflets, the minimum information content for which is set. For prescription drugs, these leaflets are supposed to contain (at a minimum) the prescribing information (also called a package insert). Various other sources of consumer (as well as physician) information on drugs can be found in. New labeling requirements for OTC drugs are one example of labeling status. These are all examples of information resources that could convey information regarding possible environmental ramifications and disposal advice comporting with the ideas of ecology of health and health of ecology.

Drugs direct-to-consumer (DTC) advertising has played an increasingly significant role in relaying information to the public regarding the many aspects of improved health, fitness, and appearance, as well as the prevention of disease. Only more recently have advertisers been required to highlight the caveats associated with their products, for example side effects or contraindications. Direct to- consumer (DTC) advertising purportedly empowers consumers, leading them to better-informed decisions and improved quality of care. But since DTC advertising often may lead to the pressuring of physicians to prescribe expensive and sometimes unnecessary medications for demanding, poorly informed patients; DTC advertisements could include information for the public regarding the proper disposition of unused products and the imperative for environmental stewardship.

The availability of licit and also illicit drugs via the Internet and black markets continues to escalate and expand, undoubtedly leading to over dispensing and dispensing

without a prescription. The added influx of drugs to the environment via illegal sales that were never anticipated by FDA during new drug approval is contributing to the overall environmental exposure burden. That many of these sales come from overseas may have ramifications for performing environmental risk assessments for drugs. Uncontrolled drug distribution channels also have profound ramifications for consumers in terms of safety and expense and also could be a major factor in both the accumulation of unused drugs and the excretion of drugs that ordinarily might never have been ingested. Both the public and the pharmacy communities might benefit by more definitive education on these issues and understanding the possible environmental consequences. This awareness could minimize unneeded drug use and attendant disposal.

The need for disposal could be lessened by reducing prescribed/purchased quantities too great to be used before expiration or increasing shelf life. Reasonable, minimal quantities of medication could be purchased or prescribed until the effects of the medication and its therapeutic effectiveness are understood by both the physician and patient.

4.1.3. Create Personal Health Record

A personal health record or PHR is to provide a complete and accurate summary of the health and medical history of an individual by gathering data from many sources and making this information accessible online.

PHRs can contain a diverse range of data but usually include information such as allergies and adverse drug reactions, regular medications, illnesses and hospitalizations, medical history, examination and progress reports of health and illnesses and billing records.

In addition to storing an individual's personal health information, some PHRs provide added-value services such as drug-drug interaction checking or electronic messaging between patients and providers. A medical record includes any of an individual's health documents. Medical records may be on "physical" media such as film (X-rays), paper

(notes), or photographs, often of different sizes and shapes. Physical storage of documents is problematic, as not all document types fit in the same size folders or storage spaces. Physical records usually require significant amounts of space to store them. When physical records are no longer maintained, the large amounts of storage space are no longer required. Paper, film, and other expensive physical media usage (and therefore cost) is also reduced with electronic record storage.

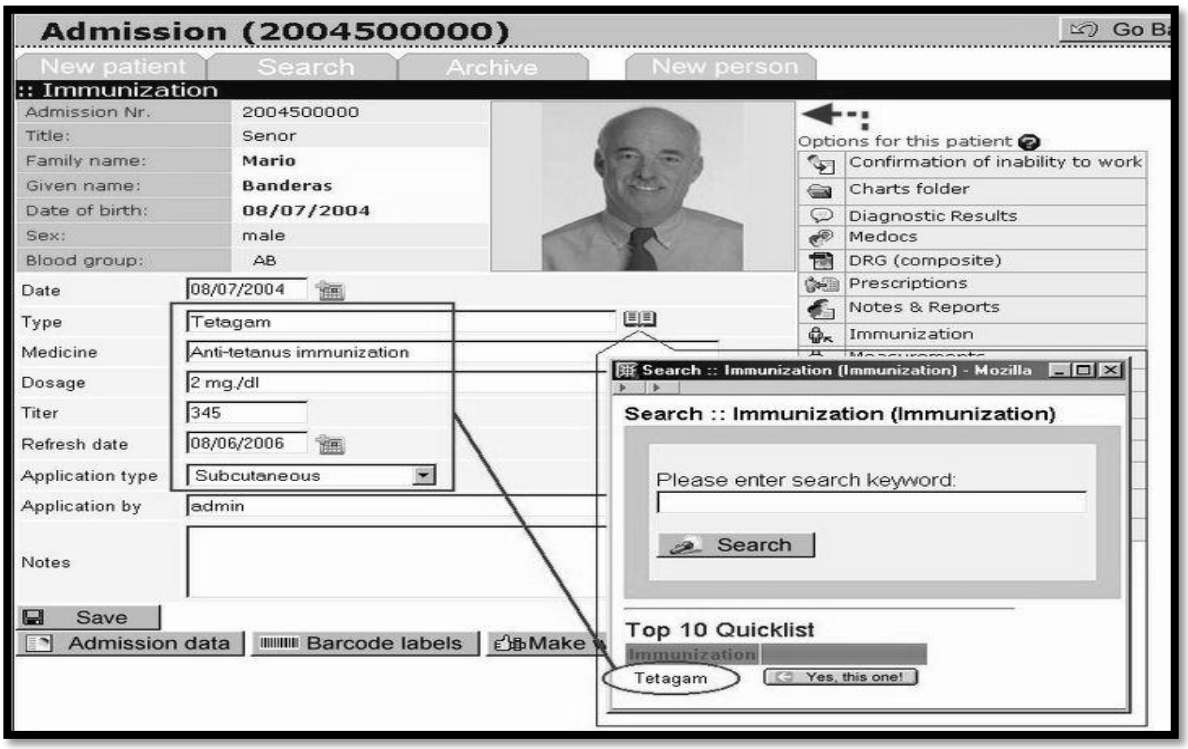


Figure 4.1. Examples of personnel health record.

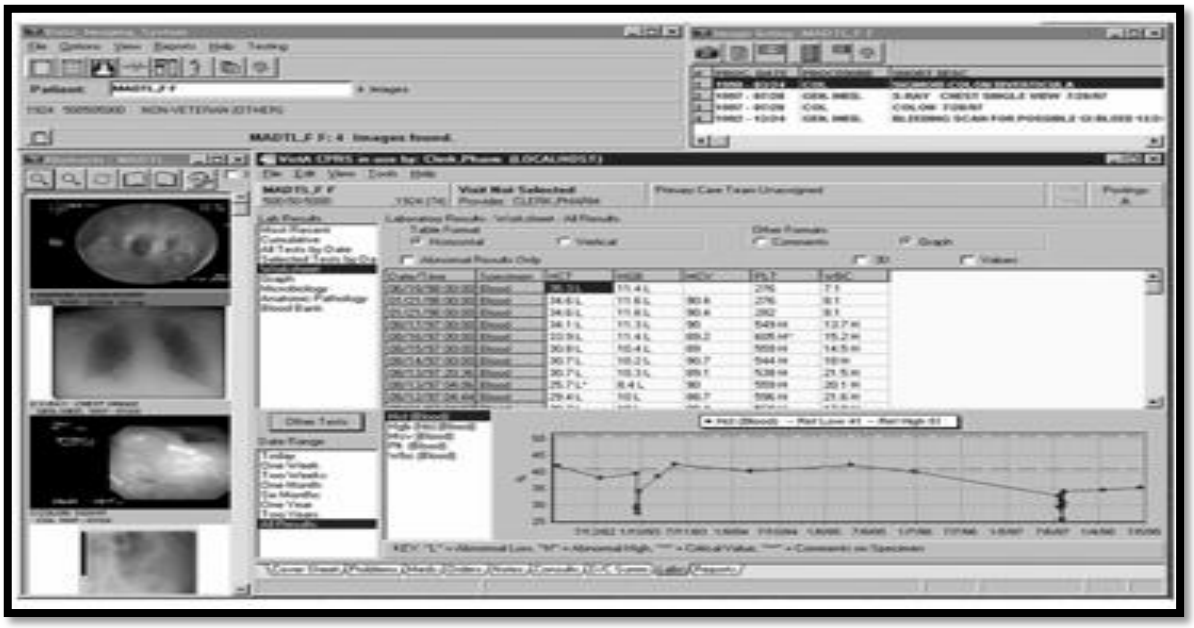


Figure 4.2. Example of information of patient in health record.

Benefits of Electronic Health Record (EHR) standardization, National Healthcare Information Network Clinicians and researchers see benefits to integrating electronic health records with data collection and analysis in clinical trials. Potential clinical trial participants can be more easily identified, administrative overhead costs can be lessened, data errors can be reduced, and adverse outcomes more rapidly identified. Besides, recording the medication of the patients we prevent the waste of medications.

4.1.4. The Emphasis on Nutrition and Health Maintenance

The key and critical disease-prevention role played by nutrition should continue to be explored and emphasized at all levels. A number of federal agencies and organizations are active in purveying information regarding the critical linkage between nutrition and health (wellness or disease prevention), including the U.S. Centers for Disease Control and Prevention (CDC 2002a), Health Canada (2002), and the U.S. Department of Agriculture (USDA 2002a, 2002b). This type of information could be made an integral, visible part of direct-to-consumer advertising for drugs (Daughton, 1999). The connections between health maintenance or improvement via proper nutrition and the reduced need for medication are well.

4.2. Eco-friendly Drug Design

New drug design and formulation should factor in new considerations for environmental or ecological friendliness or environmental or ecological proclivity. Such green PPCPs (pharmaceutical and personal care products) would maintain or improve therapeutic or cosmetic efficacy while also maximizing their susceptibility to biodegradation, photolysis, or other physicochemical alterations to yield innocuous end products. Design of more labile drugs (those that would ordinarily be degraded by or poorly transported across the gut) would further reduce excretion.

Drugs designs can be enhanced so as to promote better physiological sorption characteristics (to lessen direct excretion of the parent compound). Using smaller doses by enhancing the delivery exclusively to the target site or receptor is an objective being pursued on many fronts, including better drug design to accommodate existing membrane transporters and creating in situ synthetic transporters. The formulation of a drug can impede its sorption, especially for those with ill health or impaired gastrointestinal function. Rapid-dissolve tablets are one example of an improvement over formulations that can impede or prevent dissolution; for example, the common incipient stearic acid often impedes dissolution.

New formulations are particularly needed for insoluble drugs; current examples include liposomal delivery, polymer-drug conjugate pro drugs (with release at the target site), and special formulating approaches, such as insoluble drug delivery. Other examples include novel targeting approaches such as infusion of autologous erythrocytes that have been altered to encapsulate drugs and permit a steady, low-drug concentration to be attained for a period of weeks and that can selectively target certain sites such as macrophages.

With the materialization of innovations mentioned above, the intended consequences such as rapid healing periods due to novel targeting approaches, reductions in drug amounts and their excretion rates can be more effectively attained. Ultimately, the usage of

these kinds of drugs may lead to a decrease in drug dosage, as well as drugs' negative environmental effects.

4.2.1. The Future of Omics

The rapidly advancing omics revolution (genomics, proteomics, glycomics, metabolomics); will lead to the development of countless new classes of drugs (some with mechanisms of action never before encountered by any organism, and therefore posing the attendant questions as to the possibilities for previously unconsidered effects on non target organisms). But at the same time, identification of genetic idiosyncrasies will allow the selective targeting of specific subpopulations of patients for treatment with these same new drugs thereby allowing for their reduced use across the larger population. Pharmaco genomics holds great promise to:

i. Greatly increase the numbers of low-use drugs (those specifically tailored to narrowly define patient populations, effectively vastly increasing the number of therapeutic niches),
ii. Increase the numbers of high-use (blockbuster) drugs (by addressing therapeutic targets of minimal genetic variability across the population to yield drugs of extremely broad tolerability).

By increasing the efficiency of drug discovery (minimizing failures), the reduced costs will in turn catalyze yet more new-drug discovery. According to FDA, new generation genomics have less risk for health and environment.

4.2.2. Dirty Drugs to Designer Drugs

With better designed drugs (vs. those with a broad spectrum of molecular actions, dirty or promiscuous drugs), by increasing the specificity of drug action at the target receptor, not only could adverse reactions be minimized, but with extremely narrow MOAs (molecular actions) it would also prove easier to predict the potential for effects on non-target species.

Another issue, regarding drug invention or design, is the development of drugs with higher potencies (and therefore lower doses) as a result of greater systemic availability. Drug potency is partially a function of absorption efficiency (lower doses necessitated by higher absorption efficiency). Recently, reduced molecular flexibility (as measured by the number of rotatable bonds) coupled with lower polar surface area (or total hydrogen bond count) was shown to reflect good oral bioavailability, independent of low molecular weight (MW) or lipophilicity. A substantial increase in the designer drugs, instead of dirty drugs, will be beneficial not only the environment, but also for the patients to whom these drugs are to be prescribed.

4.3. Drug Delivery

Eco-friendly strategies to implement in the area of drug delivery include those relevant to prescribing, dispensing, patient compliance, and medication delivery mechanisms.

4.3.1. Prescribing

Both physicians and the public could be made more aware and better informed about the medical and environmental consequences of overprescribed medications. It is necessary to engage the medical community and the public in this issue. Guidelines could be developed and promulgated for minimizing inappropriate drug use (misuse, overuse, and abuse). Regarding the linkage between human and ecologic health, progress on this front has been most developed for the issue of antibiotics where physician knowledge and patient expectations are commonly at odds and antibiotics are sometimes prescribed (because of patient expectations) in situations where they are not justified. Inappropriate use also involves failure to identify putative pathogens and to perform susceptibility testing before selecting the most effective antibiotic.

The literature continues to document circumstances where antibiotics have long been used but should not have been; a recent example is their inappropriate use for bronchitis. Others who should attempt to minimize the misuse of antibiotics are veterinarians, aqua

culturists, and agriculturists to lessen the incidence of resistance development in native bacteria and human pathogens. An example of a creative approach to minimizing the use of antibiotics for the common cold is presented. By giving patients antibiotic prescriptions that could be filled only 3 days thence, overall use was 48% as opposed to 89% for those having immediate access to antibiotics for treating common cold symptoms nearly halving their use and avoiding exposing the patient to unnecessary medication.

By informing physicians and the public about the chemical properties of medications, not only could a decrease in cases of inappropriate use be achieved but also an outstanding decrease in such substances' effects on the environment could be attained. Another problem related with prescribing is dosage of the medications. The therapeutically effective dose for many drugs can be significantly lower than that initially recommended by the manufacturer. Sometimes the effective dose for a drug can be many orders of magnitude lower than previously realized, largely a result of incomplete knowledge of MOAs (molecular actions). Markets have to reduce patient risk by reducing side effects and even addiction while minimizing the potential for environmental effects. Most hospital side effects deaths are related to dosage and side effects may be a leading cause of hospital death in most countries in the world.

4.3.2. Individualization of Therapy

Drug manufacturers could provide the medical community with more easily implementable information (and requisite unit doses) to tailor drug dosages for the individual (especially for long-term maintenance drugs) on the basis of the sometimes complex interplay among body weight, age, sex, health status, nutritional status, timing/circadian rhythm, subtle genetic distinctions (e.g., accommodation for single-nucleotide receptor polymorphisms using new toxic genomics tools), and known individual drug sensitivities. Several companies are currently involved in approaches based on genetic variability's to personalize drug therapy. Currently, customized doses and formulations are often obtainable only from private pharmacy compounders (not drug manufacturers). Such individualization of therapy—also known as calibrated dosing—can minimize the requisite therapeutic dose (which is frequently higher than needed).

Available tests for drug metabolizing enzymes (e.g., the cytochrome P450 superfamily of monooxygenase isoforms) can distinguish fast, normal, and slow variants. These enzyme systems play major roles in the speed with which certain drugs are metabolized (whether leading to detoxification and excretion or to activation) and therefore determine the proper dosage. Advances in detection of other physiologic and metabolic characteristics of a patient can also allow for the specific targeting of a drug for its intended site (to reduce unnecessary systemic exposure). Individualized therapy can also help to address the growing trend of the healthy population that medicates on a long-term basis using a wide array of drugs as preventive measures. Outcomes from the use of medications by healthy people for durations spanning decades prompt numerous questions regarding patient safety and the consequent issue of imprudent introduction of drugs to the environment.

4.4. Technical Precautions

4.4.1. Gene – Based Therapy

The development over the past decade of methods for delivering genes to mammalian cells has stimulated great interest in the possibility of treating human disease by gene-based therapies. However, despite substantial progress, a number of key technical issues need to be resolved before gene therapy can be safely and effectively applied in the clinic. Future technological developments, particularly in the areas of gene delivery and cell transplantation, will be critical for the successful practice of gene therapy.

In the future, at the forefront of medicine, gene therapy brings people the latest research into genetic and cell based technologies to treat disease. With the improvements in gene-based therapies, a reduction in the need for medication can be attained. Ultimately, the toxic effects of drugs on the environment can be eliminated.

4.4.2. Nanotechnology

Regenerative medicine is an emerging multidisciplinary field that aims to restore, maintain or enhance tissues and hence organ functions. Regeneration of tissues can be achieved by the combination of living cells, which will provide biological functionality, and materials, which act as scaffolds to support cell proliferation. Mammalian cells behave in vivo in response to the biological signals they receive from the surrounding environment, which is structured by nanometer-scaled components. Therefore, materials used in repairing the human body have to reproduce the correct signals that guide the cells toward a desirable behavior.

Nanotechnology is not only an excellent tool to produce material structures that mimic the biological ones but also holds the promise of providing efficient delivery systems. The application of nanotechnology to regenerative medicine is a wide issue. Specifically, the fabrication of materials, such as nano particles and scaffolds for tissue engineering, and the nanopatterning of surfaces aimed at eliciting specific biological responses from the host tissue will be addressed.

