

Emerging Liabilities from Pharmaceuticals and Personal Care Products

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Abstract : There is growing awareness and concern regarding the presence of chemical constituents of pharmaceuticals and personal care products (“PPCPs”) in the environment. A recent USGS study indicated that PPCPs are present at low levels in surface water throughout the U.S. Concern is based in part on the fact that certain PPCPs: (1) are designed to have biological effects (particularly pharmaceuticals), (2) are persistent in or continually added to the environment, (3) have negative environmental effects (specifically on aquatic life) even at low levels, and (4) potentially have cumulative and synergistic effects when combined with other PPCPs. The primary route of PPCPs into the environment is sewage discharges, septic systems, and large stock yards and feedlots where the unmetabolized PPCPs are excreted by humans and animals and end up in surface water and groundwater. Given these circumstances, manufacturers of PPCPs may face a risk of increased regulation and possibly litigation similar to that faced by oxygenate manufacturers and petroleum refiners over the use of Methyl Tertiary Butyl Ether (“MTBE”). Companies can take steps now and in the future that may minimize the impact of these risks.

I. INTRODUCTION

Potential liabilities may loom for manufacturers of pharmaceuticals and personal care products (“PPCPs”) because of recent discoveries about chemicals from PPCPs in the environment. PPCPs include drugs used in human and veterinary medicine, as well as soaps, skin care products, insect repellants, sunscreens, and cosmetics that contain a great variety of other chemicals.² A recent nationwide study of PPCP chemicals by the U.S. Geological Survey (“USGS”)³ found that PPCP chemicals occur frequently in streams, even in remote areas. This study has created widespread interest in PPCPs as sources of environmental contaminants.

Certain PPCP chemicals may have harmful environmental effects even at very low levels. Furthermore, some may be persistent in the environment. Even among nonpersistent chemicals, many are used continuously at such rates that their concentrations in the environment may increase rather than attenuate. Given the above, the environmental effects of these chemicals may be long lasting and possibly enhanced by the cumulative and synergistic effects that could result when PPCPs are combined in the environment. Environmental effects of most PPCP chemicals are unknown, so these effects are not identified or known until sometime in the future. Most PPCP chemicals are generally considered safe; however, others may not be.

Two factors contribute to heightened awareness of these chemicals. One is the development of new, very sensitive analytical methods that can detect PPCP chemicals in environmental media at very low concentrations, in some cases less than one part per billion. The other is that human use of PPCPs has exploded in part due to new chemical discoveries, increased wealth, and growing population. Consequently, low levels of PPCPs are being detected widely in surface water and groundwater.

This article provides a brief overview of the types of chemicals involved, the environmental impacts associated with the chemicals, an overview of recent studies, identified potential liability and regulatory concerns, and suggestions for reducing a company's liability in the future.

II. WHAT ARE THESE CHEMICALS?

Many drugs used by humans make their way into streams, primarily by way of sewage. Types of human pharmaceuticals that have been identified in stream water include birth-control hormones, antibiotics, blood lipid regulators, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), beta blockers, antidepressants, anti-cancer drugs, Viagra, tranquilizers, retinoids, and X-ray contrast media.⁴ To make matters worse, limited studies indicate that these drugs and other PPCPs are not effectively destroyed by sewage treatment plants.⁵

Veterinary pharmaceuticals also reach the environment. Stock yards and feed lots with large herds of animals being treated with steroids, hormones, antibiotics, and other veterinary pharmaceuticals are potentially significant sources of these chemicals. The chemicals are excreted by the animals directly onto the land, are land farmed via manure spreading,

and discharged into streams by runoff. Any of these routes may result in impacts to surface water and groundwater.

Personal care products contain a wide variety of chemicals, including fragrances, soaps, detergents, emollients, preservatives, disinfectants, sunscreen agents, insect repellants, and some possibly very active chemicals contained in nutritional supplements.⁶ Personal care products can be released directly into the environment as a result of their application (e.g., as sunscreen or hair spray), or else as constituents in sewage, just as with pharmaceuticals. To illustrate the range of PPCP chemicals, the USGS study cited previously identified the following seven organic compounds as the most frequently detected: coprostanol (fecal steroid, found in 85.7% of samples), cholesterol (plant and animal steroid, 84.3%), *N,N*-diethyltoluamide (insect repellant, 74.1%), caffeine (stimulant, 70.6%), *tri*(2-chloroethyl) phosphate (fire retardant, 57.6%), triclosan (antimicrobial disinfectant, 57.6%), and 4-nonylphenol (nonionic detergent metabolite, 50.6%).⁷ In total, the USGS detected 82 different compounds out of the 95 compounds for which they analyzed.

