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P. 01

RON WYDEN
DROPOIN
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Congress of the United States

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COMMENTS:

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FIRST OF 10 PAGES



NEWS FROM
CONGRESSMAN
RON WYDIEN

1111 Longworth House Office Building Washington, D.C. 202-225-4811

FOR IMMEDIATE RELEASE
APRIL 4, 1995

CONTACT: JOSH KARDON

WYDIEN PROPOSES SWEEPING FDA REFORMS

Washington, D.C. -- Sweeping Food and Drug Administration (FDA) reforms, including relaxing pre-market testing, allowing third-party evaluations of drugs and devices, dropping export barriers, and imposing time limits on the approval process, were proposed today by consumer advocate, U.S. Rep. Ron Wyden (D-OR).

Wyden's proposal, forwarded to both President Clinton and House Speaker Newt Gingrich this morning, are premised on the notion that, "an entrepreneur-friendly FDA and consumer protection are not mutually exclusive ideals."

"The technological revolution has overtaken the bureaucratic structure of the FDA," said Wyden. "Computers, biotechnology, and other innovations are producing better healthcare products which we can't allow to be stifled by a lethargic, slow-moving or insensitive approval process."

The House Commerce Subcommittee on Oversight and Investigations is currently conducting a series of hearings on the FDA. Wyden serves as the ranking Democrat on that subcommittee.

While arguing for change in the FDA's approval processes, Wyden defended the FDA against recent attacks calling for the dismantling of the FDA. "It's time to get beyond the cheap rhetoric, ideological myth-making and half-baked anecdotes that have been peddled by a number of powerful special interest groups since the last election." Wyden expressed confidence in the FDA's ability and willingness to adapt to the times, saying, "I firmly believe the FDA's public health mission is compatible with policies that more quickly bring new products to the consumer and create additional jobs."

Wyden's 14-point FDA reform plan includes the following:

- Limiting pre-market testing requirements in return for broader post-market surveillance and reporting.
- Allow independent accrediting and testing labs to evaluate innovations using FDA standards.
- Enforce statutorily mandated time limits in approval process.
- Further harmonize U.S., industrialized world standards for imports.
- Eliminate the law which bars the export of U.S. made medical devices which have not been submitted to the FDA for approval.
- Re-focus user report demands to devices that pose the most risk.
- Make FDA device inspection and enforcement consistent.
- Better utilize existing resources for product evaluations and research.
- Speed up phase I and phase III clinical trials.
- Increase safety oversight of human tissue.
- Modify the off-label use law to encourage good medicine.
- Move breakthrough drugs to the front of the FDA process.
- Streamline biotechnology product manufacturing.

Wyden pointed out that while some of these reforms can be achieved administratively, others would require legislative authority. Wyden plans to introduce legislation addressing many of these reform later in the month. Copies of the letters detailing these proposals are available upon request.

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P. 03

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SENATOR

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CO-CHAIRMAN, FORESTRY 2000 TASK FORCE

April 4, 1995

The Honorable William Clinton
President of the United States
1600 Pennsylvania Avenue
The White House
Washington, D.C. 20500

Dear Mr. President:

I write to you, today, regarding the reform and renewal of the U.S. Food and Drug Administration. The FDA is ripe for a full review of function and management. We have an opportunity to lay the groundwork for new, 21st Century policies at this agency that are good for both consumers and entrepreneurs.

Virtually no other agency has so pivotal a role in protecting the public. But a competitive industry and consumer protection are not mutually exclusive ideals. The choice doesn't have to be between good jobs and good health. I firmly believe the public health mission is compatible with entrepreneur-friendly policies that more quickly bring new, health-sustaining products to the consumer and create additional jobs.

As the ranking member on the Commerce Subcommittee on Oversight and Investigation, I have been extensively involved in our FDA management assessment. I believe these suggestions conform with and significantly enhance the FDA reforms announced by the Administration within recent weeks, and would build on many of the reform proposals advanced by the new majorities in the House and Senate.

I would appreciate your thoughts and responses to these suggestions.

Reforming the FDA

A primary mission of the FDA is the evaluation and approval of new drugs and medical devices to determine that they are (1) safe and (2) effective for U.S. consumers.

The Honorable William Clinton
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In our efforts to change the agency, the focus should maintain these primary missions while gaining (1) operating efficiencies, (2) speedier and less costly reviews for manufacturers and (3) better therapies for U.S. consumers.

Secondary goals should include reform of the premarket evaluation process so that new drugs and devices which have breakthrough properties receive priority review and evaluation whenever feasible.

Finally, the FDA should make best efforts to improve, or at least not unnecessarily impede, U.S. producers' competitiveness in overseas markets.

In that vein, I request your response to the following proposals:

1. Pursue General Policies Relaxing Pre-Market Assessment of Efficacy

The premier complaint of device manufacturers voiced at a March 30, hearing of the Subcommittee on Oversight and Investigation was the length, demands and expense of clinical trials for the assessment of efficacy. Their criticism in many instances is well-founded. I believe we can safely limit pre-market testing requirements for devices, and phase III clinical reporting demands for drugs, in return for broader post-market surveillance and reporting.

This change, I believe, will help small entrepreneurial companies in particular reach the market sooner and at less expense. Consumers would be shielded from devices and drugs that had insufficient utility via post-market surveillance requirements.

Richard Ashman, a witness at the March 30, hearing and a Louisiana device manufacturer, called FDA decisions in this area "no brainers," and said FDA scrutiny of low-risk devices should be significantly relaxed. Ali Gallagher, another device manufacturer and witness, also liked this idea, and said that FDA oversight could be relaxed even further to allow for "continuous manufacturing improvements" so that manufacturers could make quick design up-grades based on user data.

I believe this idea has merit as well, and I would include this in FDA reforms.

The Honorable William Clinton
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Obviously, these reforms should be thoroughly tested on devices that pose comparatively lesser risk. Implantable products, for example, are not good candidates for an initial trial of these proposals but could be added at a future date.

2. Third-Party Evaluations

FDA should allow independent accrediting and testing labs to evaluate, according to FDA standards, innovations which come under FDA control. The agency should test this option with lower risk devices and then consider the results before extending third-party evaluations for implantable devices and drugs.

It would seem sensible to collect user fees for premarket review of devices through third-party evaluation, as well as to allow third parties to use fees currently collected by the FDA on drug applications.

The logical evolution of third-party review would be allowing accrediting organizations to conduct some of the plant inspections now done by the FDA for good manufacturing practices. Again, I advocate a deliberate and careful evaluation of this strategy, allowing its initial use for devices with relatively low risk before implementing third-party review more broadly.

It would seem reasonable to include analysis of toxicological studies, validation of assays and "lot" release for more complicated products with third-party review systems.

3. Enforce Statutorily Mandated Time Limits in Approval Process

Delays have been a painful item for the device manufacturers. I queried entrepreneurs who appeared as witnesses at our March 30 hearing on this point, specifically. They were unanimous in their plea for more speed and less delay.

The Administration, either by fiat or with new statutes, must demand speedier evaluations by the agency. Again, use of third-party review could eliminate some of the bottlenecks.

4. Further Harmonize U.S., Industrialized World Standards for Imports

Greater harmonization of national standards could improve our already strong balance of trade position on overseas sales of drugs and devices. The U.S. already has come some distance on this issue.

The Honorable William Clinton
Page Four

But there are opportunities for further harmonization. Foreign drug and device manufacturers, for example, must be inspected by the FDA for products approved by the agency for U.S. sales. I believe more of the good manufacturing practice inspection work should be done by foreign inspection agencies, in particular when foreign quality standards closely resemble our own.

For example, the agency should accept the European Union's EN 46001 standard for manufacturing quality inspection.

5. Export Barriers

Specifically, the agency should eliminate the so-called 801(e) controls which bar export of U.S. made medical devices which have not been submitted for FDA approval, but which are approved by the nation desiring to import.

Also, the agency should allow the export of U.S. made drugs under similar pre-conditions, if the products are appropriately labeled "for export only."

6. Re-Focus User Report Demands to Devices that Pose Risk

There is little evidence that meaningful information has resulted from requirements that users submit postmarket reports for deaths and serious injuries from devices. While in theory this system was designed to validate device safety, benefits clearly have been out-weighed by the imposition these requirements place on users. Even the agency admits the user reports system has been disappointing, if not an outright failure.

The agency must re-focus its current user reporting efforts involving devices. Instead of requiring user reports, the agency could derive as much or more information from voluntary reports through the Medwatch system.

Also, the agency must reduce apparently redundant activities in this area. A good example may be the Pacemaker Registry, a quality assurance project that was part of the Deficit Reduction Act of 1984. This program became unnecessary with the passage of the Safe Medical Devices Act of 1990, which accomplishes the same basic purpose.

The Honorable William Clinton
Page Five

7. Make FDA Device Inspection and Enforcement Consistent

According to some manufacturers, inconsistency of FDA field inspection and enforcement efforts is a problem. Absent appropriate clarification of rules and regulations, inspectors in Texas may reach different conclusions about the character, scope and importance of a good manufacturing practice violation than FDA agents in California, and may deal differently with violations.

The FDA should conduct an agency-wide analysis on this issue and, using participants from the industry, develop ways and means of increasing enforcement and inspection consistency in the agency's regulation of devices.

Consistency of approach might include use of social security numbers for device tracking (hospitals provide SS numbers for this purpose), and accelerating the adoption of an FDA proposal for a monthly reporting schedule for deaths and serious injuries.

8. Better Utilize Existing Resources for Product Evaluations and Research

Backlogs in processing applications are decreasing, but continue to be a problem for, and competitiveness drain on the industry.

The FDA should more fully and rationally invest user fee revenue to meet the goals of the user fee act. The agency should establish additional offices of evaluation with the intent of speeding reviews.

The Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health and the Center for Drug Development Evaluation and Research each review biotech products under different regulations. Sometimes, confusing and inconsistent regulation and decisions result.

For biologics, the FDA should consolidate the bulk of the activity under a single division depending on the use of the individual product, or as an alternative assign a single, inter-disciplinary team to follow the application from beginning to end. In vitro diagnostic products, for example, could be consigned solely to the Center for Devices.

The Honorable William Clinton
Page Six

9. Speed Clinical Trials, Part I

In the instance where a new drug has breakthrough therapeutic value, the FDA should grant a modified and time-limited market approval on the basis of one pivotal phase III clinical trial with a sound clinical design.

This change would dramatically reduce the costs of bringing new drugs to market, and radically reduce the current approval time.

The modified approval would be replaced with an unqualified approval if follow-up studies justified claims of safety and effectiveness. If data failed to support original claims, the agency either could extend the modified approval or demand that the manufacturer withdraw the product.

10. Speed Clinical Trials, Part II

The FDA should reduce and perhaps eliminate its current supervision and review of phase I trials.

Instead, these trials should be left to third-party review, ideally institutional review boards which are under the supervision of both the FDA and the National Institutes of Health. The IRBs already share joint custody of this activity with the FDA (patient protection and informed consent issues). This change would fully consolidate authority over phase I trials with the IRBs, and under the exclusive jurisdiction of the FDA.

11. Increase Safety Oversight of Human Tissues

The FDA cannot walk away from its responsibility to provide, or ensure, supervision in this area. It continues to develop a final regulation to replace emergency rules issued in late 1993. These regulations should include registry of all banks doing business, along with a statement of activities and a description of quality control and records-keeping systems.

However, direct supervision of these banks and the enforcement of minimal quality rules could, again, be left to third-party entities. Specifically, the FDA should allow and encourage development of an independent standards-setting organization to perform this function... and reduce the FDA resource commitment.

The Honorable William Clinton
Page Seven

12. Modify Off-Label Use Law to Encourage Good Medicine

FDA enforcement against manufacturers for violating regulations against promotion of off-label use (marketing and promotion) continues to be a source of confusion and angst for the industry, and some head-scratching at the agency. While it is important that the agency guard against promotion of unproven and perhaps dangerous use of approved therapies, manufacturers and their marketing agents complain that FDA efforts in this area have been inconsistent and have occasionally hampered good faith attempts to share scientific and clinical information.