4.4.3. Create Take – Back Program

Many pharmacies use reverse distributors for return of unsold/expired inventory (Daughton, 1999). This industry could serve as the foundation for an overarching returns industry by its expansion into a larger, comprehensive disposal and recycling program, one that accommodates the consumer sector. Great value could be added by designing an integral database that compiled information mined from consumer returns, with the objective of ultimately improving health care; such data are traditionally extremely difficult to obtain.

4.4.4. Sewage Recycling and Improvements

Straight-piping of sewage to surface waters should continue to be identified and eliminated on an ongoing basis. Privies and septic systems should be converted to

municipal systems when feasible. Improvements in capacity can reduce overflow events, a problem of escalating proportions in many urban areas. It has long been assumed that ocean discharge of sewage protects coastal exposure (by way of dilution). The possibility of sewage plume redirection to coastal areas by tidal events. As sewage discharges increase with expanding populations, the dilution previously afforded by receiving waters will continually diminish. Also under development are various toilet-to-tap plans for upgrading sewage to potable water (or at least to a level suitable for groundwater reinjection). By use of advanced water treatment technology such as reverse osmosis, nearly complete removal of all PPCPs (Pharmaceutical and Personal Care Products) can be achieved. However, all the solutes removed by reverse osmosis are concentrated in the rejected brine a waste stream that must be disposed itself.

4.5. Recycling, Reuse and Recovery

Recycling processes usually require wastes to be reprocessed or reclaimed before their constituents can be used for beneficial purposes. Examples of recycling strategies for laboratories include;

i. Separate collection of used solvents with only trace levels of contamination for use in washing purposes;
ii. Distillation recovery of solvents for reuse; and
iii. Segregation of wastes that have reclamation value, such as used oil, mercury, scrap lead and precious metal compounds, and solvents suitable for use in fuel recovery facilities.

Medicines would not even have to be remanufactured, just verified. Many tablets or capsules already are packaged individually in tamper-proof wrappings with the name and date of expiration stamped on each one. Such blister packaging is already routines for many over-the-counter medicines and physician samples.

Recycling of drugs is generally illegal. In some provinces, drugs in sealed, unopened containers may be recycled if they have been returned from a controlled environment such

as a long-term care facility. The environmental opportunity relates to reduction, re-use or recycling of the packaging, and appropriate disposal of the unused drugs. Additionally, more important then reducing the waste, is identifying and addressing the underlying reason for it. Pharmacists are in an ideal position to assess and act on the individual patient's reasons for returning medication and to assist in the safe disposal of unwanted drugs. Waste should be prevented wherever possible, through trial prescription programs, dispensing of smaller quantities, and education of patients, prescribers, government and the pharmaceutical industry on the cost of waste. According to recent study in waste management has been to treat the waste material as a resource to be exploited, instead of simply a challenge to be managed and disposed of. There are a number of different methods by which resources may be extracted from waste: the materials may be extracted and recycled, or the calorific content of the waste may be converted to electricity.

The process of extracting resources or value from waste is variously referred to as secondary resource recovery, recycling, and other terms. The practice of treating waste materials as a resource is becoming more common, especially in metropolitan areas where space for new landfills is becoming scarcer. There is also a growing acknowledgement that simply disposing of waste materials is unsustainable in the long term, as there is a finite supply of most raw materials. There are a number of methods of recovering resources from waste materials, with new technologies and methods being developed continuously.

In some developing nations some resource recovery takes place by way of manual laborers who sift through un-segregated waste to salvage material that can be sold in the recycling market. These unrecognized workers called waste pickers or rag pickers, are part of the informal sector, but play a significant role in reducing the load on municipalities' solid waste management departments. There is an increasing trend in recognizing their contribution to the environment and there are efforts to try and integrate them into the formal waste management systems, which is proven to be both cost effective and also appears to help in urban poverty alleviation. However, the very high human cost of these activities including disease, injury and reduced life expectancy through contact with toxic or infectious materials would not be tolerated in a developed country.

5. RECALLED AND REJECTED (R2) MEDICINE DISPOSAL METHODS

Pharmaceuticals are produced and used in increasingly large volumes every year. With this growth comes concern about the fate and effects of these compounds in the environment. A wide range of pharmaceuticals has been found in fresh and marine waters, and it has recently been shown that even in small quantities, some of these compounds have the potential to cause harm to aquatic life.

Most people think that disposal to trash is considered an intern solution. However, medications placed in landfills may ultimately reach wastewater treatment plants and local streams and rivers. There is good agreement both nationally and internationally that the best disposal streams solution is incineration of medications in a regulated incinerator. To be able to establish a good R2 minimization method is very important because it has very dangerous consequences. In general, expired pharmaceuticals do not represent a serious threat to public health or to the environment. Improper disposal may be hazardous if it leads to contamination of water supplies or local sources used by nearby communities or wildlife. Expired drugs may come into the hands of scavengers and children if a landfill is insecure. Pilfering from a stockpile of waste drugs or during sorting may result in expired drugs being diverted to the market for resale and misuse.

R2 medical waste management would require collected pharmaceuticals to be sorted for proper disposal. Pharmacies normally do not handle these activities, which are managed for them by reverse distribution, who are typically the legal generator of pharmacies' wastes. All waste pharmaceuticals that are collected through proper disposal channels are incinerated. Sewer disposal may theoretically be legal for certain pharmaceuticals (those not classified as hazardous waste), but wastewater treatment plants recommend against sewer discharge of pharmaceuticals (Tata et al., 2003).

5.1. Collection

First step for proper R2 disposal is collection. Waste collection varies widely between different countries and regions so it would be impossible to describe them all. Many areas, especially less developed countries, do not have formal collection system. For example, in Australia most urban domestic households have a 240-litre (63.4 gallon) bin that is emptied weekly from the curb using side-or rear loading compactor trucks. A few communities use a proprietary collection system which conveys refuse via underground conduits using a vacuum system. Urban centers curbside collection methods are the most common method of disposal, whereby the city collects waste and or recyclables and or organics on a scheduled basis. In rural areas people usually dispose of their waste by hauling it to a transfer station. Waste collected is then transported to a regional landfill. Best management practices for collected materials are;

i) Donate eligible cancer and chronic disease drugs and supplies for use by other patients.
ii) Have any mercury-containing devices such as thermometers recycled to recover the
iii) Mercury;
iv) Destroy other materials using hazardous waste incineration

Pharmaceuticals present both a public safety and environmental hazard if no secure disposal option exists.

i) A collection program is capable of collecting data that can be used to reduce waste production through educational efforts in both pharmaceutical use and prescription writing.
ii) A collection system would decrease the environmental pollution from solid waste landfills and waste water treatment discharge.
iii) Separate collection helps communicate the environmental impact of this waste stream to the responsible parties: consumers, retailers, and manufacturers.
iv) A collection system can be modeled after other take back programs for light bulbs, thermometers, batteries, and oil.

During the collection, safety is first important subject. UN prescribed contact with some pharmaceutical can pose safety hazards to pharmacy workers or collection participants. Some drugs are skin contact; some have dusts that are inhalation hazards. Reactions among certain substance are possible. Liquids may be hard to control, and spills of certain medicines could require special clean-up procedures. Safety measures have to be taken to protect the health of the collection staff receiving and managing returned pharmaceuticals. Keep medications in their original packaging in order to prevent reactions in the collection bin. Furthermore, keep accurate records of the medicines and other items you collect. These records are valuable to researchers who are currently collecting data on unused medicines to develop improved prescription and patient communication practices.

5.2. Sorting

The objective of sorting is to separate the pharmaceuticals into separate categories for which different disposal methods are required. The separation should be made into those that can be safely used and returned to the pharmaceutical supply system and those that require disposal by different methods. For example, controlled drugs (e.g. narcotics), antineoplastic drugs and antibiotics all require special methods of disposal. Substantial investment in human resources may be required for identifying and separating pharmaceuticals.

The appropriate safe disposal method recommended will depend principally on the pharmaceutical dosage form of the drugs. Segregated temporary storage areas or receptacles must be provided for each sorted category. Sorting involves an initial overall evaluation of the stockpile and subsequent division of pharmaceuticals into those suitable for use and those to be discarded. For those to be discarded a decision is made on the best method of disposal. To be efficient items should only be handled once. Pharmaceuticals suitable for use should remain in their packaging. The pharmaceuticals to be discarded should be separated from their packaging as late in the process as possible. The sorting process includes:

i) identifying each item;
ii) making a decision on whether it is usable;
iii) if usable, leaving packaging intact;
iv) if not usable, making a judgment on the optimal method of disposal and sorting accordingly.

The top priority of the sorting process is to separate out the pharmaceuticals that are categorized as controlled substances (e.g. narcotics), antineoplastic (cytotoxicanti– cancer) drugs and any other hazardous non-pharmaceutical products that may have been mixed among the pharmaceuticals. These must all be stored in separate, secure designated areas prior to their separate, safe disposal. The remaining unwanted pharmaceuticals must be further sorted into different categories by dosage form, (capsules, powders, solutions, suppositories, syrups, tablets). The following sorting categories and subcategories are suggested. While this separation is logical and appealing, experience indicates that it may not always be an efficient use of time and resources.

5.3. Landfill

To landfill means to place waste directly into a land disposal site without prior treatment or preparation. Landfill is the oldest and the most widely practiced method of disposing of solid waste. Three types are recognized. Disposing of waste in landfill is one of the most traditional methods of waste disposal, and it remains a common practice in most countries. Historically, landfills were often established in disused quarries, mining voids or borrow pits. A properly- designed and well-managed landfill can be a hygienic and relatively inexpensive method of disposing of waste materials in way that minimizes their impact on the local environment. Older, poorly-designed or poorly-managed landfills can create a number of adverse environmental impacts such as wind-blown litter, attraction of vermin, and generation of leachate where result of rain percolating through the waste and reacting with the products of decomposition, chemicals and other materials in the waste to produce the leachate which can pollute groundwater and surface water. Another byproduct of landfills is landfill gas (mostly composed of methane and carbon dioxide),

which is produced as organic waste breaks down anaerobically. This gas can create odor problems, kills surface vegetation, and is a greenhouse gas.

Design characteristics of a modern landfill include methods to contain leachate, such as clay or plastic lining material. Disposed waste is normally compacted to increase its density and stabiles the new landform, and covered to prevent attracting vermin (such as mice or rats) and reduce the amount of wind-blown litter. Many landfills also have a landfill gas extraction system installed after closure to extract the landfill gas generated by decomposing waste materials. Gas is pumped out of the landfill using perforated pipes and flared off or burnt in gas engine to generate electricity. Flaring off the gas is generally a better environmental outcome than allowing it to escape to the atmosphere as this consumes the methane 8 which is a far more potent greenhouse gas than carbon dioxide). Many local authorities, especially in urban areas, have found it difficult to establish new landfills due to opposition from owners of adjacent land. Few people want a landfill in their local neighborhood. As a result, solid waste disposal in these areas has become more expensive as material must be transported further away for disposal (or managed by other methods).

5.4. Incineration

Incineration is the most safe disposal process for the hazardous wastes. Incineration is applied to certain wastes that can not be recycled, reused or safely deposited in a landfill site. Incineration is a waste disposal method that involves the combustion of waste at high temperatures. Incineration and other high temperature waste treatment systems are described as thermal treatment. In effect, incineration of waste materials converts the waste into heat, gaseous emissions, and residual solid ash. Other types of thermal treatment pyrolysis and gasification.

It is a high temperature, thermal oxidation process in which hazardous wastes such as hospital wastes, pharmaceutical wastes discussed in this study are converted in the presence of oxygen into gases and an incombustible solid residue. This process is chosen if:

The waste is biologically hazardous,

- It is resistant to biodegradation, and persistent in the environment,
- It is volatile and therefore easily dispersed,
- It has a flash point below 40° C,
- It can not safely be disposed of in a landfill site (Seven et al., 2006).

If properly managed, incineration can serve crucial purposes as destruction of the wastes accompanied by a significant reduction in its weight and volume, and the production of a sterile solid residue.

Breaking down complex chemical chains such as dioxin through the application of heat usually cannot be done by simply burning the material at the temperatures seen in an open-air fire. It is often necessary to supplement the combustion process with gas or oil buners and air blowers to raise the temperature high enough to result in molecular breakdown. Alternately, the exhaust gases from a natural air fire may pass through tubes heated to sufficiently high temperatures to trigger thermal breakdown. Thermal breakdown of pollutant molecules can indirectly create other pollution problems. Dioxin breakdown begins at 1000°C, but at the same time poisonous nitrogen oxides and ozone begin to form when atmospheric nitrogen and oxygen break down at 1600 °C. This undesired oxide formation may require further catalytic treatment of the exhaust gases.

Besides its several advantages, this process of disposal has the considerable construction costs. Despite the fact that incineration is the only method that offers the detoxification of wastes such as combustible carcinogens and pathological waste. Incineration also reduces the volume of hazardous waste. The act of disposal should not in itself cause a threat to the environment. Waste of low radioactivity can safely be incinerated. Wastes that are not suitable for this process include those that do not contain a significant proportion of organics, or highly explosive or radioactive.

5.4.1. Increasing Multiplying Incineration Units in Turkey

Presently there are two significant incineration facilities in Turkey. The one, ISTAC Co., Istanbul Metropolitan Municipality Environmental Protection and Waste Materials Valuation Industry and Trade Co., is one of the Economic Enterprises of Istanbul Metropolitan Municipality. ISTAC was established in 1994 by Istanbul Municipality. Its activities include also the regular storage and disposal of domestic wastes, transportation and incineration of medical wastes, planting seedlings and their irrigation. In 1995 the Project of Medical Waste Management was carried out by İSTAC. In 1995 the brutal waste storage areas were abolished and hygienic waste storage units were established by İSTAC. As the name denotes, İSTAC Co. within the scope of Solid Waste Project of Istanbul Metropolitan Municipality, provides services for transportation of solid wastes, production of compost fertilizer, recycling of wastes, disposal of them via regulated storing, electric energy generation from landfills, transportation of medical waste and their disposal via incineration.

Unless the medical waste is separately collected and destroyed, it will be hard to avoid the risk of infection of people by many dangerous diseases and it will be inevitable that plenty of health, environmental and financial problems will arise. Works on medical wastes are those contributing to the formation of a “Clean City – Healthy Society” which is the slogan of ISTAC.

Medical Waste Practice of ISTAC: Waste created by health facility is collected in bags of three different colors which can be easily differentiated from one another. Domestic wastes are collected in the “blue” bag, while glass made products such as drug and serum bottles are collected in the “black” bag. Medical waste; pathological and non-pathological waste originating from the units, infected, chemical and pharmaceutical wastes as well as cutting – boring materials and infected waste; any and all human tissues and organs, urine pots whether polluted with disease effects or having any possibility for such pollution, blood or placenta wastes, bacteria cultures, infectious diseases and emergency service waste, bacteria and virus holding air filters, bandages with blood, cotton cloths and other wound-dressing and surgery waste, drug boxes, feces and items polluted with that, carcass

of experimental animals used for research purposes, waste of patients under quarantine are collected in the “red” bag. The bag has a width of 50 cm and a length of 80 cm.

Cutting – boring apparatus such as needles are located in the “yellow” Infected Waste Bucket, the lid is firmly closed and put into the red bag.

Medical Waste Team and Equipment: ISTAC CO. performs the task of collecting, transporting and destroying the medical wastes by teams which are certified, subjected to periodic health control, specially trained and equipped with special vehicles. All clothes and equipment used by the team are created specific to this task in accordance with the Regulation. Clothes of these teams are composed of specially designed garment, boots with steel bottom to protect against injuries due to scratching and cutting, eyeglasses, mask, bonnet and gloves against damages to be caused by breathing and infection. Teams undergo health controls. ISTAC’s medical wastes works and medical waste teams are frequently honored in written or oral manner by Health Facilities.

Works of District Municipalities: In line with the resolution of Istanbul Provincial Environmental Board dated 22.03.1999 with No. 3, medical waste originating from Health Institutions (clinics, outpatient clinics, health posts etc.) with a bed capacity less than 20 is collected by District Municipalities. Medical waste coming from District Municipalities which is around 1,5 – 2,5 tones daily are eliminated by being incinerated in ISTAC CO.’s Incineration Plant. Currently no fee is charged to District Municipalities for incineration.

Incineration Facility: Incineration process of medical waste is performed with full automation system in the “Medical Waste Incineration Facility” with a daily capacity of 24 tones. Waste is eliminated by being incinerated at 900 – 12000^{o}C in the facility. At the end of incineration, the waste is reduced by 95 % in volume, and 75 % in mass.

Destroying Solid and Medical Waste: Destruction of solid and medical waste arriving together with official report from the Metropolitan Municipality and requested to be destroyed in accordance with the official procedures is performed by on-site assessment together with officials from Metropolitan Municipality.

Elimination of Medical Wastes by Incineration: Waste arriving at the Incineration Plant via special medical waste vehicles are poured into the vibrating fed conveyor system. This conveyor system fills up a small container located on the weighing cells on the feeding reservoir. Waste is filled into a revolving furnace by the waste sliding system.

Inside surface of the revolving furnace is coated with refractor material, and this furnace is equipped with a burner which keeps the energy level at the lowest level in order to provide continuous purification from poisonous gases. Minimum retention period of waste in the incineration furnace is 1 hour.

Post-incineration grid ensures full incarnation. Chimney gas yielded inside the revolving furnace and post-incineration grid is delivered to a second incineration room (IYO) passing through a narrow pipe. Turbulence inside the pipe provides best mixture of the gases, which is a precondition for full incineration of the gases.