III. WHY ARE THEY A PROBLEM?

Beyond the identification and detection of PPCPs in the environment, few PPCPs have been seriously investigated to identify their environmental effects. Some of the PPCP chemicals identified are already known to produce negative environmental effects on aquatic life at very low levels. For example, over the last 10 years considerable public attention has focused on endocrine disrupters — these are chemicals such as birth-control hormones — that interfere at low levels with the normal functioning of hormones that regulate development and reproduction. Although endocrine disrupters are only one subclass of PPCP chemicals, EPA is now devoting considerable efforts to their investigation and possible regulation because of potentially serious effects on reproduction of aquatic organisms. For example, selective serotonin reuptake inhibitors (SSRIs) — widely used antidepressants such as fluoxetine — are known to cause abnormal spawning behavior in certain shellfish at concentrations as low as 30 ppt (parts per trillion). Nitro and amino-nitro musks — widely used as fragrances in personal care products — are highly toxic to aquatic life.

In addition, aquatic effects from animal medicinal products are now coming to light due to recent environmental studies involving cattle growth hormones.⁸ These anabolic steroids are widely used in the United States (although banned in Europe) to promote weight gain in beef cattle. Female fathead minnows taken downstream from several Nebraska feedlots were found to have male characteristics, and male minnows to have abnormally small testes and certain female characteristics. Water from the same locations produced androgenic effects — similar to male sex hormones — in *in vitro* assays. One specific growth promoter, trenbolone acetate, has been shown by laboratory tests to affect the reproductive endocrine functions of fathead minnows in several ways. These effects occurred at concentrations of only 0.03 µg/L.

To make matters more complex are those PPCPs that are considered endocrine disrupters. As mentioned earlier, these are chemicals that modify the normal function of endocrine, or hormonal, systems in humans and other animals. By mimicking normal hormones, they interfere with reproduction and development, and alter behavior. Most endocrine disrupters identified so far (polychlorinated biphenyls and insecticides, for example) are not used in PPCPs or their packaging materials. Similarly, most PPCP chemicals have no known endocrine disrupter effects. A few chemicals fall into both categories, however.⁹ Benzophenone, for example, is an identified endocrine disrupter that is used in soaps and perfumes. EPA is devoting considerable effort to studying endocrine disrupters, and appears to be making rapid progress considering the complexity of the issues. EPA's research program is developing and validating tests to identify possible endocrine disrupters. EPA expects to have methods in place, and to require testing of chemicals for endocrine disrupter activities, by the end of 2003. EPA's effort is likely to identify more PPCP chemicals as endocrine disrupters. As a result, the endocrine disrupter issue is likely to spill over into the PPCP issue.

Given the above, the identification and detection of PPCPs in surface water and groundwater are potentially troublesome for a number of reasons. Unlike industrial chemicals, their use is very widely distributed, instead of being concentrated at industrial plant sites in urban areas. In addition, they tend to be very biologically active — drugs are selected specifically because they *have* biological effects.

Additionally, the wide use of PPCPs may result in many different PPCPs being present in surface water at the same time. The combined effects of PPCPs are unknown, and some scientists believe that certain combinations may have a synergistic action that will produce disproportionately large effects.¹⁰ Even if not synergistic, effects of different chemicals may combine in other ways. For example, a recent study showed a combination of multiple chemicals to have an additive effect.¹¹ This study used the Yeast Estrogen Screen, a method of detecting effects of chemicals that bind to the alpha human estrogen receptor and can thus affect reproductive activity. Investigators tested mixtures of eight such chemicals, each at a concentration below the level of observable effects. In combination, however, their effects were additive, and produced a detectable effect. This finding undercuts the common practice of evaluating and regulating the environmental concentrations of chemicals individually, as though they were the only chemical present.