The FDA must undertake best efforts to clear the air on this matter.

For example, the FDA should convene a series of consensus conferences on this matter to modernize its regulatory and enforcement system, recognizing that some aspects of current enforcement do deny practitioners important new information on drugs and devices, and in some instances impair U.S. manufacturers' ability to compete with foreign rivals.

13. Move Breakthrough Drugs to the Front of the Evaluation Process

In the last Congress I proposed that manufacturers be given incentives to do high quality, clinical trials to demonstrate the comparative quality differences between several drugs or devices for treatment of a given ailment.

I believe this idea should be incorporated into FDA reforms this year.

An incentive system that would, for example, allow a product to have accelerated premarket evaluation by a combination of the FDA and the Agency for Health Care Policy and Research, would help accelerate introduction of breakthrough drugs and new applications.

14. Speeding Biotechnology Product Manufacturing

Along with allowing minor changes in manufacturing without pre-inspection, the FDA should consider changes involving current requirements for initial assessment of manufacturing practice.

For example, the FDA should accept for good manufacturing practice approval material produced at "pilot" scale manufacturing levels, allowing producers to forego the heavy costs associated with developing full-scale manufacturing capability prior to FDA approval.

The Honorable William Clinton
Page Eight

The 104th Congress will be the forum for a vigorous debate on the management and mission of the FDA. I think we have an opportunity to bring good ideas to the table, and to do the right thing for both the health industry and the U.S. consumer. I would appreciate your reflection and comments on these proposals, and would be happy to discuss them with you at your convenience.

Sincerely,



RON WYDEN
Member of Congress

cc.. The Honorable Donna B. Shalala, Secretary, Department of
Health and Human Services
The Honorable David Kessler, Commissioner, Food and Drug
Administration
The Honorable Thomas Bliley, Chairman, Commerce Committee
The Honorable John Dingell, Ranking Member, Commerce Committee
The Honorable Michael Bilirakis, Chairman, Subcommittee on
Health and the Environment
The Honorable Henry Waxman, Ranking Member, Subcommittee on
Health and the Environment
Honorable Joe Barton, Chair, Subcommittee on Oversight
and Investigations

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To: Chris Jennnigs **Date:** April 4, 1995
Fax #: 202-456-7431 **Pages:** 30, including this cover sheet.
From: John M. Haddow
Subject: GATT Impact On Generic Pharmaceuticals

COMMENTS:

Attached you will find a copy of the Schondelmeyer study. As you will see, he calculates the additional cost to the American consumer at approximately \$6.2 billion. The cost to the government through higher Medicare and Medicaid costs is estimated to be in the range of \$1.2 billion. There is no doubt that this is a windfall of huge proportions to the multi-national pharmaceutical companies. Bristol Meyer Squibb has taken a harsh stand, along with Glaxo, on not permitting any licenses under URAA. The decision by Commissioner Kessler is critical to the consumers and the elderly of this nation.

I have also attached copies of letter from Congressman Volkmer and Waxman on this issue. Senator Pryor is sending a letter to Commissioner Kessler and should have both Colorado Senators as co-signatories. Senator Graham (FL) may well sign on the letter as well. I asked Paul Kim to apprise you of the status of his letter. Both Senators Rockefeller and Byrd are also sending letters supporting the position of approving ANDAs.

We have discussed the possibility of having Dr. Kessler questioned on this issue when he testifies in the Senate this week and would appreciate your comments on that tactic. We certainly don't want to force his hand prior to his having made a decision.

The West Virginia house delegation has also sent a letter and I will forward that letter upon receipt. If I can be of any further assistance to you please call me.

HLV/jb

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PAUL M. SCHLUND
ADMINISTRATIVE ASSISTANT

Congress of the United States House of Representatives

Washington, DC 20515-0529

HENRY A. WAXMAN
29TH DISTRICT, CALIFORNIA

March 29, 1995

The Honorable David Kessler
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

I am writing to you concerning your current determination of policy relating to the interrelationship of the provisions of the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417) relating to the marketing of generic drugs, and the patent changes agreed to under the Uruguay Round Agreements Act (Public Law 103-465, the "GATT" implementation law).

As you know, as Chairman of the Subcommittee on Health and the Environment of the Committee on Energy and Commerce in the 98th Congress, I was one of the two original authors (along with Senator Orrin Hatch) of the Drug Price Competition and Patent Term Restoration Act. Our goal in passing that Act was to strike an appropriate balance between the rights of the patent holder and the ability of the generic manufacturer to move into the market in a timely manner upon expiration of the patent.

Since the passage and implementation of that Act, we have now had passage of the GATT implementing legislation, which changes patent law overall from a provision of 17 years from approval to 20 years from application, and establishes a general rule for the transition period in which provision is made for a company that has made a substantial investment in a product prior to June 8, 1995, to enter the market with the payment of equitable remuneration to the patent holder during the extra patent life allowed by GATT. The issue, of course, is the interrelationship of this transition policy with the terms governing FDA action on generics applying to enter the market under the terms of the Drug Price Competition and Patent Term Restoration Act.

I understand that Senator Hatch has written to you to express his view that under the terms of the 1984 Act, a generic drug would now be blocked from the market regardless of whether substantial investment had been made on the expectation of the

**Economic Impact of GATT Patent Extension
on Currently Marketed Drugs**

**Stephen W. Schondelmeyer, Pharm.D., Ph.D.
Professor and Director**

**PRIME Institute
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March 1995

*** This study was funded in part by a research grant from the National Association of
Pharmaceutical Manufacturers and the National Pharmaceutical Alliance.**

Economic Impact of GATT Patent Extension on Currently Marketed Drugs

Executive Summary

- At least 109 currently patented and marketed drugs will receive a windfall patent extension if GATT rules are retrospectively applied to previously filed or issued patents (Table 1).
- The average patent extension for the currently marketed drugs would be more than 12 months with some drugs receiving more than 28 months of added exclusivity.
- The windfall extension of patent exclusivity for currently marketed drugs will mean that the introduction of lower cost generics will be delayed. Therefore, the American consumer will have to pay more for prescription medications.
- FDA approved versions of generic drug products typically enter the market at a price more than 25% less than the patented brand. Within one year the price of competing generics will be 45% below the brand; at two years the price will be 60% less and at three years it will average 75% less than the brand name drug (*Kidder, Peabody: Generic Drug Industry Overview, October 5, 1994, pp.6-7*).
- FDA approved versions of generic drug products typically capture 45% of the units sold within one year of market introduction. After two years their market penetration averages more than 50% of all units sold and by the third year the penetration approaches 60% (*Kidder, Peabody: Generic Drug Industry Overview, October 5, 1994, pp.6-7*).
- The economic impact of extending the GATT rules to currently marketed drugs can be estimated by applying the recent pricing and market penetration performance of generics to the actual and projected sales volume of currently marketed drugs for the additional length of time that American consumers will have to wait for access to lower cost generics.
- The projected cost to American consumers from the windfall extension of patent exclusivity for the 109 currently marketed drugs affected by this change will exceed \$6 billion (1996 net present value) over the next two decades (Figure 3).
- Twenty of the most common prescription drugs will account for an increased cost to American consumers of over \$4.5 billion (1996 net present value) in the next two decades (Figure 7).
- There are at least 10 drugs whose patents will expire in 1995. The lack of generic competitors for just three of these drugs will cost American consumers \$1.2 billion (1996 net present value) in 1996 and 1997 (Table 1).
- The lower price and high market penetration of generics, when available, results in substantial savings to American consumers. These savings are also of benefit to Medicaid, federal and state government, private insurers, managed care, employers, unions, ERISA plans, and others who pay for prescriptions. The cost of this windfall extension of exclusivity to Medicaid alone will be about \$1 billion (1996 net present value) and the total cost to federal and state government will exceed \$1.25 billion (1996 net present value).

The projected cost to American consumers from the extension of GATT rules to currently marketed drugs has been estimated in a study conducted by the PRIME Institute at the University of Minnesota. The PRIME Institute specializes in research involving pharmaceutical benefit management, economics, and public policy issues.

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Economic Impact of GATT Patent Extension on Currently Marketed Drugs

I. INTRODUCTION

American consumers may incur an added cost for prescription drugs over the next two decades due to a GATT-related windfall extension of patent protection for already marketed medicines. Pharmaceutical firms stand to benefit while consumers, and especially private pay consumers such as senior citizens and the uninsured, will pay the cost of this added market exclusivity. Recently, the U.S. Congress adopted the Uruguay Round Agreements Act (URAA), Public Law 103-465, as enabling legislation for implementation of the General Agreement on Trade and Tariffs (GATT) in the United States. As specified in GATT, the term for market exclusivity awarded by a patent will be twenty years from the date of patent application, rather than the current patent term of seventeen years from the date of patent award. Patents filed on, or after, June 8, 1995 will benefit from this extended market exclusivity as intended by GATT.

The cost to American consumers, however, comes from the discretionary transitional approach proposed by the U.S. Patent and Trademark Office (PTO). PTO has proposed that all patents in effect on, or prior to, June 8, 1995 will be extended to 20 years from time of application, if that results in a patent term longer than the seventeen years from the date of patent issue. For those patents receiving an extension beyond the originally awarded patent term, the additional time after the original patent term is referred to as the '*delta period*'. In other words, patents which have already been awarded, and for which an expiration date has been clearly established under law, will have the windfall economic benefit of added market exclusivity time. In many sectors of the market this change may have little, if any, impact. In the pharmaceutical market, however, this discretionary transition proposal may have a substantial effect. The consequences in the pharmaceutical market from extension of previously awarded patents will include the following: (1) pharmaceutical firms holding a patent will benefit from a windfall extension in market exclusivity time; (2) pharmaceutical firms (i.e., independent generic firms) preparing generic versions of currently patented drug products will face delays in approval and may have added costs due to the delay in market entry; and (3) the consumer will have delayed access to lower-cost, generically equivalent pharmaceutical products. While each of these effects deserves substantial analysis, the focus of this study is on the added costs to consumers from delays in generic approvals and market entry.

II. METHODS FOR ECONOMIC IMPACT ANALYSIS

The purpose of this section is to explicitly describe the methods and assumptions used to estimate the economic impact of added market exclusivity due to retroactive extension of the GATT patent rules to previously filed and awarded patents. Several aspects of the methodology deserve description and comment including: (1) the method for calculating added years of exclusivity, (2) the time frame of the analysis, (3) the use of 1996 net present value to express the cost to American consumers, and (4) the expected level of generic market penetration and generic pricing.

A. Added Years of Market Exclusivity

A single pharmaceutical product today may have two, three, or more patents each with different implications for the manufacturer of the product. Patents may be issued for: the chemical composition of the drug entity or intermediate chemical entities; one or more processes by which the drug can be made; the dosage form in which the drug is delivered (e.g., a sustained release tablet); or for a specific medical indication or use of the product. The drug product, Tagamet™, recently (May 1994) went off patent with respect to the principal drug entity. However, the patent holder, (Smith-Kline Beecham), has made it known that it holds at least 26 other patents related to Tagamet and that it intends to vigorously enforce them (Scrip, No. 1927, May 31, 1994, p. 16).

The economic impact of this proposed legislation is dependent not only upon how long a given patent is extended, but also upon the total extension of any and all patents that prevent the product from facing competition in the marketplace. A compilation of drug products and their related patents was found in the Food and Drug Administration's publication titled, Approved Drug Products with Therapeutic Equivalence Evaluations, 12th edition, 1995 (also known as The FDA Orange Book). This analysis has not included antibiotic and biological drug products which may also benefit from added market exclusivity. These products will be considered in a subsequent analysis.

The patents for all products identified in the FDA Orange Book were reviewed by a law firm specializing in pharmaceutical patents to determine which patents would benefit from the windfall extension of market exclusivity resulting from the PTO's proposed *delta* period implementation of the 20 year patent term. At least 109 of these drug entities, or products, were found to have patent filing dates which would result in a patent expiration after the original 17 years from date of patent award. These 109 drugs are listed in Table 1 along with their respective current patent expiration dates and the extended patent dates which would apply if the 20 year term from time of filing is used.