Second incineration room is equipped with one support burner for maintaining the lowest temperature. Retention period is at least 1,5 seconds at 1200°C in order to ensure that the chimney gases incarnate fully.

Fuel oil is used as fuel in auxiliary burners and its quantity ranges from 30 liter to 80 liter for 1 tons of waste based on the calorific value of the garbage. After the second incineration room, the facility is equipped with a flame pipe type boiler for red-hot steam yielding and with an economizer for increasing the feeding water.

Technical Specifications of Medical Waste Incineration Plant

Furnace Capacity: 1.0 tone /hour (for 3500 kcal/kg waste) .
Calorie Value of Burnable Waste: Min. 2000 kcal / kg Max. 4540 kcal / kg.

Table 5.1. ISTAC technical specifications.

ISTAC	
Furnace Capacity (for 3500 kcal/kg waste)	1.0 ton/hour
Calorie Value of Burnable Waste (Min.)	2000 kcal/kg
Calorie Value of Burnable Waste (Max.)	4540 kcal/kg

The other significant incineration plant is in Izmit and is called İZAYDAS which is the first licensed incineration plant in Turkey. It has been serving since 1997. İZAYDAS's yearly waste capacity is 35000 tones. 75% of its capacity is from Kocaeli, 15% from Bursa, Yalova and from Sakarya and finally 10% are spared for other provinces.

Disposing processes are performed by İZAYDAS (İzmit Waste and Residue Treatment Incineration and Recycling Co.) in the frame of regulations I-D–5 Land Storage with Special Procedures, II - D–10 Incineration (in Special Furnaces) which are included in the Hazardous Wastes Control Regulation issued by The Ministry of Environment and Forestry. Since every kind of substances produced and using activities that have hazardous effects directly or indirectly over human health and environment are called wastes, their disposal should be professionally done.

In İZAYDAS Incineration Plant, the hazardous industry originate plastic and rubber waste, used oil, pharmaceutical and cosmetic waste, petrochemical waste, PVC, solvent, dye rests, adhesives and their packages, substandard and life time exceeded products, waste treatment sludge etc. and clinical waste are incinerated. Explosive material, radioactive wastes, slaughterhouse waste, feces and cadaver are not accepted to the plant. Declaration, labeling, transportation and treatment are carried out strictly appropriate to the authorized state instructions. General view of the plant Design Capacity of the Plant Combustion Capacity: 35000 tones/year (4100 kg/hour) Solid Waste: 2500 kg/hour Liquid Waste: 1600 kg/hour Calorific Value: 86 GJ/hour Generation of Electricity: 5.2 MW.

Table 5.2. İZAYDAS technical specifications.

İZAYDAS	
Plant Combustion Capacity	35000 tones/year
Hourly Combustion Capacity	4100 kg/hour
Solid Waste	2500 kg/hour
Liquid Waste	1600 kg/hour
Calorific Value	86 GJ/hour
Generation of Electricity	5.2 MW

Nevertheless, İZAYDAS does not accept the wastes because of its full capacity. This situation creates great deal of problems. Since the plant serves the surrounding industrial areas, its negation of the new recourse causes harms to the industrial organizations. For a report in the daily journal of SABAH, the industrialists were faced with the problem of indisposed wastes. The industrial organizations surrounding areas of İzmit could not cope with their industrial and hazardous wastes. As a solution, exporting the wastes to Germany came into question. Since the organizations could not store their wastes any more for the lack of storage capacity, as another way of breaking free from their wastes the industrial organizations resorted to cement factories to incinerate hazardous wastes. It was said that the Ministry of Environment and Forestry presented this solution. Because only the cement factories have high temperature furnaces. This fact shows that disposal of hazardous wastes in Turkey is an important issue awaiting expeditious solutions.

The urgent need for Turkey to execute the environmental laws and regulations in order to succeed in sustainable development process is augmenting the incineration units. In the present day, several incineration plants are in the establishment stage or have recently been established in metropolitan cities like Eskisehir, Kayseri, and Antalya. However, they are not enough to meet the immense portions of hazardous wastes. Since the crucial problems arise from the lack of adequate incineration units, in order to dispose the hazardous waste safely, augmentation of them has a significant importance.

5.4.2. Mobile Incinerator

Incinerators are innovative treatment techniques to decrease R2 medicines' negative impact on environment. It involves combustion materials and organic substances. Incineration and other high temperature health treatment systems are described as thermal treatment. Incineration of waste materials converts the wastes into the ash, flue gases, particulates, and heat which can in turn be used to generate electricity. The flue gases are cleaned for pollutants before it is dispersed in the atmosphere. Incineration with energy recovery is one of several waste-to-energy (WtE) technologies such as gasification and anaerobic digestion. Incineration may also be implemented without energy and materials recovery. Modern incinerators reduce the volume of the original waste by 95-96 %, depending upon composition and degree of recovery of materials such as metals from the ash for recycling. This means that while incineration does not completely replace landfilling, it reduces the necessary volume for disposal significantly.

Incineration has particularly strong benefits for the treatment of certain waste types in niche areas such as clinical wastes and certain hazardous wastes where pathogens and toxins can be destroyed by high temperatures. For example in chemical multi-product plants with diverse toxic or very toxic wastewater streams, this cannot be routed to a conventional wastewater treatment plant.

An incinerator is a furnace for burning refuse; modern incinerators include pollution mitigation equipment such as flue-gas cleaning. There are various types of incinerator plant design: Nowadays, most pharmaceutical companies use mobile incinerators. This new incineration provides more advantages to manufacturers.

Figure 5.1. Mobile incinerator

Financial Analysis:

Mobile incineration expenses are including machine and some equipment;

Leather Furnace man's mitts: Price £19.80 + VAT

Leather Furnace man's arm guards: Price £19.80 + VAT

Flame retardant jacket: Price 27.56 + VAT

Flame retardant coveralls: Price £32.65 + VAT

Heavy flame retardant jacket: Price £51.94 + VAT

High temperature safety visor: Price £35.76 + VAT

Leather Furnace man's gauntlet gloves: Price £17.36 + VAT

Leather Furnace man's apron: Price £36.99 + VAT

Equipment Total: Price £214 + VAT = 907 USD

Mobile incinerator price is approximately 47520 USD + VAT

Total amount is 48427 USD + VAT.

5.4.3. The Benefits of Mobile Incinerator

Incinerator has many advantages in disposing R2 medicines;

Sanitary: Waste can be destroyed as fast as it accumulates. Nothing is left to spread disease or to attract rodents and flies.

Convenient: Fill the chamber and turn on the burner. No watching required since timer automatically shuts down burner. Alternative methods frequently require more time to manage and maintain.

Thorough: One of the main features of this incinerator range is that they burn virtually smoke and smell free without the need for a secondary burner because of their patented internal design. Their simplicity of operation makes the units a key benefit on any waste disposal application by avoiding the need for constant supervision.

6. DIRECTIVES, REGULATIONS AND POLICIES

The inappropriate disposal methods of R2 medicines cause environmental pollution which in turn has negative effects on human health and other living organisms' well-being. This entails legal regulations and restrictions to endure sustainable development. Turkey have legal regulations regarding R2 minimization, collection, transportation and disposal process included in Environment Protection Law (1983), Management of Hazardous Wastes (2005) and Management of Medical Wastes (2005). Besides, Turkey is the contractor country of the international environmental protection acts. Since the protection of environment and sustainable development has also an international dimension (Şengün, 2008).

Turkey has also some obligations regarding the protection of environment in EU Acquits. Since Turkey is in the process of affiliation with EU; the Country has to fulfill some necessary obligations regarding environmental protection. These regulations will be discussed in detailed in section 6.2.

European Union starting with 1970's has become more focused on the problem of environment. In October 1972, in the Assembly of Government Presidents, the issue of environment has discussed. As a result of the Assembly, the 1st and 5th-Years Environment Action Programs were arranged and these programs served as a basis for EU environmental politics.

11 principles of environmental politics emerged (Yaşamış, 1995):

i) Instead of decontaminate the environment; the preventive politics should be preferred.
ii) In decision making process environmental effects should be regarded.
iii) Ecological equilibrium should be protected.
iv) Scientific researches would be improved.
v) The principle, "Sullying will pay" should be practiced.

vi) The activities of one country would not lead environmental side effects to other country.

vii) The members' environmental politics would not harm to developing countries' environmental politics. The environment protection activities in international and global level would be supported. The education of environment should be compulsive. The limits of environmental protection should be well defined. National environmental precautions should be concordant with other members' politics.

As far as 1986 European Single Act was signed in Luxembourg, EU Acquits have had no detailed regulations on environment. By the 25th article in the Act, the environment was inserted to the politics of EU as a separate title (Hamamcı, 1997). 25th article of European Single Act aimed to protect the environmental wealth as a common purpose of the ensemble. The same emphasis was seen in Maastricht Act (1987) which has important obligatory sentences of environmental protection for member countries. Similarly, in 1990 Dublin Summit of Presidents of Governments, the presidents maintained that environmental responsibilities are fulfilled and politics on protection would be enriched (Yaşamış, 1995).

6.1. Exemplary Policies Regarding R2 Methods

Recall procedures have a great deal of importance regarding the health and well being of the population. For this reason the steps in the recall procedure are elaborate. According to the policy of JCAHO American Society of Hospital Pharmacists' Drug-Recall Report; when a drug or a pharmaceutical product has been recalled or discontinued by the manufacturer or FDA for safety reasons, the Pharmacy will coordinate the removal, sequestering and disposal of such items from all Pharmacy dispensing areas, medication storage sites, all hospital off-site and off-campus areas in which drugs are handled or used. This is the responsibilities of the Pharmacy when a recalled drug is in use (JCAHO, 2004).

For the same reasons, when Pharmacy is informed of a product recall of substantial clinical significance, patients will be identified, informed of the recall and advised of any

necessary action as required. It is the responsibility of the Director of Pharmacy or designee to oversee the management of the drug recall procedure. Pharmacy will coordinate the identification and notification of patients who may have received a recalled or discontinued medication for safety concerns of substantial clinical significance during their admission or during an off-site ambulatory care area visit. It is the responsibility of the Inventory Control Manager and the evening Manager to coordinate the removal of recalled items from all areas. Risk Management will assist with the notification of patients regarding drug recalls for safety concerns of clinical significance.

The procedure is run as The Inventory Control Manager in conjunction with the evening Manager will coordinate the inspection and removal of recalled items from all patient care areas in which drugs are handled and used. Each recalled item that has been purchased by the Medical Center will require the completion of a Drug Recall Report Form, which includes the documentation of the specific hospital locations that were reviewed as well as the quantities of recalled items that were removed from all locations. To ensure the removal of all recalled drugs from unit dose dispensing areas and from patients who may be current recipients of the recalled item, the Pharmacy will generate a computerized Target Drug Report for the drug in question. The Target Drug Report will list the name and location of all unit dose patients receiving the recalled drug. In the case of product recalls of substantial clinical significance, Pharmacy, in collaboration with Risk Management, will inform the attending physician and the patient of the recall.

Pharmacy will notify personnel at off-site ambulatory patient care areas of any recalled or discontinued products dispensed by the Hospital Pharmacy. When necessary, owing to a safety concern of clinical significance, each site will identify and collaborate with Risk Management to notify patients and their physicians of the drug recall.

A record of the official drug recall notice as well as a record of the Drug Recall Report Form will be maintained in Pharmacy's Drug Recall Notebook. A copy of the drug recall notice will also be maintained in the recall section of the Nursing Station Inspection Notebook to alert pharmacists to look for specific recalled drugs during the monthly Nursing Station Review. The Manager for Inventory Control will insure that all recalled

items will be marked “Quarantined – Do Not Use – Recalled,” sequestered and properly secured until they are picked up by or returned to the manufacturer.

The Manager for Inventory Control will process recalled drugs as directed by the manufacturer or regulatory agency and complete all necessary documentation to denote full compliance with the details of the recall. The completed Drug Recall Report Form and all other documentation will be maintained in the Drug Recall Notebook (JCAHO, 2004). As described in above paragraphs a recall procedure requires many stages in which main figures and organizations play a crucial role in controlling, preventing and monitoring the recall process.

6.1.1. FDA Product Recall Policies

The Federal Food, Drug, and Cosmetic Act, (the law) may request a product recall if the firm is not willing to remove dangerous products from the market without FDA's written request. Only when a medical device, human tissue products, and infant formula pose a risk to human health; that the law specifically authorizes FDA to prescribe a recall and to rule on the scope and extent of the same. The manufacturers or distributors of the product carry out most recalls of products regulated by FDA voluntarily. In some instances, a company discovers that one of its products is defective and recalls it entirely on its own. In others, FDA informs a company of findings that one of its products is defective and suggests or requests a recall. Usually, the company will comply. If the firm does not recall the product, then FDA can seek legal action under the Federal Food, Drug, and Cosmetic Act. These include seizure of available product, and/or injunction of the firm, including a court request for recall of the product. This cooperation between FDA and its regulated industries has proven over the years to be the quickest and most reliable method to remove potentially dangerous products from the market. FDA guidelines for companies make clear that FDA expects these firms to take full responsibility for product recalls, including follow-up checks to assure that recalls are successful. Under the guidelines, companies are expected to notify FDA when recalls are started, to make progress reports to FDA on recalls.

The guidelines also call on manufacturers and distributors to develop contingency plans for product recalls that can be put into effect if, and when needed. FDA's role under the guidelines is to monitor company recalls and assess the adequacy of a firm's action. After a recall is completed, FDA makes sure that the product is destroyed or suitably reconditioned and investigates why the product was defective.

Generally, FDA accepts reports and other necessary recall information submitted by e-mail. In many cases, this has become routine for some firms and FDA district offices. However, FDA maintains the prerogative for investigational visits and other in-person communications where the agency considers it appropriate. Even though the firm recalling the product may issue a press release, FDA seeks publicity about a recall only when it believes the public needs to be alerted about a serious hazard.

In order to decrease the potential environmental impacts of pharmaceutical companies should integrate an intensive "R2 Action Procedure". This procedure is usually applied by pharmaceutical companies to remove a product from the market. R2 may be conducted on a companies' own initiative, by FDA request, or by FDA order under statutory authority. Furthermore, manufacturers or distributors usually implement voluntary recalls in order to carry out their responsibilities to protect the public health when they need to remove a marketed drug product that presents a risk of injury to consumers or to correct a defective drug product. A voluntary recall of a drug product is more efficient and effective in assuring timely consumer protection than an FDA-initiated court action or seizure of the product.

When we look at the European R2 projects we see that, the aim of uniform recall procedure is to:

i. Minimize the risk of injury or death to consumers by removing an unsafe product from use. Retrieve or repair as many of the defective products as possible
ii. Minimize the cost and inconvenience to consumers and the company
iii. Minimize the need for involvement by government authorities by voluntarily complying with the law.

6.1.2. R2 Policies in Turkey

In Turkey, there are no such detailed policies or regulations as we discussed above. A medication is not recalled by the mere initiation of Turkish Ministry of Health since the recall process requires higher costs. Instead, Turkish Ministry of Health adjusts FDA recall decisions to the domestic market. When a medication was found risky or defective by FDA, Turkish Ministry of Health takes necessary steps to remove it from the market. In the way to affiliate EU, Turkish institutional structures are reorganized. Therefore, undefined or insufficient place of the R2 process should be tolerated. Since the disposal of recalled medicines and pharmaceutical wastes are important issues in preventing the environmental pollution, R2 medicines are discussed under the headings of some laws and regulations.

In Turkey, The Environment Protection Law was approved in 1983 to prevent the pollution of the environment and take the required precautions about the pollution. The Law put the target as to protect and ameliorate the environment which is the common property of all citizens, to use and protect the land and natural resources in urban and rural areas in most proper way, to prevent the pollution of water, land and air, to protect the flora and the fauna of the country besides the natural and historical wealth, to improve and secure the quality of life of the citizens regulate the norms and precautions compatible with economical and social developmental goals (Resmi Gazete, 1983).

The general principles in this law are;

Corporations and real persons - citizens- are responsible for the protection of the environment and prevention of pollution. Corporations and citizens are obliged to obey the rules and regulations related with the protection of the environment.

In managing the rules and regulations on the pollution and the protection of the environment; the crucial points are maintaining the health of the citizens' and to make short and long term evaluations of the regulations with regard to positive and negative effects and costs and benefits of the regulations and precautions.

Authoritative corporations that took decisions of using land and resources have to regard the protection of the environment and avoid making negative effects on sustainable developmental strategies.

In economic activities and in determination of production methods the most appropriate technologies and methods are chosen and applied. Besides the exceptional cases, the expenditure of prevention, limitation and the struggle against the pollution is belonging to the pollutant corporations and the real persons. The persons whom pollute and destroy the environment are the real responsible entities. However, they can only break these responsibilities of payment when they prove that they took required precautions and measures to prevent pollution. In protecting the environment and preventing the pollution, determination of the precautions in their entirety is essential (Resmi Gazete, 1983).

The Environment Protection Law includes R2 under the headings of "hazardous waste" and "hazardous chemicals". According to the definition of hazardous waste, it is the waste which has physical, chemical or biological negative effects on human and other living organisms' well being. Hazardous chemicals also have disruptive effects on human and other living organisms' well being and cause to the ecological disequilibrium.

In order to coordinate and regulate the activities required by the Law, a High Environment Committee is constituted. This committee has meetings under the heading of Prime Minister, in the absence of the Prime Minister, the Minister of the "Ministry of Environment and Forestry" preside the meetings. The other members are chosen by the Prime Minister within the other ministers and undersecretaries. The mission of the Committee is to determine the targets, politics and strategies in order to provide effective environment management. The Committee determines the judicial and managerial precautions which enables inclusion of environment dimension to the economical decisions taken by sustainable developmental principles. When more than one ministry or institution has a concern on an issue regarding the environment, the ultimate decision authority is the High Environment Committee.