The long-term environmental effects or the effects of human exposure to low levels of these substances are largely unknown. Major effects on aquatic organisms are likely to be slow in being detected or observed, and thus hard to associate with PPCPs.

IV. GROWING CONCERNS

Concern with PPCPs in the United States began only recently. What has been regarded as the first symposium in North America occurred in March 2000; previously, most research on PPCPs had been conducted in Europe.¹² The recent USGS study mentioned previously showed that PPCPs are surprisingly widespread — although mostly at low concentrations — in streams throughout the United States. The USGS is conducting similar studies of ground water and drinking water, but results have not yet been released. These reports, as well as increasing numbers of technical symposia focusing on PPCPs are bringing this issue to the forefront and public awareness is likely to grow rapidly.

Previously, PPCP chemicals were largely ignored or overlooked due to the lack of sufficiently sensitive analytical methods for many chemicals. For example, to conduct its study, the USGS had to develop five new analytical methods to test for antibiotic compounds, prescription and nonprescription drugs and metabolites, steroid/hormone compounds, and other organic compounds. It is also worth noting that the USGS was

unable to analyze for certain compounds of interest because of lack of analytical standards.

Pharmaceutical usage is also increasing rapidly. By way of background, the value of pharmaceutical shipments in the United States over a 10-year period from 1990 to 1999 was tabulated and graphed to ascertain the nature of the growth of pharmaceutical usage. Figure 1 shows total value of pharmaceuticals shipped during this period, and Figure 2 shows total value of shipments for specific categories of pharmaceuticals. The total value of pharmaceutical shipments doubled from approximately \$34,000,000,000 to \$70,000,000,000 in 10 years. Drugs that comprised the highest value shipments included those drugs that affect nervous system and sense organs, followed by drugs acting on the digestive system, followed by drugs affecting parasitic and infective disease, cardiovascular disease, respiratory disease, and drugs affecting neoplasms, endocrine systems, and metabolic disease (see Table 1). While the value of shipments may not provide the complete picture regarding the growing use of these products, it does suggest that the use of pharmaceuticals will continue to increase. It seems likely that the value of shipments over the next 10 years may quadruple (through increased use and aging population) compared with 1990, suggesting that the presence of pharmaceuticals in the environment may become even more widespread.

V. PPCPS REGULATORY AND LITIGATION CONCERNS

PPCP contamination potentially encompasses tens of thousands of chemicals, its sources and receptors are geographically dispersed, and its true magnitude and effects will likely emerge over time. Given the above, and the fact that federal groundwater and safe drinking water regulation is burdened by "priority pollutants" and contaminants currently being regulated and those that are proposed for regulation (the Safe Drinking Water Act Contaminant Candidate List¹³) it is unlikely that federal regulation will be developed (anytime soon) to mitigate the potential risks (if any) associated with PPCPs. Therefore, regulatory activities involving identification, occurrence, science, regulation, and law associated with these chemicals will likely play out in the state arena (especially California). Thus, the result will be a potentially volatile mixture consisting of three parts: one part science, one part law, and one part environmental activism. It is also unlikely that the parts will be equal. Thus this volatile mix-

ture will undoubtedly cause some companies to react to put out the resultant fires where they occur first rather than in a proactive and efficient manner.

On the regulation side, regulatory activities may increasingly affect PPCP manufacturers. In the United States, environmental risk assessments of new drugs are required if the predicted concentration when entering the environment is 1 µg/L or more.¹⁴ However, this level was set to guard only against acute effects (as opposed to chronic effects) and was set on the basis of very limited toxicity information. Future levels for risk assessments will likely be lower, possibly much lower. For example, the European Agency for the Evaluation of Medicinal Products has already proposed a predicted environmental concentration of 0.01 µg/L — 100 times lower than the United States level — as the threshold for triggering more detailed investigation of medicinal products.¹⁵

Another likely area of regulation is product stewardship, the concept that someone — more likely than not the manufacturer or industry trade organization — must manage potentially harmful products throughout their life cycle such as expired PPCPs. EPA has an active program to promote product stewardship, currently covering products such as tires, batteries, electronics, and mercury.¹⁶ EPA has suggested that standardized national regulations for disposal of unwanted and expired PPCPs may be desirable, as may be as implementing “extended producer responsibility” for manufacturers and distributors. EPA lists these issues as outstanding research needs.¹⁷ Such regulations might, for example, require take-back schemes like those the battery industry has developed.