The added market exclusivity was then calculated by determining the amount of time between the original patent expiration date and the subsequent GATT-related extension of the patent. The unearned and unexpected extensions of market exclusivity for these prescription drugs ranges from as little as one month to more than 28 month (Table 1 and Figure 1). More than one-half of the drugs would benefit from one year, or more, of additional market exclusivity. The simple average across the 109 products is 12.0 months of windfall patent protection. Ten of the 109 drug products will lose their patent in 1995 and seven in 1996. Several products benefiting from exclusivity extension will lose their original patent each year from 1997 to the year 2008 and one product would benefit as late as the year 2011.

B. Time Frame of the Analysis

If implemented, the economic impact of this GATT-related extension of existing patents will continue to be felt through the first decade of the 21st century. Nearly one-fourth of the current prescription drug sales volume will be affected by this added market exclusivity. Since the effected drug products may have exclusivity extensions as far out as the year 2011, the time frame for assessing the economic impact of this proposed change in current patent expirations must take into account the cumulative economic impact that will occur over the next two decades. An economic impact analysis that uses a time frame of less than 17 to 20 years after the proposed change would not capture the full impact of this change and could grossly understate the cost of this change to the American government and public.

C. Net Present Value of Impact

Net present value is a means of reporting economic data over a long period of time so that dollar values are represented in comparable terms. For purposes of this analysis, an average inflation rate of 3% was assumed to be present for each year from 1996 to 2012. Over time the spending power of the dollar declines. For example, it would take about \$1.60 in 2012 to have the same spending power as \$1.00 in 1996 using this 3% inflation rate over that time period. All dollar values reported in this study, unless otherwise noted, have been converted to 1996 net present value or constant dollars.

D. Generic Market Penetration and Generic Pricing

Two primary factors determine the savings which American consumers can realize from access to generic competition among drug products. First, the penetration of generic drug products into the original marketer's unit volume must be estimated. The generic penetration can be assessed by examining the proportion of units (tablets or capsules) of a given drug product which are filled with generic versions of the drug product. The second factor is the price of generic drug products in relation to the original marketer's price over time. This determines the amount of savings realized for each unit of the original brand which is filled with a lower-cost generic.

Generic competition cannot begin until after one or more patents on the drugs chemical composition, manufacturing process, dosage form, or indications for use have expired. While generic competition cannot begin before the patent expires, it does not necessarily start immediately upon expiration. Generic versions of a patented drug may be delayed in entering the market because of other patents related to the originator drug product, difficulty in obtaining a source of raw material, administrative delays in approval by the FDA, or other factors. Although some delay in generic competition after patent expiration is not uncommon, for purposes of this study it will be assumed that generic competition begins immediately upon patent expiration. This is a conservative assumption which would tend to underestimate the cost to American consumers if generic competition is delayed for several months after patent expiration.

Recent empirical evidence related to these two critical factors, market penetration and pricing of generic products, was examined. An October 1994 market analysis of the generic drug market (Jerry I. Treppel and Edward A. Neugeboren, *Generic Drug Industry Overview*, Kidder, Peabody, October 5, 1994) evaluated the generic pricing and unit penetration of twenty-five major drug products that have gone off patent in the past few years. The analysis used data from IMS America, one of the leading sources of pharmaceutical market information used extensively by the pharmaceutical industry, to determine the dollar and unit sales volume for these products from 1989 to 1994. The results of that analysis are reported in Figure 2.

Recently off-patent drug products were found to have lost 3% of the units in the first month, 14% in the second month, and 21% by the third month after generic competition entered the market. After one year generics, averaged 45% of the unit volume and at two years generic penetration had grown to 52%. The effect of generic competition on prices was measured by examining the average price of generics in comparison to the originator product price over time. Generics entered the market at a price averaging 73% of the originator price. By the second month after generic competition, the price was typically at 67% of the originators price and at 12 months it was at 55%. After two years, the average generic was priced at only 39% of the originator's price.

III. ECONOMIC IMPACT OF GATT PATENT EXTENSION ON CURRENTLY MARKETED DRUGS

The relevant parties who stand to be significantly impacted by this proposed extension of existing patents include: individual Americans who purchase their own prescription medications; government and private insurance and benefit programs which pay for prescription medicines; multinational brand name pharmaceutical manufacturers; and independently-owned generic pharmaceutical manufacturers. This analysis has focused on the perspective of those who pay for prescription medicines either individually or collectively.

A. Cost to American Consumers of Windfall Patent Extension

The combined effect of generic unit penetration and pricing can be used to estimate the savings which can be achieved by generic competition in the market, and to estimate the cost to American consumers from the windfall extension of exclusivity for previously patented drugs. The generic unit volume penetration and pricing data, as described above, was used to estimate the savings derived from the availability of generics in the pharmaceutical market.

First, in order to estimate the value of the 109 study drugs to the American public, the 1992, 1993, and 1994 sales volume and rate of change, growth or decline, in sales for all 109 drugs known to be affected by the GATT-related exclusivity extension were obtained by a pharmaceutical firm through a proprietary pharmaceutical database. A growth curve for each of these 109 patented products was estimated based on the recent actual growth pattern of the drug; the drug product's stage in its life cycle; and the degree of competition expected from existing and future drug products. Using these growth curves the future sales of each product were estimated for the period 1995 to 2012.

The total expenditure that would have occurred, if all units sold for a given drug product were purchased at the originator price, was determined. Figure 3 shows the total originator sales revenue expected for the 109 study drugs when priced at the originator's brand name prices. These drugs, at originator prices, will result in a sales volume of nearly \$13 billion dollars in 1995 and due to declining demand over time, the total market value of these products will decline in terms of annual net present value to about \$10 billion by the year 2012. Second, a similar level of unit volume was assumed to remain, but generics were assumed to capture the proportion of units as shown in Figure 2 at the generic prices also shown in Figure 2. The resulting estimate for originator and generic sales revenue with the current patent expiration dates is shown as the lowest trend line in Figure 3.

Between 1995 and the year 2012 the total revenue from the 109 study drugs if all sales were for the originator without generic competition is estimated to about \$217 billion in 1996 net present value. With generic penetration of the unit volume and competitive generic prices versus the higher brand name price under the current patent rules, the total revenue for the 109 study drugs would be about \$169 billion.

The awarding of the unexpected windfall extension of market exclusivity to already patented drug products will delay generic entry into the market 12 months on average. If the GATT-related exclusivity periods are awarded to existing drug products, the competition from generics would be later than under the present patent expiration rules and consumer would lose the value of the access to generic competition for this one year period. The originator and generic sales revenue under the GATT extensions in exclusivity were estimated using the generic unit penetration and pricing rates described in Figure 2 with generic competition beginning at the later GATT-related expiration time. This sales revenue line is shown as the middle line in Figure 3. The 109 study drugs with delayed generic competition would generate sales revenue of \$175 billion between 1995 and 2012 in 1996 net present value. The cost to American consumers of the delay in generic competition is the difference between the drug product revenue under the GATT-related extension of existing patents (\$175 billion) and the revenue under the current patent rules (\$169 billion). In other words, the discretionary extension of GATT rules to previously patented drugs will result in a cost of more than \$6 billion to American consumers.

The annual generic savings lost by American consumers due to delayed generic entry (Figure 4) will range from \$200 million in some years to over \$500 million in other years. This variation in effect across the years studied is due primarily to variation in the number and market value of drugs which would have come off patent in each year. Ten drugs that would lose their patent in 1995 alone would be affected by this extension of market exclusivity. As many as 14 drug products would be affected in 2002 and 11 in 2006. The cost to American consumers of delayed generic entry is influenced by both the length of the delay and by the dollar value in the market of a given product. More than one-half of the cost to consumers results from six drugs (Figure 7). The top ten drugs account for two-thirds of the cost and the top fifty represent greater than 95% of the cost due to the GATT-related extension in patent life.

B. Pharmaceutical Firms Benefiting from Windfall Patent Extension

The 109 drug products studied represent at least 34 different parent firms and their related subsidiaries. The distribution of drug products and generic savings lost by pharmaceutical firms is displayed in Table 2. The number of drug products per marketing firm (Figure 5) range from a high of 10 (Roche-Syntex) to a low of one (12 companies). The distribution of dollars of added revenue from this GATT-related

windfall in market exclusivity also varies by company (Figure 6). Merck and Glaxo are expected to realize more than \$1 billion each from this proposed change. If one includes Bristol-Myers Squibb, the top three pharmaceutical firms account for more than one-half of all of the added revenues, or cost if you are a consumer.

C. Cost to Federal and State Governments of Windfall Patent Extension

American consumers will be impacted by this change, not only through the cost of medications directly purchased, but also through the cost of such medications to government-related health programs. Based on current expenditure patterns of Medicaid, Medicare, and other government programs such as the Veterans Administration and the Department of Defense, this extension of existing patents will cost federal and state governments more than \$1.25 billion over the next two decades. The greatest impact will come in the Medicaid outpatient program, which can expect costs to increase by as much as \$783 million, due to delayed generic competition for the 109 drugs studied in this report. An additional cost of \$125 million will come from higher prices due to delayed generic competition in the inpatient portion of Medicaid. The inpatient portion of Medicare will see a similar increase in costs (about \$200 million). Other federal and state programs will experience more than \$150 million in added costs due to this proposed change. These added costs from GATT-related extension of existing patents will be a cost that should be added to the Congressional budget.

D. Other Cost Considerations of GATT-Related Patent Extension

The magnitude of direct costs due to the GATT-related windfall patent extension for products which already have established expiration dates over the next fifteen to twenty years is expected to exceed \$6 billion. This estimate does not even include antibiotics and biologicals, which may be analyzed in a separate study. A number of significant antibiotic and biological products are expected to be eligible for windfall patent extensions and may contribute to further costs for American consumers due to delays in generic competition. Another cost factor not considered in this analysis is the substantial sunk cost incurred by a generic firm in preparing a product for generic marketing, only to find out that the patent has been extended several months to as much as two or three years. At a minimum, this will mean a delayed revenue stream for the generic firm. This delay, however, could result in far greater costs if part, or all, of the application to FDA for market approval has to be re-done. A third factor not assessed in this study is the effect of the new GATT patent term of 20 years on cost and total drug expenditures of the American public. The new 20-year patent term will mean that generics will be delayed and originators will have even longer exclusivity periods than they now have to market without generic competition.

IV. SUMMARY AND CONCLUSIONS

More than 100 drug products (at least 109) which are currently patented and on the market will receive a windfall patent extension if GATT rules are retrospectively applied to these previously filed or issued patents. The average patent extension for the currently marketed drugs would be more than 12 months with some drugs receiving more than 28 months of added exclusivity. The windfall extension of patent exclusivity for currently marketed drugs will mean that the introduction of lower cost generics will be delayed. Therefore, the American consumer will have to pay more for prescription medications.

Although the patent extension may have a positive effect on some sectors of the market, such as stimulation of additional pharmaceutical research and development, this change will also have some *very real costs* in terms of increased pharmaceutical expenditures by Americans. These increased pharmaceutical expenditures will be felt by individual American citizens, by hospital and community pharmacies, by managed care and health insurance plans, and certainly by the federal and state government health programs.

The projected cost to American consumers from the windfall extension of patent exclusivity for the 109 currently marketed drugs affected by this change will exceed \$6 billion (1996 net present value) over the next two decades. There are at least 10 drugs whose patents will expire in 1995. The lack of generic competitors for just three of these drugs will cost American consumers more than \$1.2 billion (1996 net present value) in 1996 and 1997. The lower price and high market penetration of generics, when available, results in substantial savings to American consumers. These savings are also of benefit to Medicaid, federal and state government, private insurers, managed care, employers, unions, ERISA plans, and others who pay for prescriptions. The cost of this windfall extension of exclusivity to Medicaid alone will be about \$1 billion (1996 net present value) and the total cost to federal and state government will exceed \$1.25 billion (1996 net present value).