Whatever the type of wastes or residues, it is forbidden to store, carry and remove them against the legally determined standards and methods. When there is a possibility of pollution, the person in charge has to stop the pollutive acts or to take the precautions for reducing the pollution. Otherwise, the person or the corporation gets a legal penalty (Resmi Gazete, 1983).

In 22.07.2005 published in official paper, "Medical Wastes Management Regulation" came into force. In this regulation, R2 process is defined under the heading of "Pharmaceutical Waste". The regulation, in the case of management of medical wastes, puts that it is impermissible and forbidden to release the medical waste directly or indirectly to the nature since it is detrimental to human beings and all other organisms. It is also crucial to reduce the domestic and medical wastes in its source. Special to the medical wastes, their collecting, saving, transporting and disposing methods are distinctly different from the other wastes. Producers of the medical wastes are totally responsible from the disposal of these wastes (Resmi Gazete, 2005).

The staff of the medical waste producing medical centers, the staffs that are responsible from the transporting and disposing of these materials and municipal or corporations' responsible staffs has to pass a periodic medical examination during their working.

The Ministry of Environment and Forestry determines the politics and the programs, cooperates and coordinates the waste management process and regularly controls the activities of the waste produced organizations and corporations. The Ministry also gives the license to the medical waste disposal plants.

The local higher authority has the control warrant. When there is an illegal activity, it imposes the required sanction. The local higher authority evaluates and reports the amount of collected and disposed medical wastes within the boundaries of the province asking the medical centers and municipalities. The local higher authority also gives "transporting license" to the medical waste transporting vehicles and reports the number and the condition of the vehicles to the ministry. Medical wastes' collecting, transporting and

disposing prices are determined by the mediation of “the local environment committee” through the local higher authority. Finally, the local higher authority monitors, controls and when there is an illicit activity use the warrant of sanction to the licensed medical waste disposal plants and sterilization units.

According to the Medical Wastes Management Regulation, the producers of medical wastes have to;

Establish a system of reducing the waste in its source,

- Prepare and apply a “waste management plan”,
- Use special bags and containers,
- Transport domestic and medical wastes distinct from each other and carry them by different transporting vehicles,
- Build a temporary waste store,
- Educate the staff periodically,
- Provide special clothing’s to the staff,
- Pay the disposal price,
- Record systematically the information of medical wastes and presents these data to the governorship at the end of the year.
- Save these data for 3 years, if there is a request, open the sources and information to the ministry.
- The responsibilities of municipalities are also defined in the regulation. According to the regulation, the municipalities are responsible for;
- Collecting, transporting, sterilization the wastes getting from the temporal waste stores and containers; including the detailed disposal techniques prepare, apply and publicize a waste management plan,
- Transporting wastes from the temporal stores to the disposal areas,
- Establishing or making established, running or making run the disposal or sterilization plants,
- Getting a license to the disposal or sterilization plants,
- Getting a license to the transporting vehicles,
- Providing a building license to the temporary waste stores,

- Educating their staff periodically,
- Providing special clothing's to the staff,

Record systematically the information of medical wastes and present these data to the governorship at the end of the year; and if requested open them to the control of the ministry (Resmi Gazete, 2005).

In the Medical Wastes Management Regulation, pharmaceutical waste is taken distinct from other wastes together with geotaxis and chemical wastes. These groups of wastes are evaluated as hazardous wastes and collecting separately. Their disposal process also requires a special way. The hazardous waste never send to the sewage, directly release to the air, burnt in low degrees, mixed with domestic wastes and disposed by storing. The best and appropriate way of disposing these materials is incineration which is discussed in detailed in section 8.2.5.

6.2. "Environment" in Program for Alignment with the EU Acquits

Turkey in the way to Modernization and Westernization process intended to affiliate with EU. The relationship between Turkey and EU started in 1959 with Turkey's application of association. In 1963 Ankara Act was signed as a starting point of the process of customs union. In 1995, Turkey's membership of customs union was declared. Beginning with 1999 Helsinki Summit decisions, Turkish Law System was started to affiliate with EU Law System. In 2000 Nice Summit EU's expectations from Turkey was declared by Joint Association Document. A National Program was prepared by Turkish Government in 2001 to fulfill EU expectations. In this program the government put its commitment undertaking EU Acquits. In this context the heading "environment" was one of the most important chapters since its high costs and its significant place in sustainable development process.

EU has 31 chapters in legal arrangements with 5000 regulations. The environment is one of these 31 chapters including nearly 300 regulations. That is to say, the legal arrangements with regard to environment have a special and crucial place in EU acquits

(TÜSİAD, 2002). In legal adaptation process when we consider the laws in force in EU and Turkey, we see that there is no overlap in environmental regulations. EU has some expectations according to the mutual act between these to sides. Turkey has efforts to affiliate EU environmental regulations. For this purpose, the country has to adopt some imperative laws and regulations related with environmental protection. The imperative EU laws about the Integrated Pollution Protection and Control (IPPC) and Management of Risks are shown in Table 6.1 below:

Table 6.1. EU imperative regulations on environmental protection

REGULATION	**SUBTITLE NO**
Limiting the pollute emissions arising from the incineration plants	(88/609/EEC),
Managing the air pollution emerging from industrial plants (will be omitted in 2007 and included in 96/61/EC)	96/61/EC
Council regulation on volatile organic component's emissions emerging from the industries	99/13/EEC
Management of industrial accidents about hazardous materials	SEVESO II, 96/82/EC
IPPC	96/61/EC
The regulation of allowing voluntary participation of industrial corporations' group eco-management and account control projects	761/2001/EEC
The revision of group eco-etiquette assigning system	1980/2000/EC

The above regulations would be arranged and adopted to Turkey's environmental laws. In the way to the affiliation process of EU legal structure, Turkey would face with

many problems. The current regulations and statements of waste management in Turkey are shown in table 6.2 below.

First of all the deadline of these arrangements is far from rationable to reach to the determined targets. EU expected from Turkey to realize these targets for the short run in 2001 and for the long run in 2003.

Another point in this process is the high costs of this transformation process. The predicted cost is 50 billion Euros to fulfill the committed environmental regulations. This cost is thought to be a considerable burden for Turkish economy (TÜSİAD, 2002).

There is an ambiguity among the competent authorities on the issue of exercising environmental regulations. The practices between the local and regional governance and the mechanisms of the ministry a coordination failure could be occurred. Also, there are some inconsistencies in governance of the environmental regulations in practices of authorities. Therefore, in the law of 2872 numbered Environmental Protection it is maintained that, “in any contradiction about the practices of the regulations the ultimate decisive authority is the ministry of environment and forestry” (Resmi Gazete, 1983). In order to maintain a successful management of environment, the ministry of environment and forestry should cooperate the ministries of health, agriculture, tourism and industry.

Table 6.2. Some laws and regulations related with management of waste in Turkey.

Related laws, regulations and directives	**Date**	**Remarks**	**Subtitle Number**
Management of solid wastes	14.03.1991	Includes the disposal methods of domestic wastes, vegetal wastes emerging from public garden, domestic wastes emerging from industrial plants, debris and construction wastes pollutive to the water, air and soil.	20814
Management of packaging & packaging waste	30.07.2004	Regulation includes all packaging materials' recycle and disposal methods produced in the country's industry regardless of the kind of material used in packaging or its source.	25538
Management of hazardous waste	14.03.2005	Includes the regulation, control and disposal of all hazardous materials emerging from industry.	25755
Management of medical wastes	22.07.2005	Includes the principles of collecting, sorting, temporarily storing, transportation of medical wastes emerging from the activities of heath sector institutions.	25883
Statement of general principles on using wastes as supplemental combustible	22.06.2005	Statement regulates the technical and managerial principles in recycling the wastes as supplemental combustible.	25853

7. THE SELECTED INTERNATIONAL AND NATIONAL PHARMACEUTICAL COMPANIES. A REAL CASE STUDY; IMPLEMENTATION OF A RECALL MANAGEMENT SYSTEM IN THE SELECTED PHARMACEUTICAL COMPANIES

There are eight drug types of therapeutic groups in both selected National and International companies' product portfolios. These are; Pharmacy (includes 7 groups), Mature Products, Immunology and Transplantation, Ophthalmology, Oncology, Animal Health, Consumer Health and Vision. Also Pharmacy includes seven groups; Cardiovascular Metabolism Group, Respiratory and Dermatology Group, Urology, Rheumatology, Anti – Infective Group, Neuroscience Group and Gastroenterology Group.

These are formulated in manufacturing plants that produce dosage-form pharmaceuticals such as tablets, capsules, liquid, and ointments. Presently 200 different kinds of products from the International Company and 119 from the National Company are produced.

7.1. The Selected International Pharmaceutical Company Profile

The selected international pharmaceutical company which is mentioned as International Company is a world leader in offering medicines to protect health cure diseases and improve well-being. Their goal is to discover, develop and successfully market innovative products to treat patients, ease suffering and enhance the quality of life. It is the only international company with leadership positions in both patented and generic pharmaceuticals. They are strengthening their medicine-based portfolio, which is focused on strategic growth platforms in innovation-driven pharmaceuticals, high-quality and low-cost generics and leading self-medication over-the-counter (OTC) brands. In 2005, approximately US$ 4.8 billion was invested in research and development (R&D) across all

businesses. Its group companies employ approximately 91,000 people and operate in 140 countries around the world.

The company chosen for case study is a pharmaceutical manufacturing company in Turkey with a total of 827 employees. The technical group employs 220 people in administration, production, materials, engineering, quality control operations and distributions. The International Company has shown a continuous increase in the world market growth rate with a range of 2.5 and 8.3 percent between 2000 and 2007. The main reason in the market improvements is the Company's R&D facilities. Its facility operations include the original pharmaceutical production plant with sterile and non-sterile manufacturing; warehouses and storage areas, quality control laboratories, boiler rooms, high technique engineering departments.

7.2. The Selected National Pharmaceutical Company Profile

In the pharmaceutical sector that selected national company functions, there are approximately 300 companies. At present, multinational pharmaceutical companies in Turkey have 14 production units that produce pharmaceutical raw materials.

By the year 2006, in Turkish pharmaceutical market there were 6200 products in all kinds as tablet, syrup, ampoule, etc. 4592 of them were prescription-only medicines (POM). 36% of these medicines were imported (16% generic, 84% of them originally designed) and 64% produced in the country (69% generic, 31% of them originally produced).

33% of the turnover of the total prescription-only medicine (POM) market came from generic medicines and 67% from originally designed medicines. According to unit sales, market share of the generic medicines is 51% and originally designed medicines are 49%.

In country's domestic industry, by the year 2006 the total amount of the import was 3.01 billion dollars while the total amount of export was 311 million dollars. In comparison with the year 2005, the ratio of the import grew 5.8% and the export grew 10%. The ratio of export to import in 2006 rose to 10.3%, while in 2005 it was 9.9%. The market share of

national company in unit sales is about 5%. The company had a market share in Turkey, in terms of units sold, of 5.2% in the human pharmaceuticals segment.

The company's organic growth strategy is to continue its growth in Turkey, to boost exports to selected emerging markets and to begin exporting to fully regulated markets in 2008. It is also seeking to acquire pharmaceutical companies in Turkey and in selected emerging markets including Russia, Ukraine and certain countries in North Africa and the Middle East. The National Company's total revenue in 2007 was approximately 11 million dollars.

The Company specializes in the production and marketing of human pharmaceuticals (9.7 million dollars, approximately 88% of its total revenue in 2007), active pharmaceutical ingredients (approximately 4% of its total revenue in 2007) and veterinary products (approximately 5% of its total revenue in 2007). These core operations are supported by the consumer goods business line (approximately 3% of its total revenue in 2007), which include ampoule and hygienic products manufacturing. According to the 2007 data, the Company employed a total of 1917 employees, almost all of whom are located in Turkey. These business lines represent 85 pharmaceutical products in 217 pharmaceutical forms.

7.2.1. Production Profile from the Point of R2 Activities

Total Production of the international company in Turkey is 120 million units in 2006. 63% of units are the international company's own production. 19% of units are purchased from selected pharmaceutical production sources in Turkey. 7 % of the units are packed in the company and exported. 11% of the units are imported by and then packed in the company.

Total recall production of international company in 2006 is 124,984 units which is 0.10 % of the total production and the total cost is over USD 81,872,308.

The disposal amount for the International Company's R2 medicines is approximately 77 tons in 2006. Its calculated loss based on selling price of the medicines was USD

831.350. Moreover, disposal of these medicines is carried out by İZAYDAS and İZAYDAS is paid USD 950 per ton. The per-shipment charge of the truck, which is rented for waste transportation, is USD 333.

Table 7.1. The total production and R2 production of the international company in Turkey*

Production & Recall	**Total UNIT**	**R2 UNIT**	**%**	**Total Production Cost (USD)**	**Cost R2 (USD)**	**%**
2006	120,000,000	124,984	0.1	81,872,308	831,350	0.01

*Both in units and USD in 2006

Total production of the National Company in Turkey in 2006 is 61,323,007 units with sales revenue of USD 263,948,611.

Table 7.2. The total production and R2 production of the national company in Turkey*

Production & Recall	**Total UNIT**	**R2 UNIT**	**%**	**Total Production Cost (USD)**	**Cost R2 (USD)**	**%**
2006	61,323,072	985,841	1.6	263,948,611	4,563,724	1.7
2007	96,268,928	687,247	0.7	456,516,277	6,008,855	1.3
2008 (First 6 months)	30,706,421	182,525	0.6	170,372,315	1,138,743	0.6

*Both in units and USD in 2006, 2007 and 2008 (January-June)

R2 medicines cause the company to experience financial loss and also affect the company's image and market. For this reason, the company is interested in a R2 minimization concept. Within this framework, the support of Health, Safety and Security Environment department (HSSE) is of great importance. In this study, appropriate methodology will be modified and developed to improve both the environmental and economic situation for the R2 medicines

7.3 The Assessment of R2 Situation in the International Company

The source and cause relationship of R2 medicine is assessed to generate the minimization options. The causes of R2 medicine of the related stakeholder is summarized in Table 7.2

Table 7.3. Reasons for R2 medicine.

The Rejected Medication Amount									
Responsible Stakeholders	**Reasons for R2 medicine**	**2004**		**2005**		**2006**		**2007 (January & June)**	
		Cost %	**Unit %**	**Cost %**	**unit %**	**Cost %**	**unit %**	**Cost %**	**unit %**
Government	Price Change	1	0	0	0	0	2	----	----
Wholesaler	Wrong Delivery (distribution) Related to Adverse Drug Reaction	50	51	44	46	0	37	26	16
SSI*	Cancellation of Order by SSI Hospitals	7	11	22	12	0	29	0	0
Pharmacy	Incorrect Data Entry	0	3	0	2	----	----	----	----
The International Company	-Expired date -License date -Barcode number -Labeling mix-ups -Marketing without a new or generic approval	42	35	34	40	100	32	74	84
Customer	-Duplicate Invoicing -Wrong Order	----	----	----	----	----	----	----	----
The Recalled Medication Amount									
Government	----	----	----	----	----	----	----	----	----
Wholesaler	- Removal of Product from Markets - Incorrect Data Entry	----	----	----	----	0	0	95	1
SSI*	----	----	----	----	----	----	----	----	----
Pharmacy	----	----	----	----	----	----	----	----	----
The International Company	- Failure of Pre-assesment studies - Production Processes including contamination with other products -Side or Adverse Effect -Inefficiency during treatment	100	100	100	69	100	100	5	99

*Social Security Institution

As you can see from the Table 7.3 the contribution of the wholesaler has been the highest “Rejected Medication Amount” for the years. Also the international company has been the highest “Recalled Medication Amount” for the years comes.

According to the data of the year 2004, the financial loss, the R2 medicine has been generated from chemical and microbial contamination which occurred during manufacturing from defects in labeling and packaging processes and also from the difficulties pertaining to the storage and disposal of increasing stocks of R2 drugs in a safe manner.

Table 7.4. The international company R2 reasons.

Stakeholders	Reasons For R2 medicines	2004			
		Unit	Unit (%)	Cost (USD)	Cost (%)
Government	Expire Date	3	0%	22,875	2%
Wholesaler	Incorrect Data Entry	14,139	33%	77,152	41%
SSI*	Incorrect Data Entry	6,326	15%	90,626	5%
Pharmacy	Incorrect Data Entry	1,968	4%	77,268	4%
The International Company	Incorrect Data Entry	20,366	48%	905,477	48%
TOTAL		**42,802**	**100%**	**1,173,398**	**100%**
		2005			
Government	Price Change	23	0%	615	1%
Wholesaler	Cancelled Order	750	6%	28,763	45%
SSI	SSI Hospitals Cancelled	2,459	18%	1,385	2%
	Expired	395	3%	12,739	21%
	SSI Total	**2,854**	**21%**	**14,124**	**23%**
Pharmacy	Incorrect Data Entry	292	2%	7,573	0%
The International Company	Expired	769	5%	15,427	24%
	Incorrect Data Entry	8,995	66%	4,473	7%
	The International Company Total	**9,764**	**71%**	**19,900**	**32%**
TOTAL		**13,683**	**100%**	**70,975**	**100%**
		2006			
Government	Price Change	3,515	4%	707,875	6%
Wholesaler	Wholesaler Closed	3,450	3%	1,762,520	17%
SSI	SSI Hospitals Cancelled	44,524	47%	3,543,308	34%
Pharmacy		0	0%	0	0%
The International Company	Incorrect Data Entry	43,700	46%	4,474,306	43%
TOTAL		**95,189**	**100%**	**10,488,009**	**100%**
		2007**			
Government		0	0%	0	0%
Wholesaler	Discontinue Product or Low Demand	28,131	14%	18,397	2%
	Incorrect Data Entry	715	1%	196,438	18%
	Wholesaler Total	**28,846**	**15%**	**214,835**	**20%**
SSI	SSI Hospitals Incorrect Order	231	0%	4,379	0%
Pharmacy		0	0%	0	0%
The International Company	Discontinue Product or Low Demand	165,611	85%	861,169	80%
TOTAL		**194,688**	**100%**	**1,080,383**	**100%**

* Social Security Institution

** Both units are Between January and June 2007

According to the data from 2004 and 2005, Government has the least share of R2 reasons with the economic cost of 22,875 and 615 US Dollars respectively. On the other hand, the biggest share can be attributed to the Company's own failures. From the years 2004 maximum returns causes by the company's wrong order entries with the rate of 48% and 66% percent respectively.