At present, no general regulations or standards guide the disposal of pharmaceuticals.¹⁸ The federal Drug Enforcement Administration regulates the disposal only of controlled substances such as narcotics. EPA regulates discarded pharmaceuticals as solid waste (rather than medical waste) unless they are generated at a hospital and discarded with hospital waste. A few discarded pharmaceuticals are also hazardous wastes under EPA regulations, and should be managed as hazardous wastes, with all the complexities of handling, time limits, and paperwork that this implies. Most pharmaceuticals discarded by consumers are probably flushed down the sewer or discarded with household trash.

Ultimately, PPCP manufacturers may face multiple and varying state regulations overlapped by federal regulation ranging from increased prod-

uct labeling requirements, product take-back schemes, use restrictions to product bans, depending on the PPCP.

In addition to increased regulation, PPCP manufacturers with deep pockets may also become targets for environmental activists over the next few years as more is discovered about PPCPs and their effects. While PPCPs pass through other hands — wholesalers, retail druggists, hospitals, and end users — before entering the environment, manufacturers will be seen as the source. Furthermore, Liability may arise from environmental assessments conducted as part of the drug approval process by PPCPs. Drug-approval studies conducted in accordance with the prescribed requirements that did not demonstrate a known effect may result in the company being held accountable for environmental effects (human or otherwise) that it was aware of, however did not disclose or reduce through risk mitigation measures. Future litigation may take many different forms and include product liability class action lawsuits alleging environmental damages (aquatic effects, endangered species impacts), bodily injury damages (ingestion of groundwater containing low levels of PPCP resulting in a chronic or other health effect in certain sensitive human receptors), and possibly failure to warn, among others.

With the regulatory and litigation scenario described above in mind, a similar scenario in terms of regulation, activism and litigation has played out, and continues to play out, in the area of underground storage tanks and releases of methyl tertiary butyl ether (“MTBE”). Like PPCPs, MTBE is a constituent of a widely used consumer product — gasoline. In addition, MTBE has been detected throughout the United States as a result of releases of gasoline containing MTBE from leaking underground storage tanks, spills at service stations, and automobile accidents. As a result, state regulation of MTBE, which has largely preceded federal regulation, has increased since the mid-1980s to the point that some states have sought to ban the use of MTBE entirely.

Mirroring the increases in MTBE regulation is the litigation over releases of MTBE in the environment. Prior to the mid-1990s, litigation involving leaks of gasoline from USTs arose from plaintiffs alleging property and/or personal injury damage due to a release of gasoline from a leaking underground storage tank at a local gas station. The “UST litigation” then changed in 1996, when one of the first nationwide class action underground storage tank (UST) lawsuits titled *James Peters et al v. Amoco*

Oil Company et al was filed in the state of Alabama. This lawsuit involved multiple gas stations and a nationwide class(es) of plaintiffs. The plaintiffs eventually modified their complaint to include MTBE as awareness about its occurrence grew. Litigation over MTBE began in 1998 with the filing of the first statewide class action case known as the *Communities for a Better Environment (CBE) v. Unocal et al.* Initially, the Peters case and the CBE claims alleged collusion and conspiracy (among other things) among oil company defendants. After the plaintiffs failed to prevail on these claims, the plaintiffs amended their complaints, focusing on supposed defendants' alleged early knowledge and failure to warn regarding MTBE and its fate in the environment. These cases spawned more cases that were filed in other states including Connecticut, Florida, Illinois, Maine, Texas (alphabetical order) to name just a few.

Given the tortuous path of MTBE litigation, companies may have been initially litigating issues in states where their liabilities and exposures were relatively small compared to other states say, California, New York, and Florida. Furthermore, as discovery in the early cases continued, the information was then used by plaintiffs to amend previously filed litigation, as well as file new litigation.