Table 1. Drugs Benefiting from GATT Patent Extension by Generic Name

Generic Name	Trade Name	Marketing		Patent Expires	GATT Expires	GATT Extension (months)	Generic Savings	Generic Savings
		Firm Name	Parent Firm				Lost to GATT Ext. Period 1995-2012 (Current \$)	Lost to GATT Ext. Period 1995-2012 (1996 Const. \$)
1 alclometasone dipr.	Aclovate	Glaxo	Glaxo	Nov 07, 1995	Dec 12, 1996	13.2	\$4,717,269	\$4,587,957
2 amlodipine besylate	Norvasc	Pfizer	Pfizer	Nov 07, 2006	Mar 25, 2007	4.5	\$93,728,123	\$66,239,719
3 aminone lactate	Inocor	Winthrop	Sanofi	Jul 31, 1998	Apr 06, 1999	8.2	\$5,166,599	\$4,658,393
4 astemizole	Hismanal	Janssen	J & J	Aug 26, 1999	Apr 03, 2000	7.3	\$12,398,943	\$10,851,199
5 atovaquone	Meproin	Burr. Wellcome	Burr. Wellcome	Jan 01, 2008	Aug 15, 2009	19.5	\$6,650,974	\$4,457,012
6 benazepril HCl	Lotensin HCT	CIBA Geigy	CIBA Geigy	Oct 18, 2002	Aug 11, 2003	9.8	\$2,196,051	\$1,744,132
7 benazepril HCl	Lotensin	CIBA Geigy	CIBA Geigy	Oct 18, 2002	Aug 11, 2003	9.8	\$46,413,892	\$36,863,640
8 bexectant	Survanta	Ross	Abbott	Aug 10, 2000	Mar 04, 2002	18.8	\$36,672,902	\$30,784,796
9 bupropion HCl	Wellbutrin	Burr. Wellcome	Burr. Wellcome	Mar 26, 2002	Jul 25, 2004	28.0	\$67,690,611	\$54,139,722
10 buspirone HCl	Buspar	Bristol Myers	Bristol-Myers Squibb	Jan 08, 1999	May 21, 2000	16.4	\$161,689,253	\$141,602,241
11 butoconazole nitrate	Femstat Prefill	Syntex	Roche-Syntex	Mar 07, 1997	Jul 25, 1997	4.6	\$1,028,047	\$961,214
12 butoconazole nitrate	Femstat	Syntex	Roche-Syntex	Mar 07, 1997	Jul 25, 1997	4.6	\$511,315	\$477,750
13 calcitriol	Rocaltrol	Roche	Roche-Syntex	Sep 30, 1997	Oct 13, 1998	12.4	\$12,353,819	\$11,373,867
14 calcitriol	Calcijex	Abbott	Abbott	Dec 29, 1998	Jan 28, 2001	25.0	\$20,719,259	\$18,205,127
15 captopril	Capoten	Bristol Myers	Bristol-Myers Squibb	Aug 08, 1995	Feb 13, 1996	6.2	\$103,634,794	\$101,920,603
16 captopril/HCTZ	Capozide	Bristol Myers	Bristol-Myers Squibb	Aug 12, 1997	Dec 27, 1997	4.5	\$6,624,145	\$6,148,162
17 carbidopa	Siacmet CR	Dupont Merck	Merck / Dupont	May 23, 2006	Jun 16, 2006	0.8	\$4,357,861	\$3,118,233
18 cetyl alcohol	Exosurf	Burr. Wellcome	Burr. Wellcome	Nov 23, 2001	Aug 20, 2003	20.9	\$5,559,121	\$4,513,541
19 cholestyramine	Cholybar	Parke Davis	Warner Lambert	Oct 18, 2005	Dec 20, 2005	2.1	\$0	\$0
20 clonidine	Catapres TFS	Boehr. Ingel.	Boehr. Ingel.	Dec 17, 2002	May 04, 2003	4.5	\$17,187,147	\$13,486,262
21 dapiprazole	Rev-Eyes	Storz/Lederle	Am. Home	Jan 06, 2002	Feb 07, 2003	13.1	\$34,917	\$28,035
22 desflurane	Suprane	Ohmeda	BOC Group	Sep 18, 2006	Mar 13, 2008	17.8	\$74,846,696	\$52,461,042
23 desogestrel	Ortho-Cept 21	Ortho	J & J	Dec 10, 1995	Nov 07, 1996	10.9	\$2,426,713	\$2,331,268
24 desogestrel	Ortho-Cept 28	Ortho	J & J	Dec 10, 1995	Nov 07, 1996	10.9	\$45,018,471	\$43,252,042
25 desogestrel	Desogen	Organon	AKZO	Dec 10, 1995	Nov 07, 1996	10.9	\$29,176,028	\$28,031,223
26 dezucine	Dalgan	Wyeth Ayerst	Am. Home	Aug 12, 2003	Sep 28, 2004	13.6	\$1,125,857	\$869,640
27 diltiazem HCl	Diltacor XR	RPR	Rhone-Poulenc	Jun 13, 2006	Dec 09, 2006	5.9	\$31,188,952	\$22,211,773
28 diltiazem HCl	Cardizem CD	Marion M Dow	Marion M Dow	Feb 14, 2011	May 20, 2011	3.1	\$45,818,915	\$29,075,947
29 doxazosin	Cardura	Rorrig	Pfizer	Feb 12, 1999	Oct 18, 2000	20.2	\$94,705,904	\$82,552,494
30 enoxacin	Penetrex	RPR	Rhone-Poulenc	Nov 16, 2001	Feb 04, 2002	2.6	\$81,306	\$66,719

Table 1. Drugs Benefiting from GATT Patent Extension by Generic Name
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<u>Generic Name</u>	<u>Trade Name</u>	<u>Marketing Firm Name</u>	<u>Parent Firm</u>	<u>Patent Expires</u>	<u>GATT Expires</u>	<u>GATT Extension (months)</u>	<u>Generic Savings</u>	<u>Generic Savings</u>
							<u>Lost to GATT</u>	<u>Lost to GATT</u>
							<u>Ext. Period</u>	<u>Ext. Period</u>
							<u>1995-2012</u>	<u>1995-2012</u>
							<u>(Current \$)</u>	<u>(1996 Const. \$)</u>
31 estradiol	Estrace	Bristol Myers	Bristol-Myers Squibb	Mar 13, 2001	Mar 25, 2002	12.4	\$71,408,495	\$58,922,040
32 estradiol	Estraderm	CIBA Geigy	CIBA Geigy	Apr 12, 2000	Feb 17, 2001	10.2	\$47,440,985	\$40,307,718
33 ethinyl estradiol	Tri-Norinyl-21 WL	Syntex	Roche-Syntex	Jun 28, 2000	Aug 10, 2001	13.4	\$816,461	\$690,743
34 ethinyl estradiol	Tri-Norinyl-28 WL	Syntex	Roche-Syntex	Jun 28, 2000	Aug 10, 2001	13.4	\$10,120,430	\$8,561,430
35 ethinyl estradiol	Ortho-Cyclen-28	Ortho	J & J	May 31, 1996	Jul 24, 1997	13.8	\$19,117,776	\$18,214,698
36 ethinyl estradiol	Ortho-Cyclen-21	Ortho	J & J	May 31, 1996	Jul 24, 1997	13.8	\$864,383	\$824,754
37 famotidine	Pepcid	Merck	Merck	Aug 11, 2000	Dec 27, 2001	16.5	\$217,355,562	\$183,222,361
38 famotidine	Pepcid IV	Merck	Merck	Aug 11, 2000	Dec 27, 2001	16.5	\$20,195,095	\$17,002,771
39 febamate	Felbatol	Wallace	Carter-Wallace	Dec 18, 2007	Sep 26, 2009	21.3	\$37,546,083	\$25,264,261
40 felodipine	Plendil	Astra-Merck	Merck	Apr 28, 1998	Jun 19, 1999	13.7	\$36,358,062	\$32,670,058
41 fentanyl	Duragesic	Janssen	J & J	May 13, 2003	Jul 23, 2004	14.4	\$52,741,479	\$40,860,226
42 flecainide acetate	Tambocor	3M	3M	Jan 25, 1996	Apr 01, 1996	2.2	\$2,904,184	\$2,797,214
43 fluconazole	Diflucan	Roerig	Pfizer	Oct 16, 2003	Jul 03, 2005	20.6	\$535,990,636	\$410,485,737
44 fludarabine phosphate	Fludara	Berlex	Berlex	Nov 02, 2001	Feb 24, 2003	15.7	\$6,690,580	\$5,449,826
45 fluticasone propionate	Cutivate	Glaxo	Glaxo	Mar 16, 2002	Nov 14, 2003	20.0	\$4,013,119	\$3,211,396
46 fosinopril sodium	Monopril	Bristol Myers	Bristol-Myers Squibb	Jun 29, 2001	Dec 04, 2002	17.2	\$64,607,344	\$52,058,249
47 gabapentin	Neurontin	Parke Davis	Warner Lambert	Jan 16, 2007	May 02, 2008	15.5	\$40,545,044	\$27,988,733
48 gallium nitrate	Ganite	Fujisawa	Fujisawa	Jan 17, 2005	Apr 21, 2005	3.1	\$19,024	\$14,052
49 gancyclovir sodium	Cytovene	Syntex	Roche-Syntex	Mar 16, 2003	Oct 16, 2004	19.1	\$19,098,570	\$14,786,123
50 goserelin acetate	Zoladex	Zeneca	Zeneca	Jul 10, 1997	Apr 22, 1999	21.4	\$9,237,600	\$8,480,519
51 granisetron HCl	Kytril	SK Beecham	SK Beecham	Dec 12, 2006	Mar 16, 2008	15.1	\$36,818,916	\$25,469,561
52 histrelin acetate	Suppelin	Roberts Pharm.	Yamanouchi	Jan 13, 1998	Jun 11, 1999	16.9	\$42,882	\$38,688
53 isopamidol	Isovue-M	Bristol Myers	Bristol-Myers Squibb	Jan 04, 1996	Nov 24, 1997	22.7	\$11,246	\$10,724
54 ioversol	Optiray	Mallinckrodt	Mallinckrodt	Oct 26, 2002	Apr 05, 2004	17.3	\$263,041	\$207,878
55 ioxaglate meglumine	Hexabrix	Mallinckrodt	Mallinckrodt	Mar 29, 1996	May 20, 1997	13.7	\$141,820	\$135,069
56 isradipine	Dynacirc	Sandoz	Sandoz	Jul 09, 2008	Nov 07, 2008	4.0	\$18,925,599	\$12,694,402
57 itraconazole	Sporanox	Janssen	J & J	May 12, 1998	Jun 23, 1998	1.4	\$3,284,496	\$2,971,969
58 ketorolac	Toradol	Syntex	Roche-Syntex	May 16, 1997	Jul 14, 1998	13.9	\$135,149,753	\$125,084,993
59 labetalol HCl	Normodyne	Key	Schering-Plough	May 04, 1999	Nov 28, 1999	6.8	\$10,331,688	\$9,061,866
60 labetalol HCl	Normodyne IV	Key	Schering-Plough	May 04, 1999	Nov 28, 1999	6.8	\$264,415	\$234,252