Unlike the previous years, in 2006, there are no returns from pharmacies. In addition, the maximum return in units comes from SSI, and the maximum return in economic cost stems from the Company's wrong order entries. The returns by SSI in units are higher than 47% those by the company itself 42%. On the other hand, it can be argued that the cost of returns from SSI is only a fraction of the cost of returns from the company. This difference between the costs stems from the fact that SSI procures medicines at very low prices.

The first half of the year 2007 sees no return from pharmacies and the Government. The amount of return medicine in general stem from the mistakes made by the company. In comparison with the previous years, it can be argued that there is a decrease in the quantity of returned drugs.

The company's failures in R2 medicine is the highest in comparison with the other stakeholders. On the other hand, the return and recall from both government and pharmacies has been eliminated. This can be explained in the light of the pharmacies' and the government's successful R2 operations. In addition to this, the chart below hints at the existence of a good coordination between the pharmacies and the wholesaler.

Taking into account the reasons and responsible stakeholders of R2 sources, the product type is of great importance to achieve success in minimization of R2 issues. In order to demonstrate the contribution of product types to R2 issues, their production information is summarized in Table 7.3 above.

Although the total Recall for between 2004 – June 2007 is higher than reject in units, the figures of economic losses are the opposite for the same case. In addition to the economic and corporate image disadvantages, the company has faced problems during

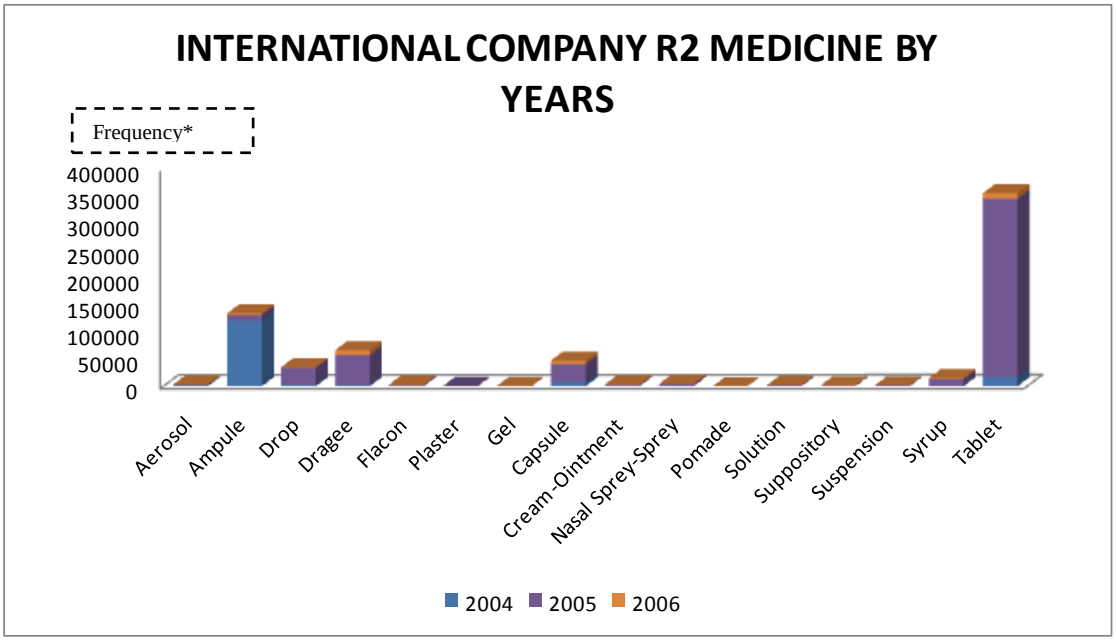
storage and disposal about R2 medicines. The hazardous incineration plants, ISTAS & İZAYDAS. Considering the regulations the R2 medicine disposal utilization has gained more importance due to environmental constraints.

Taking into account the reasons and responsible stakeholders of R2 sources, the product type is of great importance to achieve success in minimization of R2 medicines. In order to demonstrate the contribution of product types of R2 issues, their products are categorized in Table 7.4.

Table 7.5. Focus point for international company's R2 application

INTERNATIONAL COMPANY R2 MEDICINE BY YEARS						
	2004		**2005**		**2006**	
	Frequency	**Percent (%)**	**Frequency**	**Percent (%)**	**Frequency**	**Percent (%)**
Aerosol	1.977	1.3	838	0.2	63	0.2
Ampule	120.580	78.2	10.938	2.3	2.718	8.2
Drop	3.055	2.0	30.954	6.4	1.002	3.0
Dragee	2.194	1.4	55.439	11.4	8.508	25.7
Flacon	64	0.0	1.808	0.4	1.033	3.1
Plaster	0	0.0	375	0.1	0	0.0
Gel	250	0.2	298	0.1	143	0.4
Capsule	7.302	4.7	33.521	6.9	6.427	19.4
Cream Ointment	160	0.1	2.283	0.5	800	2.4
Nasal Sprey-Sprey	708	0.5	3.274	0.7	102	0.3
Pomade	0	0.0	0	0.0	5	0.0
Solution	88	0.1	1.637	0.3	180	0.5
Suppository	77	0.0	1.190	0.2	287	0.9
Suspension	128	0.1	1.463	0.3	20	0.1
Syrup	250	0.2	13.128	2.7	1.352	4.1
Tablet	17.396	11.3	327.982	67.6	10.413	31.5
Total	**154.229**	**100**	**485.128**	**100**	**33.053**	**100**

Table shows that ampoule, dragee, flacon, capsule and tablet have the highest contribution to R2 activities. Ampoule has an R2 rate of 78% in units and 63% in USD in the year 2004. In 2005, 2006 and 2007, Tablet accounts for the highest R2 rates in units, as well as the highest R2 cost in 2007. Flacon has an R2 rate of 44% in units, corresponding to the year 2005. In 2006, capsule has an R2 rate of 48% in USD.



*R2 medicine forms' unit return to company

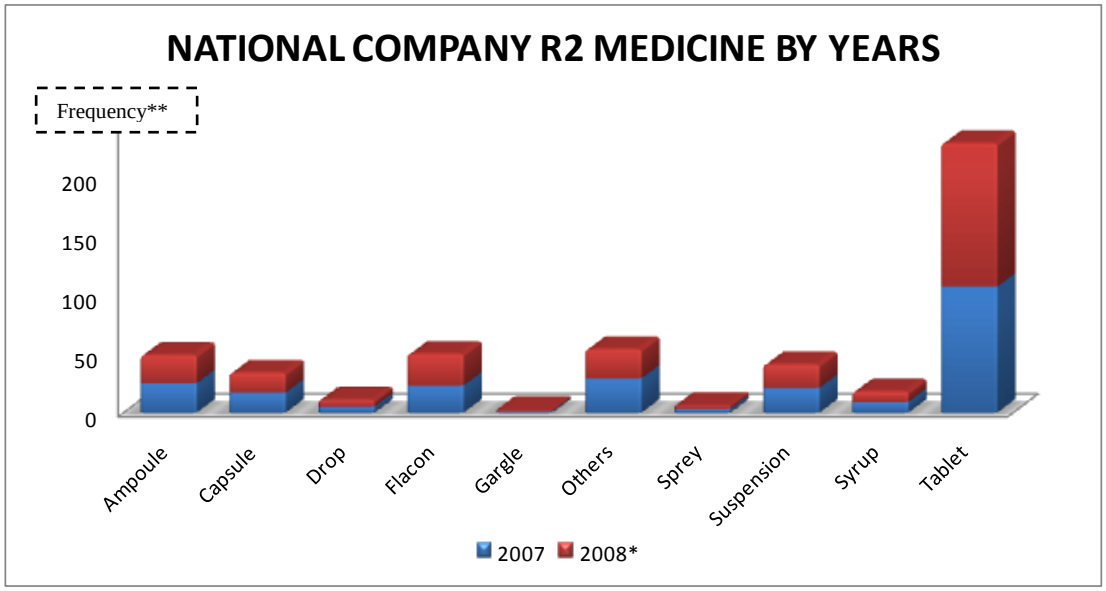
Figure 7.1. International company R2 medicine by years

Table 7.6. National company's total R2 medicines categorized by years according to product type.

NATIONAL COMPANY R2 MEDICINE BY YEARS				
	2007		**2008***	
	Frequency	**Percent (%)**	**Frequency**	**Percent (%)**
Ampoule	25	10.4	24	9.4
Capsule	17	7.1	17	6.7
Drop	5	2.1	6	2.4
Flacon	23	9.6	27	10.6
Gargle	1	0.4	1	0.4
Others	29	12.1	25	9.8
Sprey	3	1.3	3	1.2
Suspension	21	8.8	20	7.9
Syrup	9	3.8	9	3.5
Tablet	107	44.6	122	48
Total	**240**	**100**	**254**	**100**

*Between January and July of 2008

Table shows that ampoule, flacon, suspension, capsule and tablet have the highest contribution to R2 activities for the National Company. Tablet has an R2 rate of 45% in units in the year 2007. In 2008, Tablet accounts for the highest R2 rates in units, as well as the highest R2 unit in 2007 with 48%. Flacon has an R2 rate of 9.6% and 10.6 in units, corresponding to the years 2007 and 2008 respectively. In 2007, Capsule has an R2 rate of 7.1% and 6.7% in unit respectively.



*Between January and July of 2008

**R2 medicine forms' unit return to company

Figure 7.2. National company R2 medicine by years

7.4. The Selected Companies' R2 Medicines Forms

The audit focus points for R2 minimization activities are determined according to the medicine form for the last 2 years for the national company, and 3.5 years for the international company.

According to the data related to the years 2004, 2005, 2006, 2007 and the first half of 2008 for national and international companies, Table 7.6 shows that ampoules, tablets, capsules, bottles are considered to be the most important forms of medicine to be evaluated.

8. RESULTS AND DISCUSSION

In terms of production volumes compared to R2 enable both companies. The total R2 production covers to 1.6 % of total company production capacity and 1.7% of total production cost. Total production and cost of the R2 medication can compare to both national and international company. National Company's R2 production capacity and cost is higher than International Company. R2 medicines cause the company to experience financial loss and also affect the company's image and market. For this reason, the company is interested in a R2 minimization concept.

Table 8.1. The total production and R2 production of the national and international Company in Turkey*

Production & R2 Medication	**Total UNIT**	**R2 UNIT**	**%**	**Total Production Cost (USD)**	**Cost R2 (USD)**	**%**
International Company	120,000,000	124,984	0.1	81,872,308	831,350	0.01
National Company	61,323,072	985,841	1.6	263,948,611	4,563,724	1.7

*Both in units and USD in 2006

The selected companies have been assessed from the point of R2 sources and causes. The managerial board of International Company has approached the recommendations on short and long term bases. The application of sustainability measures were considered according to the general development policy of the companies and their production profile and market. Taking into account the economic, managerial and environmental aspects of R2 minimization options the short term solutions cover the next 2 year activities whereas the action plan covering from 3 up to 7 years are accepted to be long-term solutions.

8.1 Short Term Solutions

8.1.1. Establishment of Company for R2 Medicine Minimization Management Committee

For a successful recall management, an integrated R2 strategy has to be developed for the companies. Setting up an R2 committee is obligatory for the R2 minimization activities. The responsibilities of Company R2 Committee have been defined according to FDA (Food and Drug Administration) and the GMP (Good Manufacturing Practice) standards. Concerning the structure of R2 committee, the following issues are dealt with; giving support to the head of Quality and Compliance in evaluating potential product recalls and rejects; organizing R2 system and to managing R2 in accordance with the requirements given in GMP Quality. Company R2 Committee ensures a local R2 procedure that is established and maintained in order to comply with the requirements of the GMP Quality and of specific national regulations, to investigate all serious complaints and defective products, and to reach a decision or recommendation, as appropriate, regarding a product recall. Company R2 Committee also coordinates the Company's senior managers and local Health Authorities to be involved in related R2 case and prepares an information letter and coordinates the contacts to other Health Authorities who are not involved in the recall case, but who need to get informed.

The R2 system must be capable of being initiated promptly and at any time, including outside regular working hours. The requirements with regard to the R2 committee, R2 type and R2 level are described. It must be ensured, that R2 actions are closely coordinated with the Corporate Communication department. Regarding this fact, local Health Authority should be involved in decision making process.

The information on the product defect is assessed by the R2 Assessment committee. The members of the R2 Assessment Committee will represent the department of manufacturing country business organization, Quality Assurance and Head Compliance. The relevant information is assessed by the R2 Assessment Committee. The R2 Assessment Committee informs the Chairman of the R2 Committee. Based on the information received and the results of the completed investigations, the R2 Assessment

Committee decides on the R2. If the decision is taken not to initiate an R2 process, this is documented and recorded in the R2 Assessment Committee's minutes. In case of a -no recall- decision a report is to be issued outlining the reasons for the -no recall- decision. All relevant documents are to be archived. If the decision is taken to recall, the local recall process is started.

Based on the information received and the results of the extended investigations, the R2 Assessment committee reaches a decision. If a recall is deemed likely, the Chairman of the R2 Committee (Recall Coordinator) / Head of Quality Assurance is informed of this decision. If the results of the investigation indicate no potential for a recall, the investigation is finalized; the final conclusions are drawn and documented in the investigation report.

8.1.2. Procedures on a Potential R2 Medication

Based on the information received and the results of the first investigation a decision on the potential for a R2 is made by the coordination of the Quality Assurance (QA) responsible person in conjunction. In addition to QA responsible person and other Committee members R2 Assessment Committee members who gather and assess information should be informed on the potential recall.

However, in case the results of the investigation indicate no potential for an R2, the investigation is finalized; the final conclusions are made and documented in an investigation report. The Company executives are informed about the decision with the relevant reasons.

R2 minimization procedure is implemented by the Company R2 Committee. It defines corrective actions, in order to prevent further damage and to limit the potential adverse impact of the defective product to a minimum degree. The corrective actions must be completed according to the defined action plan.

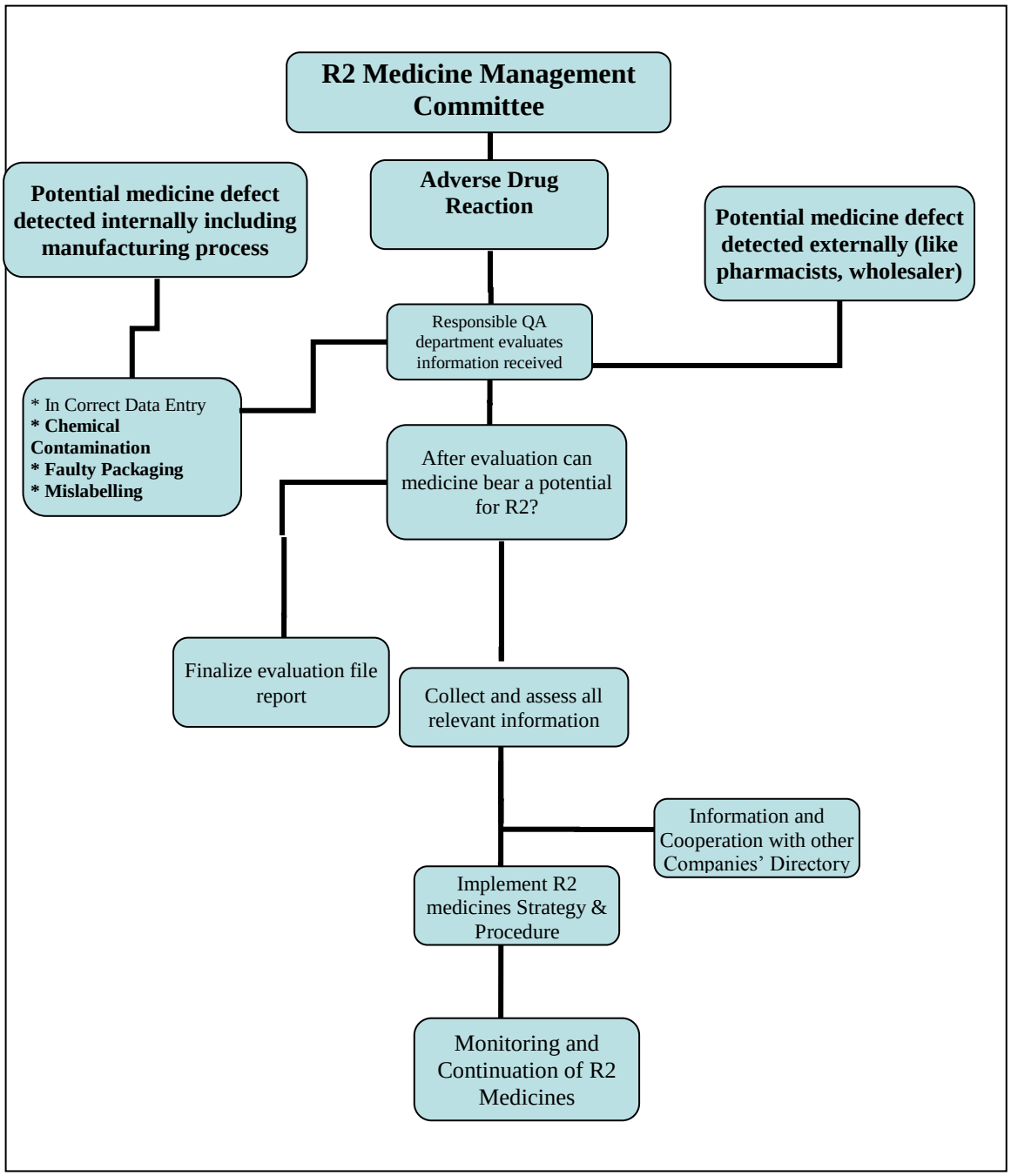


Figure 8.1. R2 minimization procedure process flowchart for short term action plan

8.2 Long-term Solutions

In order to carry out a tailor made appropriate recall medicine minimization strategy; there are a number of factors common to all recalls that need to be considered by the Pharmaceutical company.