VII. WHAT CAN A PPCP MANUFACTURER DO?

PPCP manufacturers fortunately have some lead time that they can use to minimize the impacts of the potential liabilities associated with PPCPs. A first step for companies is to further acquaint themselves with the possible environmental impacts of PPCPs and their components. They may want to consider reviewing the ingredients used in their products in order to identify higher-risk chemical components and ingredients and proactively reformulate the products where justified.

Manufacturers need to stay aware of evolving analytical methods for detecting PPCPs, because improvements in detection methods may drive public concerns, as they make it possible to detect more PPCP constituents in the environment. Furthermore, the priority in development of methods will likely focus on PPCP ecological toxicity and use.

Increased state regulation followed by federal regulation is likely. The regulatory development appears to be starting in Europe and is likely to spread to state legislatures prior to the federal legislature. Therefore, manufacturers of PPCPs will have to be aware of these impending changes

before they take place in order to minimize the impact of the changes on company operations and profits. As part of this increased regulation, it is likely that increased reporting by PPCP manufacturers will be required by regulators to ascertain the magnitude of the PPCP chemicals in the environment and evaluate the need for increased regulation. PPCP manufacturers will also want to ensure that use and disposal of their products is conducted in a manner that ultimately reduces the amount that ends up in the environment. This could be done through improved dispensing so that only the amount that is needed is used (reduce overuse) improved labeling as well as product (unneeded or expired) take-back programs with pharmacies and stores selling PPCPs.

Finally, PPCP companies should remind their personnel not to create speculative documents regarding PPCPs and their environmental impacts. Speculative memos — not clearly based on facts — should be avoided. Sensitive documents regarding these subjects, including e-mails, should be directed to legal counsel and not forwarded to others. The purpose is not to conceal but to avoid creating misleading impressions if the documents are ever examined by anyone outside the company, particularly a plaintiff's attorney who will attempt to reconstruct the company's state of knowledge 15 to 20 years later (as occurred in the MTBE litigation) on the basis of a such documents. In addition, company personnel should rigorously adhere to the company's document retention policy and other internal mechanisms for retaining and managing required documents. Such policies should be reviewed and updated periodically by the company's legal counsel.

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tal LLC, 1299 Pennsylvania Avenue NW, Washington, DC. 20004, or to McBrideM@Capenviron.com. Mr. McBride also can be contacted at (202)383-7415.

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⁴ Daughton and Ternes, 1999, p. 926-932.

⁵ Daughton and Ternes, 1999, p. 922.

⁶ Daughton and Ternes, 1999, p. 926-932.

⁷ Kolpin, and others, 2002. "Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999 – 2000: A National Reconnaissance, *Environ. Sci. Technol.* Vol. 36, No. 6, pp. 1202 – 1211, 2002.

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¹⁴ Codified at 21 CFR 25.31 (b). See "National Environmental Policy Act: Revision of Policies and Procedures", 62 Fed. Reg. 40570-40600 (the final rule that established this standard) for discussion.

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Table 1 - Pharmaceutical Preparations - Value of Shipments from 1990 to 1999

Year	Pharmaceuticals (except Biologicals)	Neoplasms, Endocrine and Metabolic	Nervous System and Sense Organs	Cardiovascular	Respiratory	Digestive	Skin	Vitamin, Nutrient and Hematinic	Parasitic and Infective Disease	Veterinary Use
1990	\$ 33,954	\$ 2,743	\$ 7,219	\$ 4,815	\$ 3,724	\$ 4,840	\$ 1,558	\$ 2,588	\$ 5,411	\$ 1,057
1995	\$ 48,864	\$ 4,076	\$ 9,228	\$ 5,988	\$ 5,196	\$ 8,593	\$ 2,171	\$ 4,812	\$ 7,196	\$ 1,605
1996	\$ 51,844	\$ 4,788	\$ 10,123	\$ 6,912	\$ 4,994	\$ 8,494	\$ 2,185	\$ 5,281	\$ 7,304	\$ 1,763
1997	\$ 57,419	\$ 5,466	\$ 11,708	\$ 8,799	\$ 5,641	\$ 9,482	\$ 1,867	\$ 5,088	\$ 7,795	\$ 1,572
1998	\$ 65,712	\$ 7,633	\$ 13,605	\$ 9,368	\$ 6,725	\$ 9,502	\$ 2,245	\$ 5,851	\$ 8,780	\$ 2,003
1999	\$ 69,950	\$ 7,902	\$ 15,282	\$ 9,695	\$ 8,136	\$ 8,719	\$ 2,589	\$ 6,142	\$ 9,176	\$ 2,309
Total	\$ 327,743	\$ 32,608	\$ 67,165	\$ 45,577	\$ 34,416	\$ 49,630	\$ 12,615	\$ 29,762	\$ 45,662	\$ 10,309

Dollars in Millions

Source: U.S. Census Bureau, Statistical Abstract of the United States: 2001, 121 Edition.