Table 1. Drugs Benefiting from GATT Patent Extension by Generic Name
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<u>Generic Name</u>	<u>Trade Name</u>	<u>Marketing Firm Name</u>	<u>Parent Firm</u>	<u>Patent Expires</u>	<u>GATT Expires</u>	<u>GATT Extension (months)</u>	<u>Generic Savings Lost to GATT Est. Period 1995-2012 (Current \$)</u>	<u>Generic Savings Lost to GATT Est. Period 1995-2012 (1996 Const. \$)</u>
61 lomefloxacin HCl	Maxaquin	Searle	Monsanto (Searle)	May 05, 2005	Jul 14, 2007	26.3	\$12,672,084	\$9,275,827
62 loratadine	Claritin	Schering-Plough	Schering-Plough	Aug 04, 2000	Jun 19, 2002	22.5	\$519,488,499	\$436,099,410
63 lovastatin	Mevacor	Merck	Merck	Nov 04, 1999	Jun 15, 2001	19.4	\$519,850,176	\$448,172,731
64 methylphen HCl	Alkeran	Eurr. Wellcome	Eurr. Wellcome	Mar 05, 2008	Nov 18, 2008	8.5	\$4,217,129	\$2,844,669
65 mesna	Mesnex	Bristol Myers Oncolog	Bristol-Myers Squibb	Dec 02, 1999	Mar 06, 2001	15.1	\$15,225,684	\$12,957,854
66 metolazone	Mykrox	Fisons	Fisons	May 14, 2002	Apr 29, 2003	11.5	\$770,310	\$616,045
67 misoprostol	Cytotec	Searle	Monsanto (Searle)	Nov 17, 1998	Jul 29, 2000	20.4	\$19,227,278	\$17,154,843
68 mometasone furoate	Elocon, cream	Schering-Plough	Schering-Plough	Feb 28, 2006	Nov 02, 2006	8.1	\$17,754,287	\$12,671,418
69 mometasone furoate	Elocon, lotion	Schering-Plough	Schering-Plough	Oct 04, 2005	May 27, 2007	19.7	\$12,282,560	\$8,876,105
70 monoctanoin	Moctanin	Ascol	Ascol	May 27, 1997	Dec 02, 1997	6.2	\$77,775	\$71,713
71 nafarelin acetate	Synarel	Syntex	Roche-Syntex	Nov 18, 1999	Jun 11, 2001	18.8	\$4,056,107	\$3,497,595
72 nicardipine HCl	Cardene	Syntex	Roche-Syntex	Oct 12, 1995	Feb 15, 1996	4.1	\$3,639,561	\$3,577,045
73 nicardipine HCl	Cardene SR	Syntex	Roche-Syntex	Oct 12, 1995	Feb 15, 1996	4.1	\$4,323,605	\$4,238,010
74 nicardipine HCl	Cardene IV	Wyeth Aycart	Am. Home	Oct 12, 1995	Feb 15, 1996	4.1	\$216,199	\$211,685
75 nicotine	Nicotrol	Parke Davis	Warner Lambert	Apr 10, 2007	Feb 12, 2008	10.1	\$4,670,405	\$3,223,036
76 nicotine	Prostep	Lederle	Am. Home	Aug 07, 2007	Apr 29, 2008	8.7	\$2,428,923	\$1,669,239
77 nicotine	Nicoderm	Marion M Dow	Marion M Dow	Apr 02, 2008	Jun 14, 2008	2.4	\$3,961,834	\$2,698,874
78 nizatidine	Axid	Lilly	Lilly	Mar 01, 2002	Oct 02, 2002	7.1	\$104,215,617	\$83,852,688
79 norfloxacin	Noroxin	Merck	Merck	Jan 27, 2004	Jan 22, 2005	11.9	\$21,006,732	\$15,903,796
80 norfloxacin	Chibroxin	Merck	Merck	Nov 05, 2002	Nov 14, 2003	12.3	\$546,084	\$432,780
81 octreotide acetate	Sandostatin	Sandoz	Sandoz	Jul 26, 2002	Nov 21, 2002	3.9	\$6,810,215	\$5,452,621
82 ofloxacin	Floxin	Ortho	J & J	May 10, 2002	Sep 02, 2003	15.8	\$119,997,357	\$95,598,359
83 ofloxacin	Floxin IV	Ortho	J & J	May 10, 2002	Sep 02, 2003	15.8	\$17,914,786	\$14,268,741
84 omeprazole	Prilosec	Merck	Merck	Nov 22, 2005	Apr 20, 2007	16.9	\$812,192,277	\$586,890,482
85 ondansetron HCl	Zofran	Cerenex	Glaxo	Jun 28, 2005	Jun 24, 2006	11.9	\$122,788,164	\$89,402,850
86 pamidromate disodium	AreDia	CIBA Geigy	CIBA Geigy	Dec 08, 2004	Jul 29, 2005	7.7	\$13,721,782	\$10,064,372
87 paroxetine HCl	Paxil	SK Beecham	SK Beecham	Dec 29, 2006	Sep 24, 2008	20.9	\$558,898,513	\$390,689,487
88 pergolide mesylate	Permax	Lilly	Lilly	Jan 10, 2006	Oct 26, 2007	21.5	\$16,730,931	\$11,896,010
89 potassium chloride	Klotrix	Apothecoon	Bristol-Myers Squibb	Feb 20, 1996	Jun 10, 1996	3.6	\$646,598	\$623,136
90 pravastatin sodium	Pravachol	Bristol Myers	Bristol-Myers Squibb	Jan 09, 2004	Oct 20, 2005	21.4	\$372,630,963	\$272,531,323

Table 1. Drugs Benefiting from GATT Patent Extension by Generic Name
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Generic Name	Trade Name	Marketing		Patent Expires	GATT Expires	GATT Extension (months)	Generic Savings	Generic Savings
		Firm Name	Parent Firm				Lost to GATT Ext. Period 1995-2012 (Current \$)	Lost to GATT Ext. Period 1995-2012 (1996 Const. \$)
91 prednicarbate	Dermatop	Hoechst	Hoechst	Dec 30, 1999	Aug 02, 2000	7.1	\$1,021,455	\$872,347
92 propofol	Diprivan	Stuart	Zeneca	Nov 01, 1996	Mar 19, 1997	4.5	\$42,416,953	\$40,251,171
93 quinapril HCl	Accupril	Parke Davis	Warner Lambert	May 10, 2005	Feb 24, 2007	21.5	\$156,469,046	\$113,674,184
94 ranitidine HCl	Zantac, tablets	Glaxo	Glaxo	Dec 05, 1995	Jul 25, 1997	19.7	\$1,079,935,183	\$1,046,930,747
95 ranitidine HCl	Zantac IV	Glaxo	Glaxo	Apr 29, 2003	May 11, 2004	12.4	\$15,962,351	\$12,425,449
96 ranitidine HCl	Zantac, capsules	Glaxo	Glaxo	Jul 02, 2008	Feb 22, 2010	19.7	\$29,831,661	\$20,427,808
97 rocuronium bromide	Zemuron	Organon	AKZO	Jan 16, 2007	Apr 13, 2008	14.9	\$16,001,554	\$10,768,087
98 tacrine HCl	Cognex	Parke Davis	Warner Lambert	Dec 23, 2003	Oct 25, 2004	10.1	\$53,635,804	\$40,668,551
99 tecozosin HCl	Hytrin	Abbott	Abbott	Sep 05, 1995	Oct 14, 1995	1.3	\$14,439,344	\$14,215,637
100 terfenadine/pseudoephedrine	Seldane-D	Marion M Dow	Marion M Dow	Mar 03, 1998	Apr 10, 1999	13.2	\$73,673,455	\$66,435,710
101 timolol maleate (ophth.)	Timoptic-XE	Merck	Merck	Aug 29, 2006	Sep 25, 2006	0.9	\$852,117	\$606,334
102 tosseamide	Demdex	Boehr. Mannheim	Boehr. Mannheim	Apr 18, 2006	Aug 11, 2006	3.8	\$2,101,959	\$1,500,698
103 tosseamide	Demdex I.V.	Boehr. Mannheim	Boehr. Mannheim	Apr 18, 2006	Aug 11, 2006	3.8	\$50,850	\$36,305
104 trimetrexate glucuronate	Neutrexin	U.S. Bioscience	U.S. Bioscience	Mar 15, 2000	Oct 31, 2000	7.6	\$1,284,657	\$1,094,047
105 vecuronium bromide	Norcuron	Organon	AKZO	Oct 27, 1998	Aug 20, 1999	9.8	\$43,384,948	\$38,890,483
106 venlafaxine HCl	Effexor	Wyeth Ayerst	Am. Home	Aug 13, 2002	Dec 13, 2002	4.0	\$23,138,006	\$18,513,532
107 zidovudine	Retrovir	Burr. Wellcome	Burr. Wellcome	Feb 09, 2005	Sep 17, 2005	7.2	\$28,295,389	\$20,874,499
108 zidovudine	Retrovir IV INF	Burr. Wellcome	Burr. Wellcome	Feb 09, 2005	Sep 17, 2005	7.2	\$284,352	\$209,727
109 zolpidem tartrate	Ambien	Searle	Monsanto (Searle)	May 10, 2005	Oct 21, 2006	17.4	\$146,407,972	\$106,668,014
Total						12 months	\$7,378,178,144	\$6,095,262,142

SOURCE: PRIME Institute, University of Minnesota, February, 1995.

Table 2. Drugs Benefiting from GATT Patent Extension: Number of Drugs & Amount of Revenue per Marketing Firm

By Number of Drugs With GATT Extension			By Added Revenue to Marketing Firm		
Marketing Firm	# of Drugs with GATT Extension	Generic Savings Lost to GATT Extension (1996 net pres. value)	Marketing Firm	# of Drugs with GATT Extension	Generic Savings Lost to GATT Extension (1996 net pres. value)
Roche-Syntex	10	\$173,248,769	Merck	9	\$1,288,019,546
Merck	9	\$1,288,019,546	Glaxo	6	\$1,176,986,207
Bristol-Myers Squibb	9	\$646,774,333	Bristol-Myers Squibb	9	\$646,774,333
J & J	9	\$229,173,255	Pfizer	3	\$559,277,950
Glaxo	6	\$1,176,986,207	Schering-Plough	5	\$466,943,051
Burr. Wellcome	6	\$87,039,171	SK Beecham	2	\$416,159,048
Schering-Plough	5	\$466,943,051	J & J	9	\$229,173,255
Warner Lambert	5	\$185,554,505	Warner Lambert	5	\$185,554,505
Am. Home	5	\$21,292,132	Roche-Syntex	10	\$173,248,769
CIBA Geigy	4	\$88,979,862	Monsanto (Searle)	3	\$133,098,684
Pfizer	3	\$559,277,950	Marion M Dow	3	\$98,210,531
Monsanto (Searle)	3	\$133,098,684	Lilly	2	\$95,748,698
Marion M Dow	3	\$98,210,531	CIBA Geigy	4	\$88,979,862
AKZO	3	\$77,689,793	Burr. Wellcome	6	\$87,039,171
Abbott	3	\$63,205,560	AKZO	3	\$77,689,793
SK Beecham	2	\$416,159,048	Abbott	3	\$63,205,560
Lilly	2	\$95,748,698	BOC Group	1	\$52,461,042
Zeneca	2	\$48,731,690	Zeneca	2	\$48,731,690
Rhone-Poulenc	2	\$22,278,492	Carter-Wallace	1	\$25,264,261
Sandoz	2	\$18,147,023	Rhone-Poulenc	2	\$22,278,492
Boehr. Mannheim	2	\$1,537,002	Am. Home	5	\$21,292,132
Mallinckrodt	2	\$342,947	Sandoz	2	\$18,147,023
BOC Group	1	\$52,461,042	Boehr. Ingel.	1	\$13,486,262
Carter-Wallace	1	\$25,264,261	Berlex	1	\$5,449,826
Boehr. Ingel.	1	\$13,486,262	Sanofi	1	\$4,658,393
Berlex	1	\$5,449,826	3M	1	\$2,797,214
Sanofi	1	\$4,658,393	Boehr. Mannheim	2	\$1,537,002
3M	1	\$2,797,214	U.S. Bioscience	1	\$1,094,047
U.S. Bioscience	1	\$1,094,047	Hoechst	1	\$872,347
Hoechst	1	\$872,347	Fisons	1	\$616,045
Fisons	1	\$616,045	Mallinckrodt	2	\$342,947
Ascot	1	\$71,713	Ascot	1	\$71,713
Yamanouchi	1	\$38,688	Yamanouchi	1	\$38,688
Fujisawa	1	\$14,052	Fujisawa	1	\$14,052
Total	109	\$6,095,262,142	Total	109	\$6,095,262,142

**Table 3. Generic Savings Lost by Americans Due to GATT Extension of Existing Patents:
Dollars in 1996 Net Present Value 1995-2012***