R2 Mangement Committee includes the nature of the deficiency in the product, the incidence of complaints, consumer safety, distribution networks, recovery procedures, resources for corrective action and availability of alternative products. Pharmacy, wholesaler, retailer and consumer whose responsibilities should be well defined play the main role for R2 generation. In order to succced R2 medicine minimization strategy could integrated.

Table 8.2. Organizational chart of R2 management.

ORGANIZATIONAL CHART OF R2 MANAGEMENT					
DEFICIENCY IN PRODUCTS		**INCIDENCE OF PRODUCTS**		**DISTRIBUTION OF NETWORK**	
COMPANIES / PROCUDERS	**WHOLESALER**	**RETAILER**	**PHARMACY**	**NURSING**	**CONSUMER**
RESOURCES FOR CORRECTIVE ACTION	**RECOVERY PROCEDURES**		**AVAILABILITY OF DIFFERENT PRODUCTS**		**CONSUMER SAFETY**

8.2.1. Governmental Responsibilities

Solution approached should be considered with managerial, economical, health and safe aspects. The efficient medicine minimization strategy development requires related stakeholders' involment. In Turkey, the weakness of the financial support and inadequacy in technical knowledge and equipment has been the reasons for ineffective waste management system. Beginning from the year 1999, the affiliation process with EU legal system necessitated the arrangements including finance, technical knowledge and implementation, also social consensus and regulations about waste management. EU regulations on waste management take a significant part in general EU laws and regulations since.

The European Union practices and regulations form general principles of waste management. Every year, approximately 2 billion tones of waste, including particularly hazardous waste, are produced in the Member States and it is rising steadily. Stockpiling waste is not a viable solution and destroying it is unsatisfactory due to the resulting emissions and highly concentrated, polluting residues. The best solution is, as always, to prevent the production of such waste, reintroducing it into the product cycle by recycling its components where there are ecologically and economically viable methods of doing so. The EU Act Directive has a framework for coordinating waste management in the Member States in order to limit the generation of waste and to optimize the organization of waste treatment and disposal. On this issue, there is an Act Directive 2006/12/EC of the European Parliament and of the Council of 5 April 2006 on waste**.** European Parliament and of the Council Directive consolidates and replaces Directive 75/442/EEC as subsequently amended.

The aim of this consolidation is to clarify and rationalize the legislation on waste but it does not change the content of the applicable rules. According to this regulation.

1. The measures apply to all substances or objects which the holder disposes of or is obliged to dispose of pursuant to the national provisions in force in the Member States. They do not apply to gaseous effluents or to radioactive waste, mineral

waste, animal carcasses and agricultural waste, waste water, and decommissioned explosives where these types of waste are subject to specific Community rules.

2. The Commission has published guidelines based in particular on the case law of the Court of Justice of the European Communities (CJEC) to help the authorities responsible and the private sector determine whether or not a product is considered waste.

3. Member States must prohibit the abandonment, dumping or uncontrolled disposal of waste, and must promote waste prevention, recycling and processing for re-use. They must inform the Commission of any draft rules concerning the use of products which may give rise to technical difficulties and excessive disposal costs and which may encourage a reduction in the quantities of certain wastes, the treatment of wastes for recycling or re-use, the use of energy from certain types of waste, and the use of natural resources which may be replaced by recovered materials.

4. The measures provide for cooperation between the Member States with a view to establishing an integrated and adequate network of disposal installations (taking into account the best technologies available) so as to enable the Community as a whole to become self-sufficient in waste disposal and the Member States to move towards that aim individually. This network should enable waste to be disposed of in one of the nearest appropriate installations, so as to guarantee a high level of environmental protection.

5. Member States must ensure that any holder of waste has it handled by a private or public waste collector or a disposal undertaking, or disposes of the waste himself in compliance with these measures.

6. Undertakings or establishments treating, storing or tipping waste on behalf of third parties must obtain a permit from the competent authority relating, in particular, to the types and quantities of waste to be treated, the general technical requirements

and the precautions to be taken. The competent authorities may periodically check that the conditions of the permit are being complied with. They also monitor undertakings which transport, collect, store and tip or treat their own waste or third parties' waste.

7. Recovery centers and undertakings disposing of their own waste also require a permit.

8. In accordance with the "polluter pays" principle, the cost of disposing of waste must be borne by the holder who has waste handled by a waste collector or an undertaking and/or by previous holders or the producer of the product giving rise to the waste.

9. The competent authorities designated by the Member States for the implementation of these measures are required to draw up one or more management plans relating, in particular, to the types, quantities and origins of the wastes to be recovered or disposed of the general technical requirements, any special arrangements for particular wastes, and suitable disposal sites and installations.

Related Acts: Communication from the Commission to the Council and the European Parliament of the 21th February 2007 on the Interpretative Communication on waste and by-products (COM/2007/0059 final).

The Commission clarifies the concepts of a product, production residue and by-product, based in part on CJEC judgments. It also sets out guidelines to help the authorities responsible determine what is to be classified as waste and what is not. Thus, a production residue is not classified as waste if the further use of the material is a certainty and not a mere possibility, and if it can be used again without any further processing and as part of the continuing process of production. In addition, the by-product must not be a material which the producer is obliged to dispose of or the use of which is prohibited. Furthermore, there are various factors which identify a material as waste, in particular the fact that no other use than disposal can be envisaged, that the intended use has a high environmental impact or requires special protection measures, that the treatment method is a standard

waste treatment method, that the undertaking perceives the material as waste or that if the undertaking seeks to limit the quantity of material produced. Lastly, the Commission lists examples of products which are waste and others which are not.

As compared to EU decisions and its practices it is seen that in the European Union Environmental directives there is an extensive waste list. According to that list:

Desicion 2000/532/EC as the Commission Decision of 3 May 2000 replacing Decision 94/3/EC establishing a list of wastes pursuant to Article 1(a) of Council Directive 75/442/EEC on waste and Council Decision 94/904/EC establishing a list of hazardous waste pursuant to Article 1(4) of Council Directive 91/689/EEC on hazardous waste. This Decision establishes a single Community list incorporating the hazardous waste listed in Decision 94/904/EC and the waste listed in Decision 94/3/EC. It repeals those two decisions with effect from 1 January 2002.

This Decision has been amended by the following Council decisions:

Decision 2001/118/EC

Decision 2001/119/EC

Decision 2001/573/EC

Table 8.3. Related EU directives and EU decisions.

Acts	
Waste Management EU Directives	**Relative EU Directives / Decisions**
Directive 2006/12/EC on Waste Framework Directive	Directive 75/442/EEC Waste Framework Directive
	Directive 94/45/EC Hazardous Waste Regulations
	Direcitive COM/2007/0059 final Interpretative Communication on waste and by-products
	Decision 2000/532/EC List of Waste Pursuant
	Directive 259/93/EEC Waste Shipment Regulation
Waste Management EU Directives	**Relative EU Directives / Decisions**
Decision 2000/532/EC List of Waste Pursuant	Deicision 94/3/EC List of Waste Pursuant
	Directive 75/442/EEC Waste Framework Directive
	Directive 94/904/EC List of Hazardous Waste Pursuant
	Directive 91/689/EEC Single Community List Incorporating the Hazardous Waste
	Decision 2001/118/EC List of Waste Pursuant
	Decision 2001/119/EC List of Waste Pursuant
	Decision 2001/573/EC List of Waste Pursuant

However, between our country and EU there is no coincidence of legal regulations. Turkey has been adopting the regulations that EU implemented on the protection of the environment. “The environment” should have a priority in Turkey’s sustainable development strategies. As a legal obligation and an international commitment, the “national waste management strategy” and the “regional and local waste management plans” should be prepared by Turkish government without loss of time. The waste

management strategies in Turkey should be detailed in laws and regulations as in most developed countries like EU countries and USA, including the problem of R2. Turkish Ministry of Environment and Forestry being as the ultimate decision executer should establish a deliberate monitoring system.

Table 8.4. Governmental responsibilities.

Problem	The affiliation process with EU legal system necessitated the arrangements including finance, technical knowledge and equipments, also social consensus and the laws and regulations about the management of waste.
Obstacles	The weakness of the financial support and inadequacy in technical knowledge and equipment has been the reasons for ineffective waste management system.
Solution	Turkish Ministry of Environment and Forestry being as the ultimate decision executer should establish a deliberate monitoring system. The government should enrich waste management capacities by preparing plans and projects for the minimization and the disposal of the waste.
Responsible Institution	Turkish Ministry of Environment and Forestry
Explanation	The government's waste management politics would be successful in meeting the politics of minimization of the waste before its formation, the politics of transportation and storage, recycle, reuse and recovery, disposal, financing and the politics of penalization

Table 8.5. SWOT analysis of governmental responsibilities.

STRENGTH	**WEAKNESS**
1. Governmental authority on practicing imperatives. 2. Consistency of succeeding in sustainable development plans.	Absence of proper and detailed regulations on R2 management. 3. Lack of coordination among the related institutions. 4. Inadequate attention to environmental problems.
OPPORTUNITIES	**THREATS**
1. The affiliation process with EU. 2. EU's imperative laws and regulations. 3. Increasing sensitivity of environmental problems. 4. The governmental power of organization (government's administrative and coercive authority in practice). 5. The government's unifying power of all actors in society. 6. Economic advantage 7. Sustainability 8. Social responsibility 9. Pharmaceutical market growth potential	1. Existence of illegal and unlicensed waste treatment plants. 2. Existence of inadequate and disqualified equipments. 3. Lack of hierarchal management procedures. 4. The weakness of the financial support and inadequacy in technical knowledge and equipment. 5. The limitation of "time" by EU legal process. 6. Increasing competition between European countries

8.2.2. Responsibilities of the Pharmaceutical Companies

Table 8.6. Pharmaceutical companies responsibilities**.**

Problem	Pharmaceutical companies have many responsibilities to reduce R2. In order to reduce recalled medications, pharmaceutical companies' primary goal should be financing innovation process paying more attention to design eco-friendly and safe medications.
Obstacles	High costs of innovation process and Recall Management.
Solution	In order to reduce the waste production, the pharmaceutical companies should reduce the usage of unreturned materials. Secondly, the companies have to prepare an R2 management strategy.
Institutional Cooperation	Wholesaler, Media, Pharmacies, Hospitals and Health Staff and Government.
Explanation	Pharmaceutical companies should arrange an R2 Committee to reduce presence of R2 and evaluate the potential R2 medicines.

Table 8.7. SWOT analysis of pharmaceutical companies

STRENGTH	**WEAKNESS**
1. Preparing an R2 management strategy. 2. Arrangement of an R2 Committee to reduce presence of R2 3. Health Authority should involve in the decision making process. 4. Innovative Strategies. 5. The use of high technology and science	1. The R2 committee would be an ideal organization which may not available in many pharmaceutical companies. 2. This hierarchal organization of R2 management process may be un successfully managed.
OPPORTUNITIES	**THREATS**
1. Investigatement of all serious complaints and defective products. 2. Health Authority is informed in a timely manner and in agreement with requirements. 3. Social responsibility 4. Business and environmental ethics 5. Market 6. Updating the regulation implementation	1. Product defects; related to the quality, safety or efficacy, and may bear a potential health risk to the patient. 2. Illegal re-packaging or other illegal manipulations. 3. The lack of R2 committee. 4. The possible financial limitations.

8.2.3. Waste Treatment Companies

Waste treatment companies get license from the Ministry of Environment and Forestry.The waste treatment companies should arrange an “Environment Committee” which carries out the process of waste management. The wastes in the company should be separated as domestic or industrial. Domestic wastes are generally recycled. Among the industrial wastes there are also some materials such as scrap metal and iron which can be recycled.

The companies should prepare an inventory including the type of waste, stock sheet of waste, the time interval of collecting process, the amount of package, etc. On the inventory of waste, it should be investigated as to how the amount of waste can be reduced by managerial and technical operation. The recycling methods of the available wastes should be decided.

The reusable materials as scrap metals, paper, plastic, would be separated from the industrial wastes to recover. The hazardous wastes would never be mixed with domestic wastes. The staff in corporation should be educated for the process of the management of the waste.

The managers should build a storage which is surrounded by grills for the prevention of the leakage, having a concrete ground and covered upper surface sheltering the wastes from the rain. According to the type of waste the surroundings of the storage should be covered to prevent hazardous exhalation and volitale gases.

The possible danger emerging from the reaction of wastes would be eliminated by sorting and the wastes must be labeled. The separately collected wastes should never mix with water. The inner surface of the container should be coated with polyethylene in order to prevent contagion of the waste. The bulky wastes should be pressed; the wet wastes should be dried up. This precaution will lower the costs.

Table 8.8. SWOT analysis of waste treatment companies.

STRENGTH	**WEAKNESS**
1. Waste treatment companies should be licensed to work, and the licensor should ensure that they are controlled, their actions are monitored. 2. The waste treatment companies should arrange an "Environmental Committee" which carries on the process of waste management. 3. Waste treatment companies make a considerable contribution to the protection of the environment.	1. There are no sufficient Waste Treatment Companies in Turkey. 2. The amount of waste produced in industry is over the capacity of few waste treatment companies. 3. The importance of these companies is not properly understood.
OPPORTUNITIES	**THREATS**
1. Nearly all domestic wastes are recycled. 2. Some of the industrial wastes are recycled like scrap metal and iron. 3. The staff can be educated periodically. 4. The government can exhort the private sector to multiply the waste treatment companies.	1. Availability of illegal/unlicensed waste treatment companies. 2. Insufficient equipment and technical facilities. 3. Availability of uneducated staff. 4. Failure in management. 5. Scarcity of waste treatment companies.

8.2.4. Responsibilities of Health Services, Pharmacy and Related Workers

Health services reducing the using of the toxic and the hazardous materials. Purchasing, using, temporary storage and disposal is the four different types of medication.

Purchase of medication: In hospitals, the chemical, pharmaceutical and other hazardous materials should be purchased by hospital purchasing units. In order to reduce the waste, less wastable and hazardous materials should be preferred.

The stock management of the products should be carefully pursued. Non-endurable medications should not be purchased excessively. Instead, they should be frequently purchased in small quantities.

Use of medication: After purchasing, all medications and medical products should be checked, their expiration date must be controlled and the old products should be used in advance. The medical materials or medications should be used completely. In cleaning and nursery activities, production of the waste should be prevented. Instead of chemical disinfection, physical disinfection should be preferred. In health service, the current chemical wastes should also be monitored. Doctors, nurses and the pharmacies should inform the patients about medications and the delivery of medications and the remained or unused medications. Moreover, the recycling or disposal methods of the remained or unused medications should be explained to the patients by the doctors, nurses and the pharmacies.

Temporary storage and transport: The pharmaceutical wastes including R2 should be collected and sorted in hospitals within blue or white boxes, endurable plastic bags and containers by hospital staff. After that, remaining or expiring pharmaceutical wastes or medications should be stored in hospitals storage units or sent to the companies.

Disposal: Pharmaceuticals' classification should be effectively done in the disposal process, in order to reduce the risk arising from the disposal of pharmaceuticals. To avoid

R2 products resulting from warehouses' or pharmacies' errors, it is necessary that both warehouses and pharmacies check their stocks thoroughly.

Table 8.9. Health servies companies responsibilities

Problem	Presence of toxic and hazardous materials in health sector
Obstacles	Purchasing, using, temporarily storing, transporting and disposal of medications.
Solution	Precautions should be carefully taken in the process of purchasing, using, temporarily storing, transporting and disposal of medications.
Institutional Cooperation	Health sector staff, wholesaler, pharmacies.
Explanation	In the health sector, the use of the toxic and the hazardous materials should be reduced by taking necessary precautions.

Table 8.10. SWOT analysis of health sector.

STRENGTH	**WEAKNESS**
1. Availability of an effective management of waste in hospitals. 2. Avoidance of hazardous products. 3. A proper stock management of the products. 4. A successful management of purchase in hospitals. 5. Give attention to sort the wastes. 6. Collection of wastes in hospitals within blue or white boxes, endurable plastic bags and containers.	1. Ineffective waste management process. 2. Deficient coordination among the actors in health sector. 3. Insufficient information flow in health sector.
OPPORTUNITIES	**THREATS**
1. The contribution of the doctors, nurses and the pharmacies on R2 management process. 2. To give hospital staff periodical education. 3. Informing patients by health sector staff in the sense that they use medications and dispose the R2 products safely.	1. Lack of supervision in health sector. 2. An urgent need to unify health sector. 3. Incompetence in following the current developments and innovations in health industry.