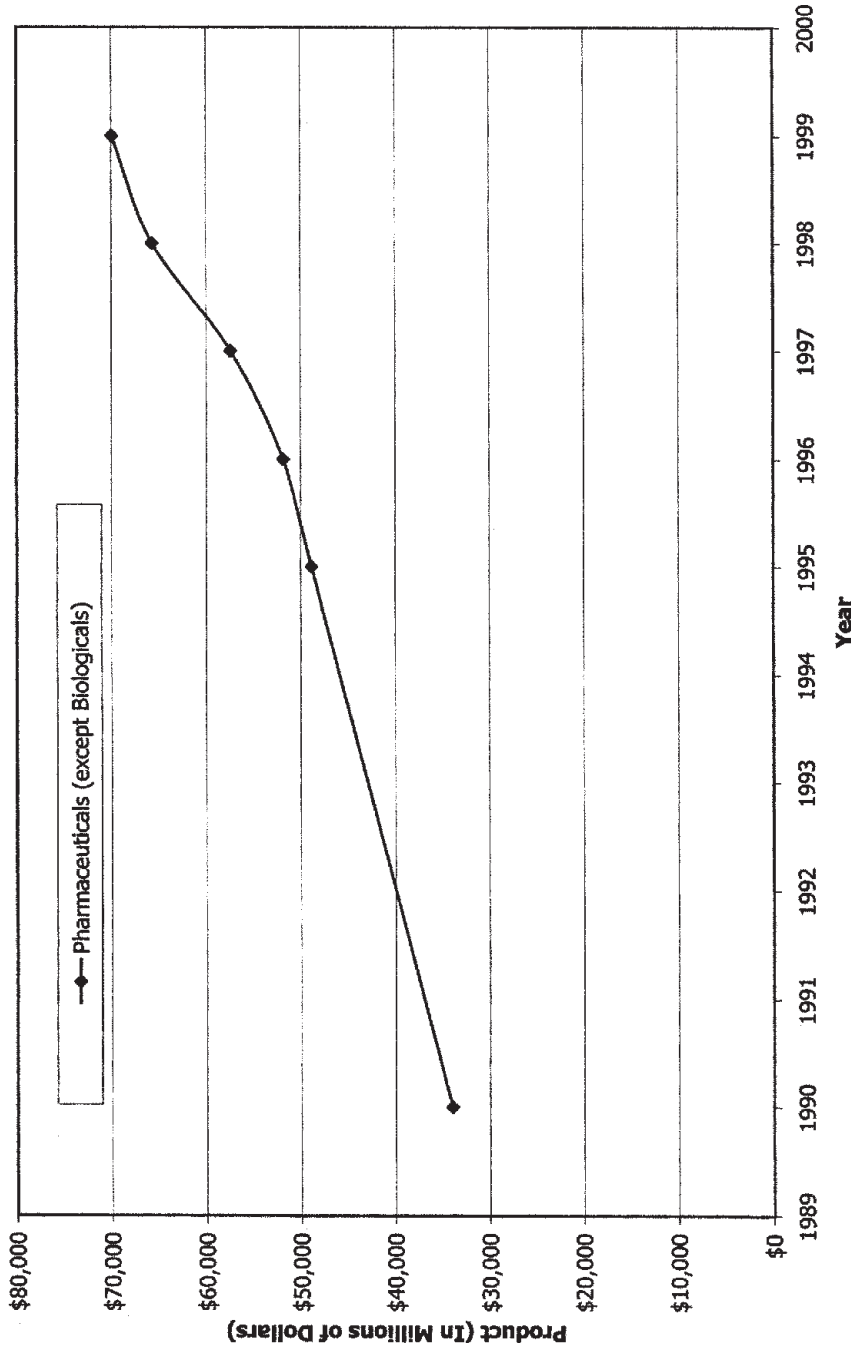


Figure 1. Pharmaceutical Preparations - Value of Shipments from 1990 to 1999
Source: U.S. Census Bureau, Statistical Abstract of the United States: 2001, 121 Edition