	Orig. Sales w/o Generic Competition	Generic Savings w/ Current Patent Rules	Originator & Generic Sales w/ Curr. Patent Rules	Generic Savings After GATT Ext. Period	Originator & Generic Sales After GATT Ext. Period	Generic Savings Lost to GATT Ext. Period
1995	\$12,805,448,328	\$21,250,458	\$12,784,197,870	\$3,295,975	\$12,802,152,354	\$17,954,483
1996	\$13,286,663,585	\$467,689,680	\$12,818,973,905	\$117,303,771	\$13,169,359,814	\$350,385,909
1997	\$13,464,093,286	\$899,754,991	\$12,564,338,295	\$351,810,276	\$13,112,283,010	\$547,944,715
1998	\$13,426,325,249	\$1,294,902,444	\$12,131,422,805	\$833,973,937	\$12,592,351,312	\$460,928,507
1999	\$13,273,395,267	\$1,549,507,971	\$11,723,887,296	\$1,363,612,017	\$11,909,783,250	\$185,895,954
2000	\$13,064,691,141	\$1,809,459,915	\$11,255,231,226	\$1,472,509,477	\$11,592,181,664	\$336,950,438
2001	\$12,830,397,677	\$2,150,132,940	\$10,680,264,738	\$1,614,019,185	\$11,216,378,492	\$536,113,754
2002	\$12,584,611,829	\$2,424,789,801	\$10,159,822,027	\$1,884,987,707	\$10,699,624,122	\$539,802,094
2003	\$12,336,194,596	\$2,674,283,600	\$9,661,910,996	\$2,317,062,512	\$10,019,132,084	\$357,221,087
2004	\$12,085,647,968	\$2,870,295,338	\$9,215,352,630	\$2,599,600,824	\$9,486,047,144	\$270,694,514
2005	\$11,837,377,765	\$3,047,874,976	\$8,789,502,789	\$2,674,257,137	\$9,163,120,628	\$373,617,840
2006	\$11,587,402,880	\$3,430,565,469	\$8,156,837,411	\$2,871,816,336	\$8,715,586,544	\$558,749,133
2007	\$11,340,674,309	\$3,840,742,208	\$7,499,932,101	\$3,252,853,340	\$8,087,820,969	\$587,888,868
2008	\$11,091,277,690	\$4,171,808,323	\$6,919,469,367	\$3,577,921,292	\$7,513,356,398	\$593,887,031
2009	\$10,846,660,983	\$4,286,131,023	\$6,560,529,960	\$4,072,218,904	\$6,774,442,079	\$213,912,119
2010	\$10,599,460,860	\$4,272,868,925	\$6,326,591,936	\$4,241,882,194	\$6,357,578,666	\$30,986,731
2011	\$10,360,641,461	\$4,230,202,964	\$6,130,438,497	\$4,198,989,708	\$6,161,651,754	\$31,213,256
2012	\$10,120,795,127	\$4,342,741,832	\$5,778,053,295	\$4,331,626,125	\$5,789,169,002	\$11,115,707
1995-2012	\$216,941,760,002	\$47,785,002,859	\$169,156,757,142	\$41,779,740,717	\$175,162,019,284	\$6,005,262,142

* All dollar amounts are expressed in 1996 net present value dollars.

SOURCE: PRIME Institute, University of Minnesota, February, 1995.

**Table 4. Generic Savings Lost by Americans Due to GATT Extension of Existing Patents:
Current Dollars 1995-2012***

	Orig. Sales w/o Generic Competition	Generic Savings w/ Current Patent Rules	Originator & Generic Sales w/ Curr. Patent Rules	Generic Savings After GATT Ext. Period	Originator & Generic Sales After GATT Ext. Period	Generic Savings Lost to GATT Ext. Period
1995	\$12,372,413,844	\$20,531,844	\$12,351,882,000	\$3,184,517	\$12,369,229,327	\$17,347,327
1996	\$13,286,663,585	\$467,689,680	\$12,818,973,905	\$117,303,771	\$13,169,359,814	\$350,385,909
1997	\$13,868,016,084	\$926,747,641	\$12,941,268,444	\$362,364,584	\$13,505,651,500	\$564,383,057
1998	\$14,243,988,456	\$1,373,762,003	\$12,870,226,453	\$884,762,950	\$13,359,225,506	\$488,999,053
1999	\$14,504,197,390	\$1,693,189,197	\$12,811,008,193	\$1,490,055,669	\$13,014,141,721	\$203,133,528
2000	\$14,704,424,979	\$2,036,563,075	\$12,667,861,904	\$1,657,322,389	\$13,047,102,590	\$379,240,686
2001	\$14,873,947,390	\$2,492,593,373	\$12,381,354,017	\$1,871,090,597	\$13,002,856,793	\$621,502,776
2002	\$15,026,684,655	\$2,895,325,831	\$12,131,358,824	\$2,250,773,901	\$12,775,910,754	\$644,551,930
2003	\$15,171,963,333	\$3,289,031,508	\$11,842,931,825	\$2,849,694,628	\$12,322,268,704	\$439,336,880
2004	\$15,309,737,260	\$3,636,004,259	\$11,673,733,001	\$3,293,096,547	\$12,016,640,713	\$342,907,712
2005	\$15,445,093,075	\$3,976,785,537	\$11,468,307,538	\$3,489,298,999	\$11,955,794,076	\$487,486,538
2006	\$15,572,500,525	\$4,610,393,125	\$10,962,107,400	\$3,859,481,013	\$11,713,019,512	\$750,912,112
2007	\$15,698,145,495	\$5,316,485,453	\$10,381,660,042	\$4,502,709,770	\$11,195,435,725	\$813,775,683
2008	\$15,813,509,916	\$5,948,001,134	\$9,865,508,781	\$5,101,260,234	\$10,712,249,682	\$846,740,900
2009	\$15,928,687,332	\$6,294,327,908	\$9,634,359,425	\$5,980,190,749	\$9,948,496,583	\$314,137,159
2010	\$16,032,635,587	\$6,463,097,632	\$9,569,537,955	\$6,416,227,421	\$9,616,408,166	\$46,870,211
2011	\$16,141,541,812	\$6,590,518,384	\$9,551,023,428	\$6,541,889,147	\$9,599,652,665	\$48,629,236
2012	\$16,240,905,109	\$6,968,825,782	\$9,272,079,327	\$6,950,988,334	\$9,289,916,775	\$17,837,447
1995-2012	\$270,235,055,826	\$64,999,873,364	\$205,235,182,462	\$57,621,695,220	\$212,613,360,606	\$7,378,178,144

* All dollar amounts are expressed in current year dollars for each year reported.

SOURCE: PRIME Institute, University of Minnesota, February, 1995.

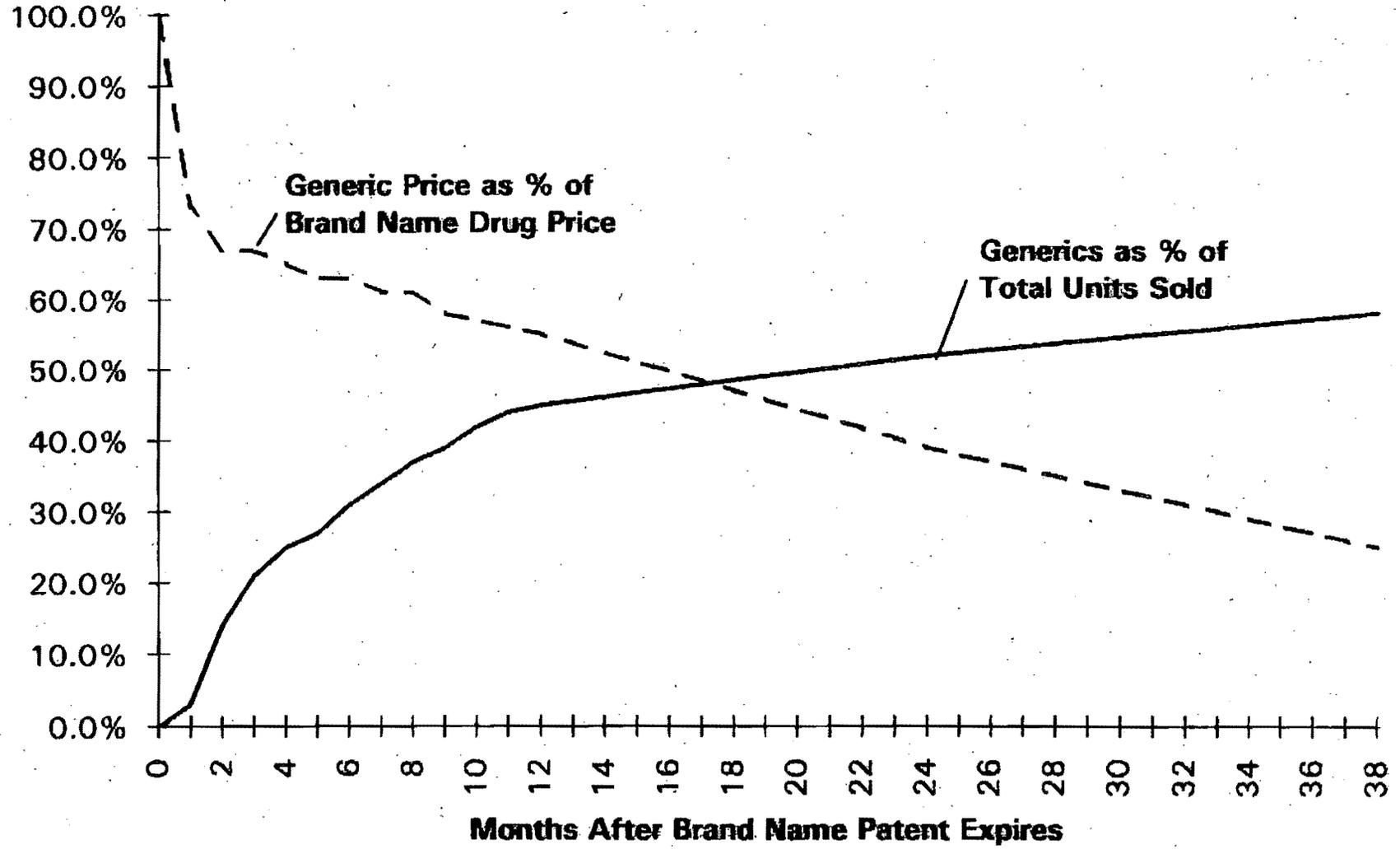
Table 5. Cost to Federal & State Governments Due to GATT Extension of Existing Drug Patents: 1995-2012*

	Generic Savings Lost to GATT Ext. Period (1996 net pres. value \$)
Medicaid Outpatient	\$783,103,239
Medicaid Inpatient	\$125,531,821
Medicare Inpatient	\$199,281,766
Other Federal & State Govt.	\$154,229,429
<hr/>	
Total Federal & State Govt.	\$1,262,146,255

* All dollar amounts are expressed in 1996 net present value dollars.