8.3. A Discussion of the Regulations and Decisions in Effect in EU Countries

Proposal for a Directive of the European Parliament and of the Council of 21 December 2005 on waste. The aim of this proposal is to revise the framework Directive on waste management. The proposal incorporates the content of the Hazardous Waste Directive and the Waste Oil Directive into the new Directive. It also introduces an environmental objective and clarifies certain concepts (recovery, disposal of waste). It introduces procedures for establishing minimum quality standards and requires Member States to develop national waste prevention programs. Commission Communication of 21 December 2005: "Taking sustainable use of resources forward": A Thematic Strategy on the prevention and recycling of waste". This strategy sets out guidelines and describes measures aimed at reducing the pressure on the environment caused by waste production and management. The main thrust of the strategy focuses on amending the legislation to improve implementation, and on preventing waste and promoting effective recycling

Application of legislation: Report from the Commission to the Council and the European Parliament of 19 July 2006 on the implementation of Community waste legislation - Directive 75/442/EEC on waste, Directive 91/689/EEC on hazardous waste, Directive 75/439/EEC on waste oils, Directive 86/278/EEC on sewage sludge, Directive 94/62/EC on packaging and packaging waste and Directive 1999/31/EC on the landfill of waste, for the period 2001-2003 [COM(2006) 406 final]. Between 2001 and 2003 domestic waste generation increased in the 15-member European Union (before EU enlargement in 2004). Recycling has made progress, but recycling rates vary widely between the Member States. Furthermore, landfilling continues to be the dominant form of waste disposal (with 44% of waste handled in this way). The framework Directive has been fully implemented, but infringement proceedings have been instituted against a number of Member States for failure to correctly transpose the definition of waste. All Member States have now drawn up and notified waste management plans and most Member States have attained a high degree of self-sufficiency in waste disposal.

Report from the Commission to the Council and the European Parliament of 19 May 2003 on the implementation of Community waste legislation - Directive 75/442/EEC on

waste, Directive 91/689/EEC on hazardous waste, Directive 75/439/EEC on waste oils, Directive 86/278/EEC on sewage sludge and Directive 94/62/EC on packaging and packaging waste regulations for the period 1998-2000. In this report the Commission notes that additional efforts will have to be made to ensure the full application of the framework Directive on waste, particularly to implement the hierarchy of principles in waste management: prevention, recycling, energy recovery and safe disposal.

Commission Report to the Council and the European Parliament of 10 January 2000 on the implementation of Community waste legislation for the period 1995-1997 (Directives 75/442/EEC, 91/689/EEC, 75/439/EEC and 86/278/EEC).

In this document the Commission notes that the implementation of Directive 75/442/EEC is unsatisfactory. Most Member States have not correctly transposed the Directive, while others (Greece and Spain) have failed to communicate their national transposition measures to the Commission.

Commission Communication to the Council and the European Parliament of 27 February 1997 concerning the application of Directives 75/439/EEC, 75/442/EEC, 78/319/EEC and 86/278/EEC on waste management. In this document the Commission notes certain reluctance on the part of the Member States to implement the provisions of Directive 75/442/EEC. Some Member States have not even incorporated the Directive into national law and most have failed to communicate their national transposition measures to the Commission.

Table 8.11**.** EU directives and application of legislation.

Application of Legislation	**Relative EU Directives**
19 July 2006 [COM(2006) 406 final] Period 2001-2003	Directive 75/442/EEC Waste Framework
	Directive 91/689/EEC Hazardous Waste
	Direcitive 75/439/EEC on Waste Oils
	Decision 86/278/EEC Sewage Sludge
	Directive 94/62/EC Packaging and Packaging Waste
	Directive 1999/31/EC Landfil of Waste
19 May 2003 [COM (2003) 250 final] Period 1998-2000	Directive 75/442/EEC Waste Framework
	Directive 91/689/EEC Single Community List Incorporating the Hazardous Waste
	Directive 75/439/EEC Waste Oils
	Directive 86/278/EEC Sewage Sludge
	Directive 94/62/EC Packaging and Packaging Waste
10 January 2000 [COM(1999) 752 final] Period 1995-1997	Directive 75/442/EEC Waste Framework
	Directive 91/689/EEC Single Community List Incorporating the Hazardous Waste
	Directive 75/439/EEC Waste Oils
	Directive 86/278/EEC Sewage Sludge
27 February 1997 [COM(97) 23 final]	Directive 75/439/EEC Waste Oils
	Directive 75/442/EEC Waste Framework
	Directive 78/319/EEC Waste Oils
	Directive 86/278/EEC Sewage Sludge

Each individual should be aware of the environmental pollution. Everybody ha**s** some responsibilities to save the environment. The unused, remained or expired medications would be effectively recovered or disposed of in order not to cause harmful effects to the nature and other living organisms' well being.

- Patients should use their medications according to the prescription.
- Patients should be interested in the campaigns of recovery.
- Patients should avoid from the excessive use of medications, if it is not necessary.
- The consumers or the patients should sort their waste according to the type of waste. The unused medications would not merely be put into the trash or dump into the toilets.
- The patients should be aware of the methods of recovery or disposal. According to this information, they should choose the appropriate way to recover or dispose the R2 medicines.
- The patients should know that, as opposed to general prejudice when pharmaceuticals pass their expiry date they do not automatically become hazardous, they simply become less efficacious. The patients should know that, most pharmaceuticals such as aspirins and pain relievers are relatively harmless to the environment; they do not present a serious threat to the public or environment unless handled recklessly.

Among European Union principles some important notions are notable: every citizen is a consumer and the European Union takes great care to protect their health, safety and economic well-being. It promotes their rights to information and education, takes steps to help them safeguard their interests, and encourages them to set up and run self-help consumer association.

The effective cooperation between each stakeholder and pharmaceutical company representatives should be carried out except for consumers.

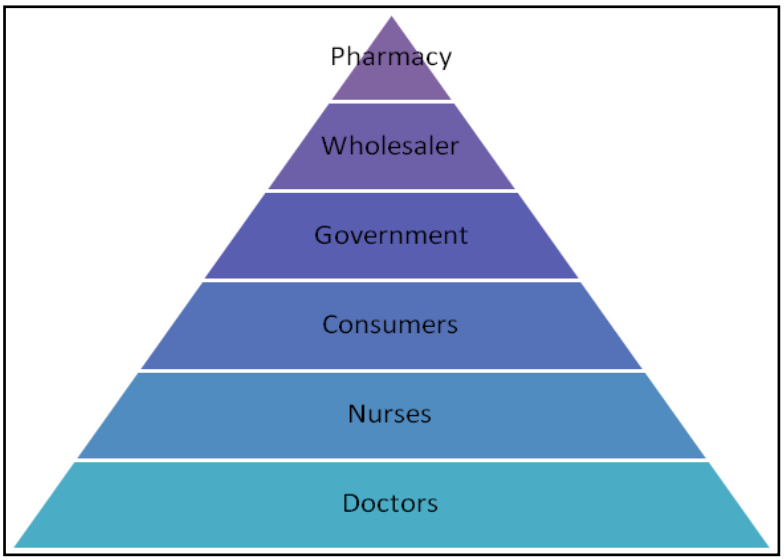


Figure 8.2. Hierarchy of the responsible stakeholders in R2 minimization.

Table 8.12. SWOT analysis of the consumer attitudes.

STRENGTH	**WEAKNESS**
1. Consumer awareness of environmental pollution. 2. Consumer awareness of how to recover or dispose the R2 medicines. 3. Consumers' contribution to the campaigns of recovery.	1. Excessive consumption of medications. 2. Consumer preference of OTC medications. 3. Consumers'/patients' inappropriate disposal methods of R2 (dumping to the toilet, throwing away trash)
OPPORTUNITIES	**THREATS**
1. Increasing focus on environmental issues. 2. The flow of information about the protection of the environment.	1. The lack of information about R2 minimization methods. 2. The lack of information about R2 disposal methods.

8.4. Medicine Order Management

8.4.1. Electronic Data Interchange (Data Exchange Program) Between the Company and Wholesaler

EDI (Electronic Data Interchange) system has been widely used in pharmaceutical companies to decrease / prevent data errors in orders.

Retrospectively speaking, another source of error for the Company's R2 products is incorrect data entries. An elaborate computerized system, namely the Electronic Data Interchange and abbreviated as the EDI, can be devised in order to eliminate this problem. To ensure effective functioning of the system, the warehouses which place orders to the Company should be entitled to utilize this program as well. For a pilot study, a variety of warehouses that make large sums of purchases can be selected (Hansen and Hill, 1989). The selected warehouses should be given access to the system, with their personnel trained to run the system, thereby reducing errors in order entries. Detailed information on the system can be found in the Literature Survey section.

Financial Analysis of Electronic Data Interchange: Company and Wholasaler's R2 generation cost with incorrect data is approximately total 5,685,609 USD/year. Medicine Order Management with EDI capital cost is approximately 2,500,000 USD/year (Innovis Company)**.** Medicine Order Management' operating cost is approximately 1,250,000 USD/year (Innovis Company and Pharmaceutical Company). The Company's profit is 1,935,609 USD/year.

Table 8.13. Financial Analysis of Electronic Data Interchange for R2 Medicines between 2004-2007 (June).

Financial Figures	**Average Cost (USD)**
Incorrect data entry from wholesaler and company	1,250
Capital cost for the Electronic Data Interchange Software (EDI)	3,750
EDI's Operating Cost	
Running cost	0
Payback period	3.5 year

As you can see from the Table 8.13 Electric Data Interchange Software cost is 3750 US Dollar/year. It is cheaper than Company and the Wholesaler's incorrect data generation one year cost. And the company has a profit 1,935 USD/year. Note that we presume that incorrect data generation cost will be finish after EDI Software started to using. In long term only the amortization of sorfware will be disadvantage.

8.4.2. Medicine Order Management Software between Wholesaler and Pharmacy

To avoid R2 products resulting from warehouses' or pharmacies' errors, it is necessary that both warehouses and pharmacies check their stocks thoroughly. Since most of the R2 products are the consequences of the unsuccessful order management. For that reason, an electronic order placement network is to be established between the warehouse and pharmacies. The operation of the system, whose instances can be found in Turkey and all over the world, should be made commonplace. The details of the system, also named E-warehouse, are given in the Appendix.

Table 8.14. Financial analysis of medicine order management software for R2 medicines.

Financial Figures	**(USD/year)**
The Pharmacy R2 Medicine Generation Cost	84,841
The Wholesaler's R2 Medicine Generation Cost	302,353
TOTAL	**387,194**
Medicine Order Management Software Cost	40
Profit	**387,154**

As you can see from the Table 8.12 Medicine Order Management Software cost is 302,353 US Dollar/year. It is cheaper than Pharmacy and the Wholesaler's R2 Medicine generation one year cost. The Company has a profit 387,154 US Dollar/year.

8.5. New Technology: Mobile Incinerator

In Turkey, all recall medicines are treated by incinerator. Appropriate disposal of R2 medications are very big problem for Pharmaceutical Companies. There are only two incinerator centers called İSTAC and İZAYDAS. İZAYDAS's capacity is full. Mobile incinerator is a good option for all pharmaceutical companies in Turkey.

Financial analysis of mobile incinerator;

International Company' R2 generation cost is 831,350 USD/year

International Company' R2 production unit is 124,984 unit/year

International Companies' R2 disposal expenses:

- The disposal amount for The Company' R2 medicines are approximately 77 tons in 2006. Payment for İZAYDAS TRY 1.140 per ton. Total amount is TRY 87,780.
- The per-shipment charge of the truck, which is rented for the wastes' transport, is TRY 400. Total amount is TRY 80,000.

Sub total is TRY 167,780 = 201,336 USD

Mobile incinerator price is approximately (include all equipments) = 48,429 USD

Total the company expenses are 249,765 USD / year
The Company' profit is 581,585 USD.

International Companies' R2 disposal amount:

The disposal amount for The Company' R2 medicines are approximately 77 tons
Mobile incinerator burn capacity is approximately 50 kg per hour.
If Pharmaceutical Company use mobile incinerator, its waste amount (77 tons) is burned until 64 days 2 hours.

8.6. A Case Study: "Protect poor people, send a box of medicine" (Yoksulu kolla, bir kutu ilaç yolla)

The aim of the campaign has to be more visionary and could capture the public's imagination and encourage patients (people) in a broad program of reduced use. This campaign aims to inform people about R2 medicines and its disposal methods. The pharmaceutical company and Turkish Red Crescent Society cooperated for the campaign with the phrase "Yoksulu kolla, bir kutu ilaç yolla"**.**

To enable patients to use less medication, a Patient Health Record system should be developed and reached to a wider target population to monitor the medication use of each patient. Thus the course of illnesses may be monitored better and use of medications by patients may be controlled. Those medications not consumed may be re-called for others' use. Moreover, in this system each patient's medical history and medication usage history may be traced in the long run. Moreover, in the database medications prescribed before may be kept to prevent further usage and prescription of the same medication which was not effective in the previous treatment.

However, although this system seems to load burden on current patient monitoring system and prevent it from working, this will be an addition to the new system and use the same data with the current one, which will benefit for both sides. Moreover, the patients using medications unconsciously may be monitored and detected, thus specific patients

may be educated. Besides, dose limitation may be implemented. The patient receives how much she or he needs, in order to recover.

Recent practices for content management systems show the productivity of the technology. On this system, stocks are checked online and monitored where the specific product exists and are to be brought where needed. Moreover, additional documentation provided medication may be divided to each unit. For example, a unit of medication has six tablets of pills and doctor prescribed only three of tablets and patient takes the dose as prescribed with prospectus. However, when the rest of the tablets are prescribed, next patient has normally no prospectus. But if a CMS (current patient monitoring system) **is** used, prospectus might be printed at the point of sales (POS) and each time the rest is prescribed, a prospectus may be provided for the next users. What's more, chronic users do not take a prospectus and unit printed each time, which will be environment friendly.

Figure 8.3. Citymap of the selected pilot region Güngören

At the beginning of the campaign, a pilot region is selected, which is Gungoren in the campaign. In Gungoren, Turkish Red Crescent Society Gungoren Quarter should be contacted with to specify and establish collection centers for unused and recalled medications with the written permission from Ministry of Health of Turkey. Assigned staff will be taking collected medications regularly to categorize and separate the usable from the unusable. Separation and categorization will be said to be carried out by Turkish Red Crescent Society.

A collection system would like to for the customer (patients) with an illustration of a secure drop box for collection in a pharmacy is given below. The container would be within eyesight of the pharmacist counter. The consumer would deposit medications in their original containers.

However, besides implementing the system, the advertisement of the system is also important. For publication of the campaign, posters and banners on billboards will be hung and the campaign will be announced through TV and magazine advertisements and big LCD screens set in hospitals. Moreover, leaflets will be handed out in crowded places. Celebrities will encourage the public to participate in the campaign. By visiting doctors and pharmacists, feedback about current system and deficiencies on the system will be detected and the system convenient for them will be projected. Before the launch of campaign, official permission from local authorities, such as municipal, governor and chief doctor of the select hospital will be issued.

For the campaign,

• Specifying state hospitals and pharmacies where those medications will be collected in the pilot region:

The District Polyclinic of Bağcılar Teaching & Research Hospital, Health Cabin of the Güngören Municipality, The Anakent Municipality Emergency Services, The Fıratlı Clinic in Güngören, The Mother & Child Health Center in Güngören Köyiçi, The Central Polyclinic of Güngören, The Central Health Center of Güngören, The Special

Development and Health Polyclinic of Güngören, Güngören Tuberculosis Dispensary, The Veterinary & Health Directorate of Güngören, Istanbul Metropolitan Municipality Health Center in Güngören, Güngören Private Hospita), İlgi Private Hospital in Güngören. Pharmacies are Güneştepe, Şehnaz, Yonca, Gülay, İkizler, Reyhan, İnci, Güler, Furkan, Esra, İdil, Güngör, Şirin, Şimşek, Balkan, Uğur, Köksal, Halil Can, Erdem, Derman, Plevne, Ayça, Nur, Fatos, Nobel, Tekeli, Nuray, Ebru, Alp, Haznedar.

Medical representatives of the campaign's sponsor (The International Company) will distribute all printed campaign documents. Assigning contact persons for those point**s** of recall collection (PORC) PORC's voluntarily taking part in the campaign.

To summarize the steps:

i. To define the potential of the select hospitals and pharmacies to take part in the campaign.
ii. Official permission from authorities
iii. Briefing to target hospitals and pharmacists and call for participation into the campaign.
iv. Preparation and distribution of advertisement, publications, documentations by the sponsor with the motto "Yoksulu kolla, bir kutu ilaç yolla" (Visit PORCs to support the poor people)

Note: For security and safety reasons, the collected medications will be checked by pharmacists and double-checked by Turkish Red Crescent Society (TRCS). Those medications will be collected regularly and processed, and the usable medications delivered to people in need by TRCS.

Table 8.15. National pharmaceutical companies project budget for expenditures.

Activities		**Unit**	**Unit Price USD**	**Total Cost USD**
Printed Materials	A4 single cards	10000	0.2	2000
	Banner	50	1.000	50000
	Brochures	10000	1	10000
Advertisement		1	5000	5000
Agency payment		1	3000	3000
Collection box		10	2500	25000
Total Pharmaceutical Companies Budget				**95000**

As you can see at Table 8.13 Pharmaceutical Companies are needs to allocate at least 9000 USD. If we analyse the figures the highest expenditure is Printed Materials as 62000 USD. It conteins single cards in A4 format, banner and brochures. This campaign helps to improve company' image and awareness in the pharmaceutical market.