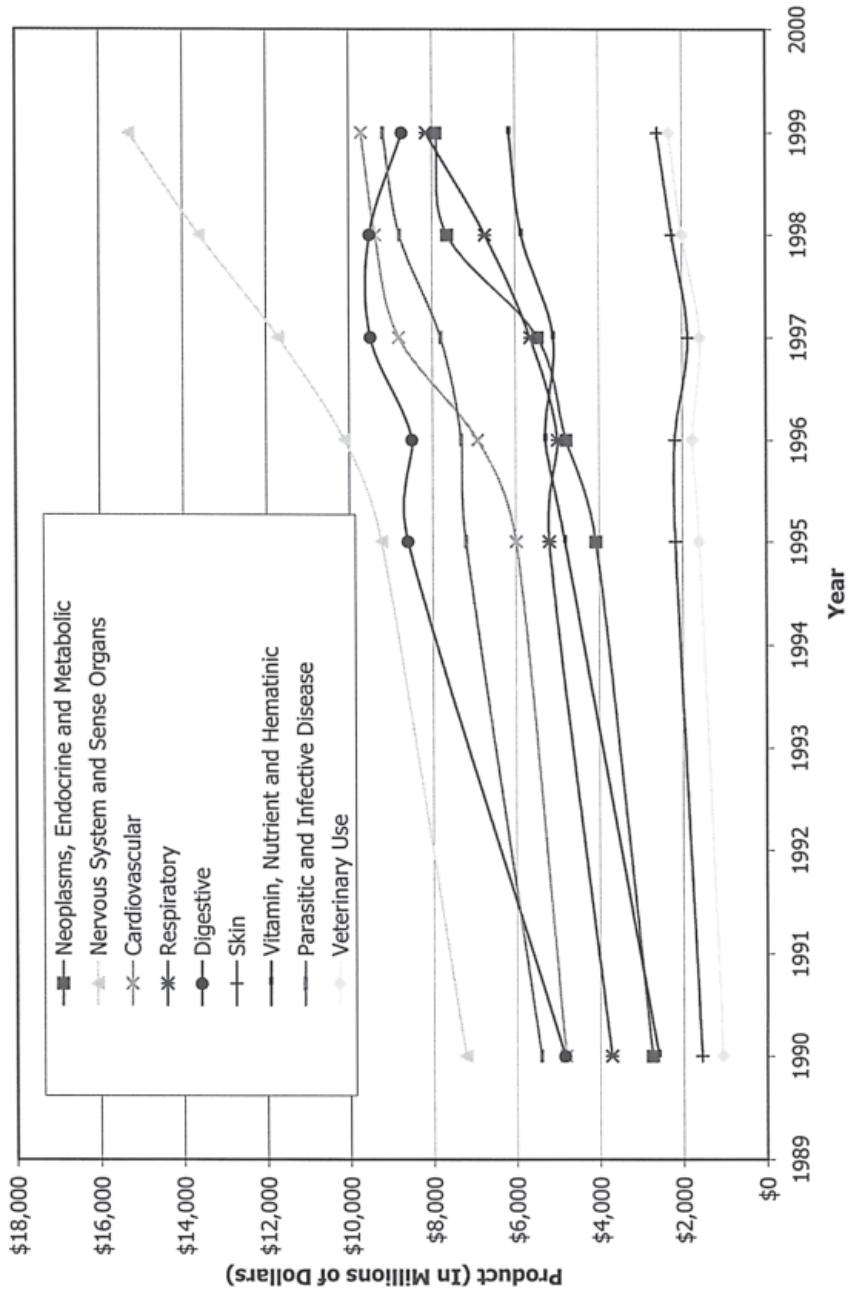


Figure 2. Pharmaceutical Preparations - Value of Shipments from 1990 to 1999
 Source: U.S. Census Bureau, Statistical Abstract of the United States: 2001, 121 Edition