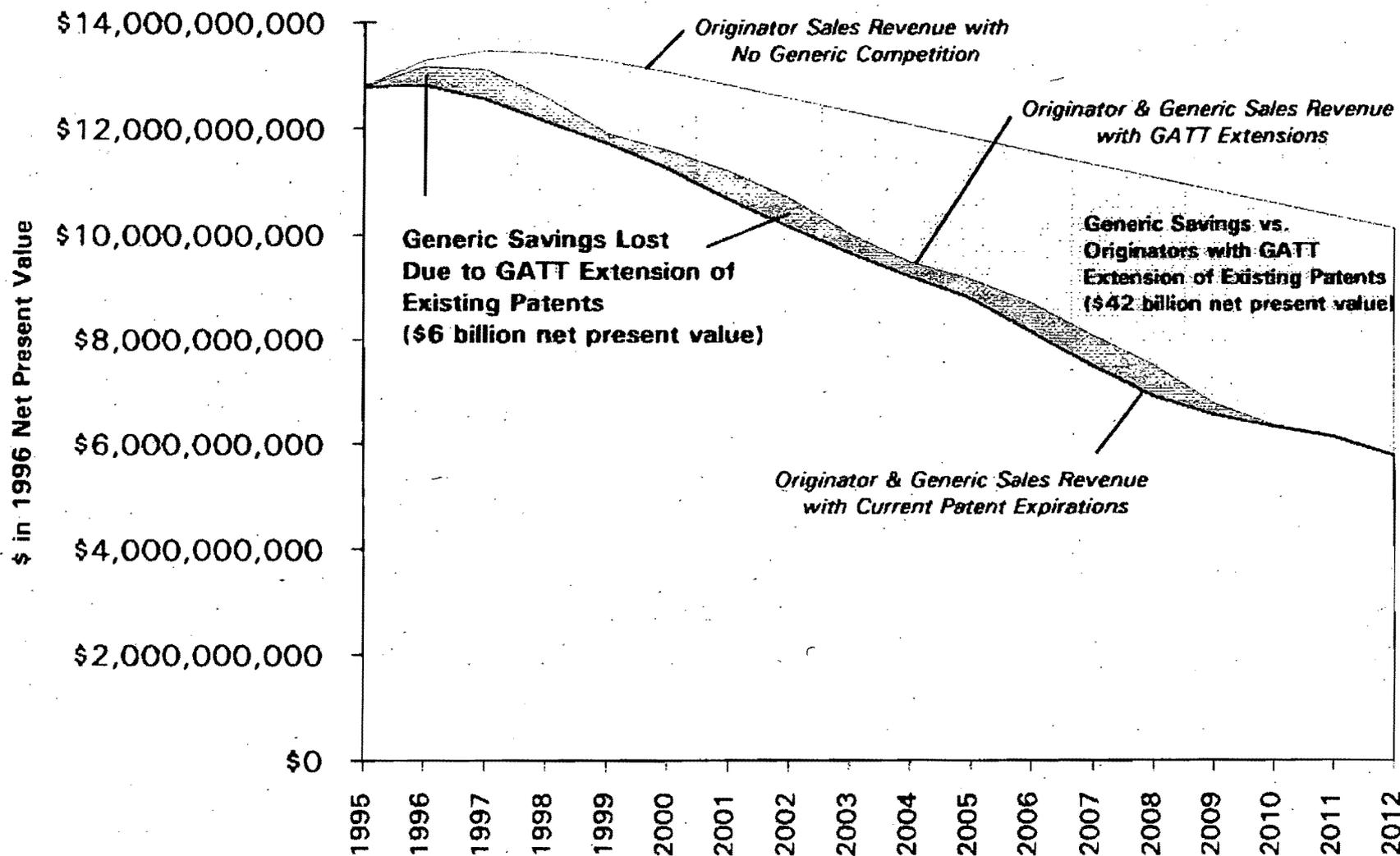
SOURCE: U.S. resident population from Statistical Abstracts of the United States, 1994, p. 24.

Figure 2. Generic Penetration of Brand Name Market by Units Sold and Price per Unit



SOURCE: Compiled by the PRIME Institute, University of Minnesota from data found in Generic Drug Industry Overview, Kidder, Peabody, Oct. 5, 1994

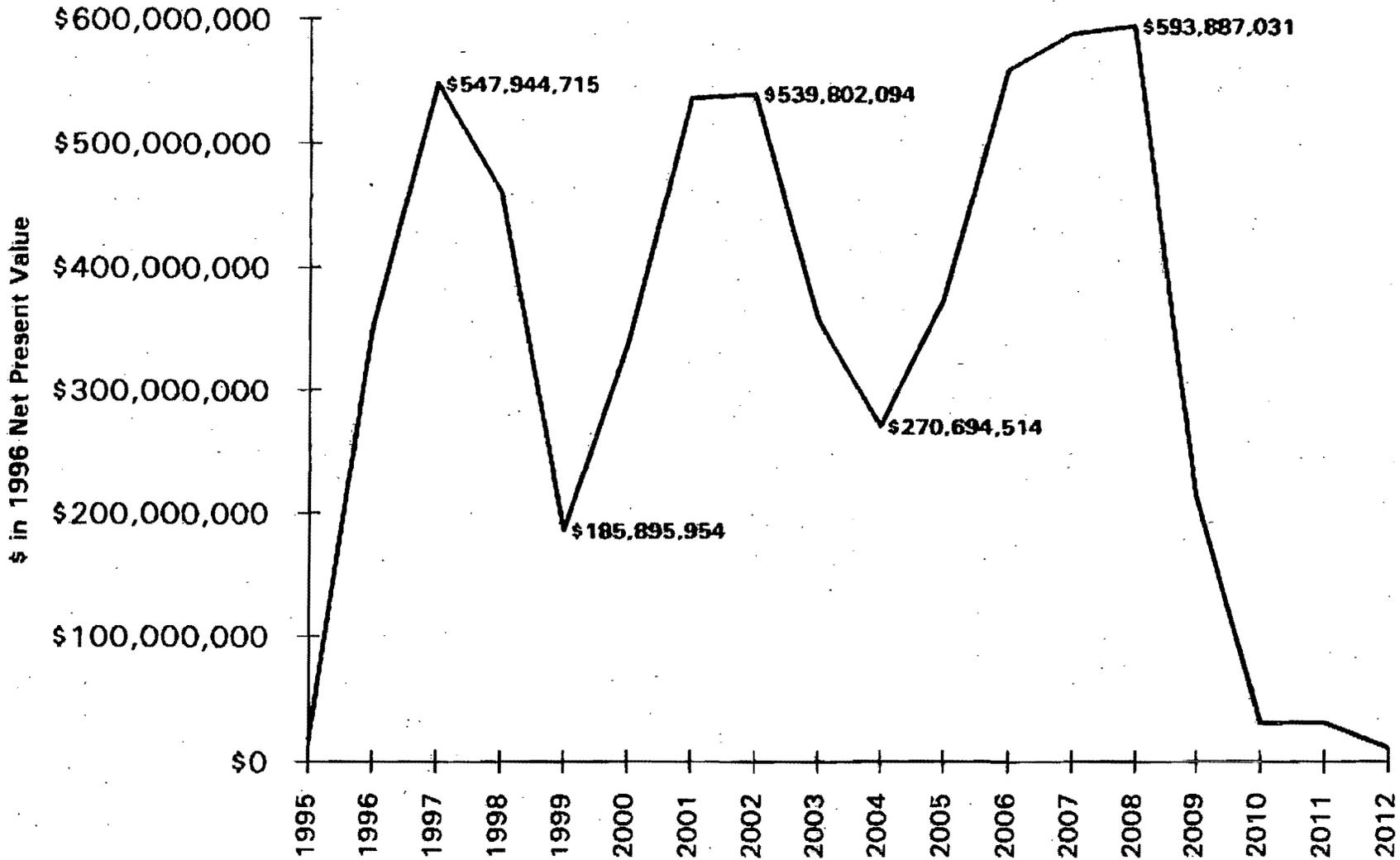
Figure 3. Generic Savings Lost by Americans Due to GATT Extension of Existing Patents: 1995-2012



SOURCE: PRIME Institute, University of Minnesota, February 1995

GATTFS3A.XLC:2 3/22/05

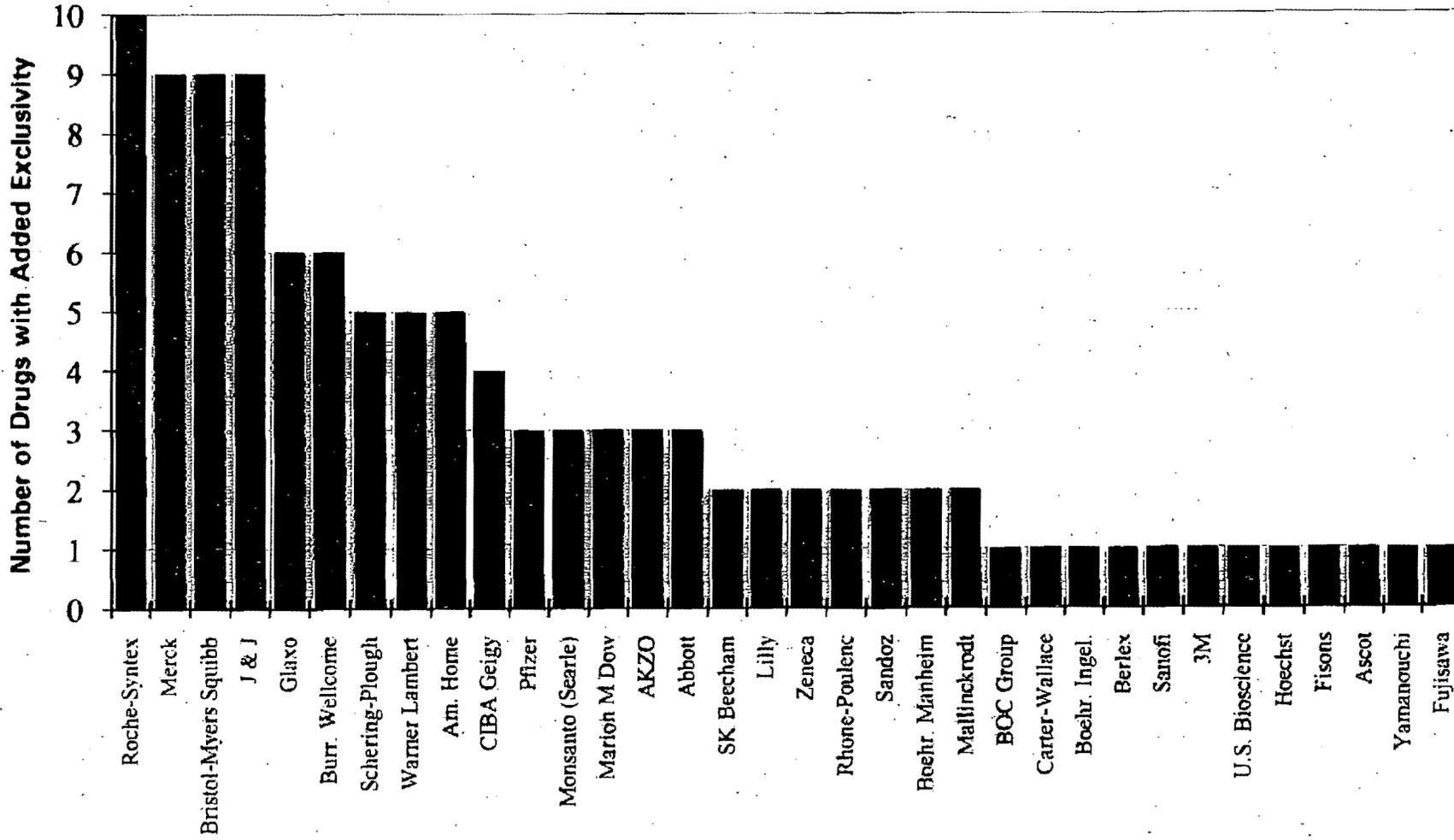
Figure 4. Generic Savings Lost by Americans Due to GATT Extension of Existing Patents: 1995-2012