8.7. The Customer Awareness Program

In order to minimize R2 medicals a customer awareness program should be launched. The aim of the awareness program is to publicize the potential environmental and health impacts of unused medications when they are flushed into sewer system. Medications that are flushed down the toilet or thrown straight into the garbage can and do find their way into waterways. Those drugs are present in water that supports many species of fish and other wildlife. The Program is to promoted healthy style of live and alternative therapeutic treatments would be efficient to reduce the consumption of several pharmaceutical substances and their release in the environment. A campaign informing patients about the environmental aspects of drugs is also proposed. The campaign goal is that patients should not dispose unused drugs in the garbage or in the sewer, but return it to the pharmacy. On that account, to avoid unused drugs, prescriptions should be better corresponding to the duration of the treatment.

On the other hand, certain people consulted indicated that many participants are not sure about their role in the greater scheme of things. They know too little about the R2 Procedure to be sure what is expected of them. It was suggested that awareness of recall application among hospital staff, pharmacists and other professionals needs to be higher. They need to know what they have to do and how to do it. Consultations with consumers indicated their chief concern is to have accurate, balanced information available in a timely manner through different media and that the message is consistent.

The risk assessment framework for recalls should be written up as a formal guideline. It will always be true that consumer recalls need to generate greater awareness. The system works well if announced by the media, but that is a hit-and-miss process, unrelated to the actual risk. The recall process is only assessed by what was done previously (inputs), not what the outcomes are, as they are too hard to measure.

The consumer outreach campaign will feature educational brochures and websites with information for both consumers and medical professionals. There will also be promotional events held in several cities across the country designed to generate greater awareness of the importance of proper medication disposal and the harmful effects it can have on the environment and public health. In this campaign, the public should be informed about the problem of safe disposal of donated expired pharmaceuticals, and it is aimed at describing and quantifying the annual cost of waste to the patient.

8.7.1. Public Information

Public should be informed about the problem of safe disposal of donated expired pharmaceuticals. Key points to present to the media are as follows:

i. The vast majority of pharmaceuticals are donated with the intention to help; there are only rare occurrences of “dumping” by unscrupulous companies to gain tax relief or off-load unwanted stock;
ii. As opposed to general prejudice when pharmaceuticals pass their expiry date they do not automatically become hazardous, they simply become less efficacious;

iii. Most pharmaceuticals such as aspirins and painkillers are relatively harmless to the environment; they do not present a serious threat to the public;

iv. The risk from disposal of pharmaceuticals is low provided it is properly handled. Pharmaceuticals' classification should be effectively done in disposal process.

v. Pharmaceutical disposal should be undertaken at minimum financial cost and with minimum risk to public health and the environment considering the local circumstances;

vi. Disposal of pharmaceuticals should be carried out under the supervision of regional and national authorities, which organize it according to strict criteria; it must not be carried out by individuals. Information on pharmaceutical disposal must be carefully handled as it may be politicized and sensationalized. If the public and media are not kept judiciously informed of the efforts to dispose of expired pharmaceuticals safely, the disposal work may be severely hampered by misinformation propagated by uninformed journalists and politicians. Good public relations, including comprehensive dissemination of information, are, therefore, an important element in achieving satisfactory safe disposal. Create definitive, consistent guidance for proper disposal guidance for R2 medicines announced during the campaign.
Take unused, unneeded, or expired prescription drugs out of their original containers and throw them in the trash.

Mixing prescription drugs with an undesirable substance, such as used coffee grounds or kitty litter, and putting them in impermeable, non-descript containers, such as empty cans or sealable bags; will further ensure the drugs are not diverted.

Flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

Take advantage of community pharmaceutical take-back programs that allow the public to bring unused drugs to a central location for proper disposal. Some communities have pharmaceutical take-back programs or community solid-waste programs that allow the public to bring unused drugs to a central location for proper disposal. Where these exist, they are a good way to dispose of unused pharmaceuticals.

The FDA advises that the following drugs be flushed down the toilet instead of thrown in the trash: Actiq (fentanyl citrate), Daytrana Transdermal Patch (methylphenidate), Duragesic Transdermal System (fentanyl), OxyContin Tablets (oxycodone), Avinza Capsules (morphine sulfate), Baraclude Tablets (entecavir), Reyataz Capsules (atazanavir sulfate), Tequin Tablets (gatifloxacin), Zerit for Oral Solution (stavudine), Meperidine HCl TabletsPercocet (Oxycodone and Acetaminophen), Xyrem (Sodium Oxybate), Fentora (fentanyl buccal tablet). The following methods of disposal are currently considered safer and more environmentally friendly than flushing down toilets or sinks:

Disposal in the municipal trash collection, taking precautions to ensure that children or animals cannot access the material. Non-descript packaging is advisable to avoid trash harvesting for potential reuse.

Check whether local household hazardous waste collection programs in your area accept medications for destruction.

Registered generators of medical waste may also dispose of medications with their regulated medical waste management company. Pharmaceuticals may be listed as “over classified” waste on medical waste tracking forms.

Although a few pharmacies will facilitate proper disposal of unused and expired medications, the majority will not. A total of 301 patients at an outpatient pharmacy completed a survey about medication disposal practices and beliefs. More than half of the patients surveyed reported storing unused and expired medications in their homes, and more than half had flushed them down a toilet. Only 22.9% reported returning medication to a pharmacy for disposal. Less than 20% had ever been given advice about medication disposal by a health care provider. Previous counseling was highly associated with returning medications to a pharmacy (45.8% vs. 17.1%, $P < .001$) and was the variable most associated with returning medications to a provider (28.8% vs. 10.0%, $P < .001$). Previously counseled respondents were significantly more likely to believe that returning

medications to a pharmacy (91.5% vs. 60.3%, P < .001) or a medical provider (74.6% vs. 47.3%, P < 0.001) was acceptable.

The results of this study suggest that there is a role for patient education about proper disposal of unused and expired medications. Clear guidance for how patients should dispose of unused and expired medications is lacking. Medications improperly disposed of can make their way into groundwater, surface water, and even drinking water.

There are several options. The first is to contact your pharmacy. Many pharmacies now have drug recycling programs in place. Some take it back at any time; others hold periodic drives to collect expired medicine. Either way, they'll take back your expired medication and see to it that they're disposed of in the proper manner. If your pharmacist doesn't take back your old drugs, he or she may have an alternate recommendation. If he or she has no advice, call around. Another pharmacy in your area might take expired medicine.

Another option is to take any old pills and pulverize them. Return them to their child-safe container and place the container inside several thick zip lock plastic bags or a thick plastic container. This can now be tossed into the household trash. There are several problems with this method, however. Many people don't like to waste their bags and containers. Plastic doesn't always degrade so easily if at all. In addition, there's still a chance the medicine can leak out and present a hazard. Besides, one thing we don't need is more landfill.

Since expired medicine is considered hazardous waste, it stands to reason it should be disposed as such. Contact your local hazardous waste facility to see its recommendations. If your city or town has a website, there are probably instructions on how to dispose of hazardous waste. See if medicine is listed. If it is, you can either bring it to the hazardous waste site or set it out for pick up on the designated date. Even if nothing is listed on the website, you can call the facility to either see if this is something it handles, or if it has a recommendation.

Lastly, there are organizations that donate expired medicine to third world countries. Even though your medicine may have expired, it may still be good long past the printed date. Rather than have it waste away in your medicine cabinet, why not donate it where it will be put to good use? An internet search will provide you with such organizations.

8.7.2. Organizing Publicity

To recall and reuse the medicines, organizing publicity has a crucial importance. As a first step the type of publicity would be decided. If the issue is announced successfully, significant recall and reuse would be realized.

The traditional way of publicizing recalls is to advertise in newspapers. However, it is needed to consider alternative types of publicity depending on the risk associated with using the product, where the product has been distributed, and with the particular consumers who need to be reached. In some cases where only a few products have been sold and they can all be traced, there may be no need for a general media notice. The best guide is to use the type of publicity most likely to get the message across to the relevant consumers quickly enough to minimize the risk of injury. For this purpose;

- Advertising in daily or community newspapers
- Displaying signs in retail outlets for the product
- Issuing a media release to newspapers, radio and television
- Writing to known customers, including by registered mail
- Advertising on radio and television
- Advertising in retail flyers (e.g., supermarkets, retail chains and department stores often send flyers to householders)
- Asking relevant industry and community organizations to publicize the recall in their newsletters
- Advertising in special-interest publications if appropriate
- Advertising prominently on the web site, and/or
- Having contact with known customers by email or facsimile should be the ways of publicizing R2 medicines.

Media release is an appropriate way to reach the masses. Organizing a campaign using television or radio programs, advertising in newspapers enables advantages. A media release can result in free publicity about the recall on radio, television and in newspapers, with coverage on television news or current affairs programs being particularly effective. A media release should be short, clear and written in simple language. It should contain the names, address, phone numbers and email addresses of people who can be contacted for further information.

Advertising the recall in newspapers published in areas where the product has been distributed can make people more conscious about the issue. It is important to place recall advertisements where consumers are most likely to see and read them. Advertisements can be placed in the first five pages of newspapers if possible. In all instances the example hatched border with the safety triangle and the recommended minimum dimensions should be used. The recall advertisements also contain a clear description of the product, including the name, the date product is sold, the potential risk, and what action the consumer should take.

If the recall is a consequence of an identified breach of a Trade Practices Act mandatory standard, or of a hazard identified by Turkish Ministry of Health, the conduct of the recall should be negotiated with the Ministry. Such negotiation would include: placement of recall advertisements; form and content of advertisements; and the corrective action to be taken by the suppliers and by affected consumers.

The following is the example of the format for a recall advertisement. The recall advertisement should:

- Be at least two columns in width, with a suggested minimum size of 10 by 12 centimeters
- Use the example hatched border with the safety triangle in the upper left-hand corner-this is an internationally recognized safety symbol
- Use a font size of at least 10 point for the print in the advertisement
- Include the words 'Product Safety Recall' prominently at the advertisement.

Preparing publicity material the points should be regarded as:

i) A clear description of the product, including the name, make, model, distinguishing
ii) Features, batch or serial number should be specified.
iii) A drawing or photograph of the product if available should be used.
iv) Clear identification of the supplier, including logo, trademark or letterhead, street, postal, e-mail and web site address, facsimile and telephone number should be inserted.
v) A statement of the hazard and the associated risk should be clearly identified.
vi) Dates when the product was available for sale should be pointed out.
vii) What immediate action consumers should take (e.g., cease use, store safely) should be mentioned. Who consumers should contact to receive a refund or have the product repaired or replaced (e.g., manufacturer, wholesaler, agent or retailer) should be advertised. Business and after hours telephone numbers for further information, preferably toll-free, and advice that the recall is at the expense of the supplier should be placed in an publicity material.

These principles would be considered in the campaigns for reusing the medications. The campaign for reusing the medications called, "Yoksulu Kolla Bir Kutu Ilaç Yolla" could be much more successful at the last instance, if publicity should be used effectively. In the last stage, taking the feedback from the campaign, the scope of the campaign would be broader including each region of the country and the publicizing activity would be carried out by the major media organs.

9. CONCLUSION

R2 medicines include permanent removal of deficient medicines, which may involve temporary removal from the market or from use for correction. R2 can also be defined as permanent removal of medicines from supply or use for reasons relating to deficiencies in the quality, safety or efficacy of the goods.

R2 is undesirable in its nature since it increases marketing costs for pharmaceutical firms, causes the expenses incurred in the development of new drug products, increases the cost of medication wastage, and creates pharmaceutical waste being hazardous for human and for environmental protection. Whether the poor compliance of patients, excessive and irrational prescribing, or the lack of control of the sales of prescription medications in the community pharmacy cause R2 medicine waste. It is also defined as any drug product, either dispensed by a prescription or purchased over-the-counter that is never fully consumed. This situation creates a kind of pharmaceutical waste which is universal among developed countries.

R2 minimization methods could be successfully realized when related actors effectively carry out their responsibilities. It is not forgotten that every person has responsibility for R2 minimization and protection of environment in general. Therefore, solutions for R2 management include the engagement of governmental, institutional and individual aspects all together. Waste management strategy includes a hierarchal priorities list. According to this scheme, waste management precedes “minimizing waste”, “reuse the waste material”, “recycle”, “recovery” and finally “disposal”. The most important point is how successfully we can minimize the waste. Up to the “disposal” stage, there are many things to do in order to avoid waste creation. Absolute avoidance of R2, minimization R2 in its source and reuse, recycle and recovery of R2 medicines are the effective minimization methods of medical wastes which were emphasized in this dissertation.

The governmental practice has a significant place in absolute avoidance from R2 formation. Besides the laws and regulations implemented by government, the preventive

policies and strategies play an important role on R2 reduction. These policies and strategies can be classified as restructuring of Turkish Ministry of Health to enhance its core functions of setting priorities, ensuring quality and managing public health processes, including preventive services, training of health care practitioners and patients, taking precautions for uncontrolled drug distribution channels, emphasizing disease-prevention role played by nutrition and improving health information systems. The absolute R2 reduction also depends on environmental or ecological friendly drug design which promotes better physiological sorption characteristics. With the innovations in eco-friendly drug design, the intended consequences such as rapid healing periods due to novel targeting approaches, drug amounts can be reduced and their excretion rates can be more effectively attained. Ultimately, the usage of these kinds of drugs may lead to a decrease in drug dosage, as well as drugs' negative environmental effects.

Prescribing medications also reduces R2 formation. Physicians should avoid prescribing overmuch medication. The excessive dosage of the medications not only cause pharmaceutical waste by the patients' unused but also may bring side effects, and even deaths if excessively used. The therapeutically effective dose for many drugs can be significantly lower than that initially recommended by the manufacturer. By informing physicians and the public about the chemical properties of medications, not only could a decrease in cases of inappropriate use be achieved but also an outstanding decrease in such substances' negative effects on the environment could be attained.

Individualization of therapy would be an appropriate solution which can minimize the requisite therapeutic dose that is frequently higher than needed. Available tests for drug metabolizing enzymes can distinguish fast, normal, and slow variants. These enzyme systems play major roles in the speed with which certain drugs are metabolized, and by considering whether those drugs may lead to detoxification and excretion or to activation, these enzyme systems help determine the proper dosage.

Some technical precautions to reduce R2 formation can be identified as advancing gene-based therapy to eliminate the toxic effects of drugs on the environment, and nanotechnology which hold the promise of providing efficient delivery systems. Besides

them, many pharmacies use reverse distributors for the return of unsold/expired inventory. That could serve overarching returns to the industry by its comprehensive disposal and recycling program. The technical improvements like upgrading in sewage system also help to prevent hazardous effects of R2. By use of advanced water treatment technology such as reverse osmosis, a complete removal of all pharmaceutical and personal care products could be achieved. Recycling, reuse and recovery strategies are included in the process of reducing waste in its source. In R2 minimization, recycling, reuse and recovery strategies display distinctive character. Because medications have different structure from other hazardous or domestic wastes. The basic recycling strategies for wastes are rebuilding the wastes (e.g. by washing), distillation of solvents for reuse and segregation of wastes that have reclamation value, such as used oil, mercury, scrap lead and precious metal compounds, and solvents suitable for use in fuel recovery facilities. However, medicines would not even be remanufactured, they are just verified. Recycling of drugs is generally illegal. In some provinces, drugs in sealed, unopened containers may be recycled if they have been returned from a controlled environment such as a long-term care facility. In some developing nations some resource recovery takes place by way of manual laborers who sift through un-segregated waste to salvage material that can be sold in the recycling market. However, the very high human cost of these activities including disease, injury and reduced life expectancy through contact with toxic or infectious materials would not be tolerated in a developed country.

Being as a waste form, the nature of the medications itself does not allow to recycling and reuse. For this reason, in R2 prevention strategies, the prevention of R2 in its source has a priority. To reduce pharmaceutical wastes as R2 it is necessary to eliminate conditions for R2 formation. Nevertheless in the stage of recycling, reuse and recovery specific campaigns would be a way to re-evaluate R2. The campaign for “Yoksulu Kolla Bir Kutu Ilaç Yolla” aims to enable patients to use less medication and also reuse their redundant medications. Those medications will be collected regularly and processed, and delivered the usable medications delivered to people in need by Turkish Red Crescent Society. The campaign will contribute to meeting the need for medications of people who are not capable to buy medications. It also provides the reasonable recycle and reuse of the R2.

R2 management system requires the engagement of government, pharmacy, wholesaler, doctors, nurses, environment services, employing the concepts of safety, infection control, quality assurance, training, administration, the inclusion of media organs to the process. It also requires the implementation of new systems, professionals within local environmental protection agencies are beginning to assist the regulated community in developing practical compliance models. It will take the involvement of the entire supply chain, from manufacturers through distributors to hospitals. However, the minimization strategies of R2 could be ended by disposal process despite the inclusion of mentioned actors.

The pharmaceutical disposal should be undertaken at minimum financial cost and with minimum risk to public health and the environment considering the local circumstances. The most appropriate way to dispose pharmaceutical wastes would be the method of incineration. Unfortunately, the incineration of medical wastes is not a usual way of disposal in our country. The common method for disposal is the collection of these wastes together with the municipal solid wastes, without any precautions, and to deposit them in the open-dumping places. To avoid environmental pollution using landfill of hazardous pharmaceutical waste, the incineration plants' capacity should be increased, the new incineration plants should be established or pharmaceutical companies should be authorized to build mobile incineration units.

The successful R2 management will be possible only when the proper minimization and disposal methods are applied. In the way to realize principles of the sustainable development, the government, the companies, pharmacies and health sector workers, the media organs and the patients/consumers will have to fulfill their responsibilities on an effective R2 management.

Note: All calculations are made, with US Dollar currency taken into consideration. To ensure consistency between numerical figures, 1 USD is considered as equivalent to 1.2 TRY.

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APPENDIX A

The Citymaps of the selected pilot region Güngören

Figure A.1. Citymap of the selected pilot region Güngören