SOURCE: PRIME Institute, University of Minnesota, February 1995

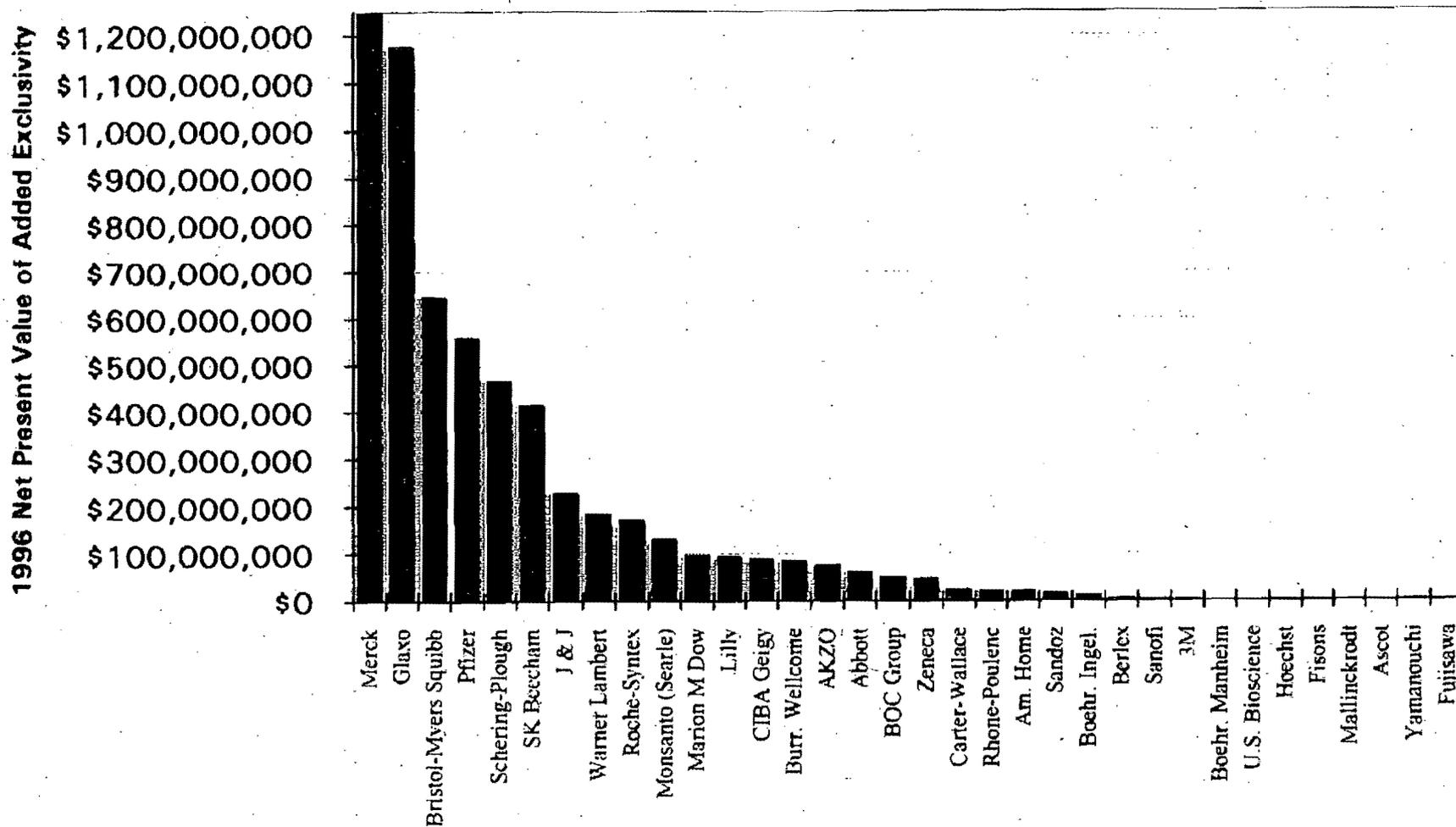
GATT4.XLC-1 3/22/95

**Figure 5. Pharmaceutical Firms Benefiting from
GATT Patent Extension
by Number of Drugs with Added Exclusivity**



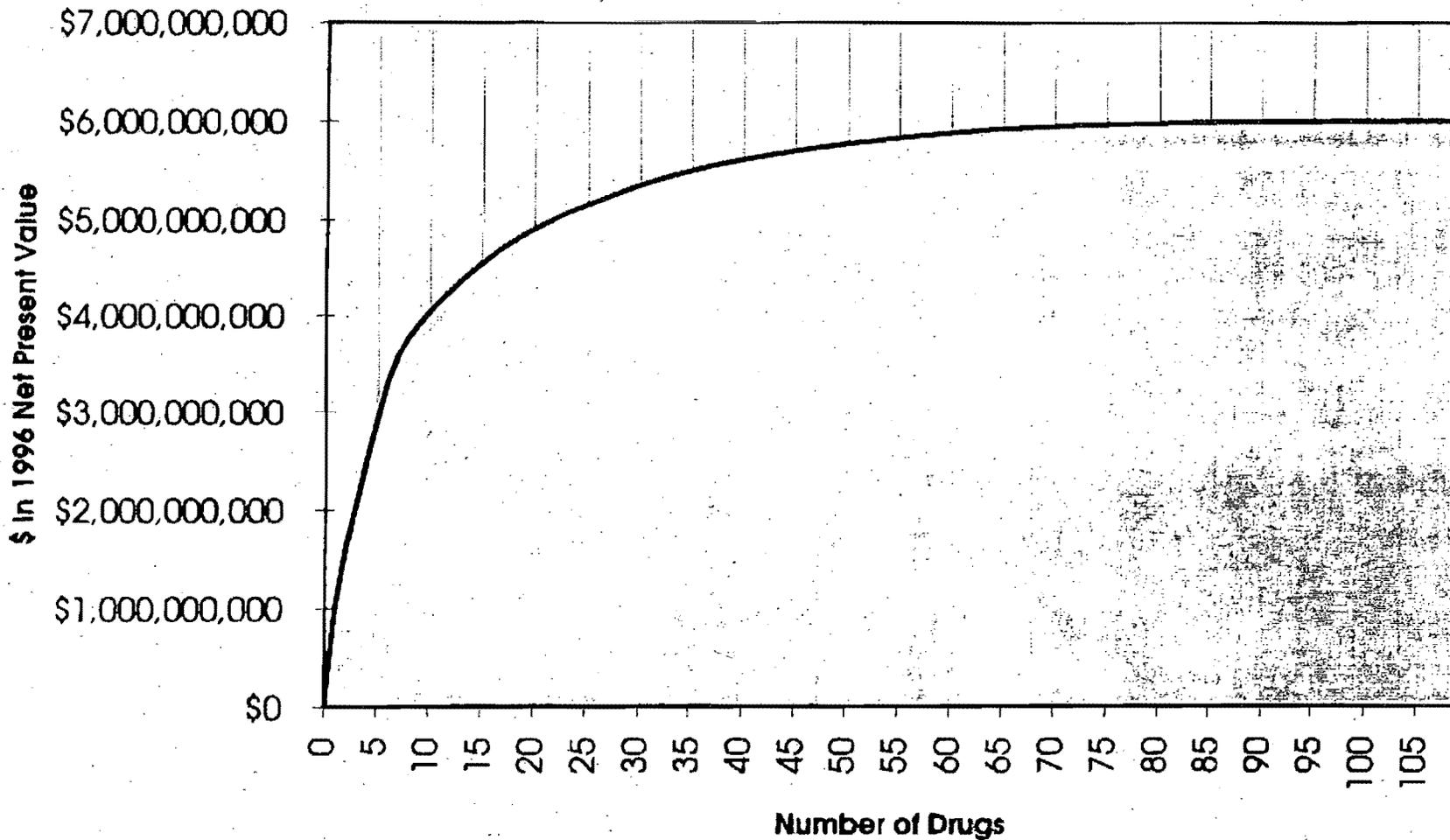
Source: Compiled by the PRIME Institute, University of Minnesota, February 1995.

Figure 6. Pharmaceutical Firms Benefiting from Patent Extension Due to GATT by 1996 Net Present Value of Benefit



SOURCE: Compiled by the PRIME Institute, University of Minnesota, February 1995

Figure 7. Cumulative Amount of Added Revenue to Marketing Firms Due to Drugs Benefiting from GATT Patent Extension



SOURCE: PRIME Institute, University of Minnesota, February, 1995

GATF7.JLC-3/21/95

DRAFT -- 3/30/95

**REINVENTING
REGULATION OF DRUGS
AND MEDICAL DEVICES**

National Performance Review

April, 1995

OVERVIEW

"Today, Americans don't have to worry about safety or effectiveness when they buy [drugs and medical devices]--from cough syrups to the latest antibiotics or pacemakers. The Food and Drug Administration has made American drugs and medical devices the envy of the world and in demand all over the world. And we should never forget that, either. And we are going to stick with the standards we have--the highest in the world. But strong standards need not mean business as usual in every area."

President Clinton, March 16, 1995

Introduction

Reforming the Federal government's regulatory processes, while maintaining critical public health and safety standards, has been and will continue to be a top priority for the Clinton Administration. Consistent with this commitment, President Clinton and Vice-President Gore asked Health and Human Services Secretary Donna Shalala to help them carefully examine FDA's regulatory requirements.

As part of the Vice-President's reinventing government initiative, the FDA has been reviewing its regulatory processes to determine which requirements could be reduced or eliminated without lowering health and safety standards. This report contains recommendations resulting from the initial phase of that review.

Background

The Food and Drug Administration is the Agency within the Department of Health and Human Services charged with ensuring that drugs, vaccines, and medical devices are safe and effective and that foods meet basic safety standards. In carrying out these and other responsibilities, FDA oversees more than \$1 trillion worth of products, which account for 25 cents of every dollar spent annually by American consumers.

FDA was created in 1906 to protect Americans from unsafe foods and drugs. In 1976, FDA's responsibilities were expanded to include medical devices. During this Administration, FDA has taken significant initial steps to streamline the regulatory process. These recent initiatives have resulted in new products being brought to market sooner; but more can be done.

A Record of Accomplishment

FDA's recent regulatory improvements include:

o Shortening Review Times for New Drugs and Devices

- 1) FDA now uses expert review panels to expedite the review of certain biotechnology products (for example, a joint committee of FDA experts oversaw the licensing in record time of the drug interferon beta 1b to treat certain patients with multiple sclerosis).
- 2) Under the Prescription Drug User Fee Act of 1992, drugs are now reviewed more quickly. This law authorizes FDA to charge user fees for drug applications, and to use these additional resources for the reviews of new drugs, vaccines, and biotechnology products.

Already, review times for new chemical drugs have dropped from an average of 30 months in 1992 to 20 months in 1994.¹ By 1997, FDA will be getting these products to market in a year or less, as fast or faster than anywhere else in the world, with no sacrifice in review quality. [APPROVAL CHART]

- 3) Medical devices are benefiting from a number of new processes that speed up their review; for example, devices that provide significant medical advances are now given priority review.
- 4) Animal drugs are now reviewed in a more efficient manner that resulted in a record number of 38 new drugs approved in 1994.

o Eliminating Unnecessary Regulatory Burden

- 1) The FDA exempted 148 categories of low risk medical devices from premarket review in December 1994, relieving manufacturers from submitting applications to the Agency and waiting for their approval.

¹ The 1994 median review time for all new chemical drugs was 17.5 months; (the subset of drugs reviewed in 1994 under the user fee program were reviewed in a median time of 13.5 months).

- 2) The FDA has helped to assure safe and high quality mammography by using existing private sector standards to certify mammography facilities, which are mostly small businesses. Utilizing these standards allowed the FDA to implement the requirements of the 1992 law that all of these facilities be accredited and certified.
- 3) FDA has begun a joint program with the Customs Service to automate the entry of imported products into the U.S. The program allows an importer to notify FDA by computer of import entries and receive prompt permission to enter this country.
- 4) FDA has issued a proposed regulation to permit regulated companies to use electronic records and signatures in place of paper. This will save industry substantial costs by simplifying record-keeping and speeding the filing of applications and other regulatory documents.

As noted in the President's State of the Union address and his recent announcement highlighting some of the recommendations in this report, this Administration is committed to promoting results and not rules. The reforms this report advocates will reduce paperwork and eliminate unnecessary regulation. In so doing, they will strengthen the economy while maintaining health and safety.

Principles for Reforming FDA Regulation in Carrying out this Review

In carrying out its regulatory review, the Agency carefully considered the financial burdens that its requirements impose on industry and consumers and looked for ways to allocate or eliminate these burdens. In reforming its procedures and requirements, FDA followed these principles:

- o Using performance standards, rather than command and control regulations, whenever possible;
- o Expediting product review, without sacrificing the health and safety of the public;
- o Eliminating unnecessary requirements that may have been appropriate once but are not now necessary to public health; and
- o Utilizing modern automated technology as a tool in streamlining internal Agency management and as an aid to industry in meeting their regulatory requirements.

Regulatory Reform Recommendations

FDA is proposing a number of reforms that reinvent how FDA regulates. The reforms included in this report are estimated to save the drug and device industries \$500 million per year in unnecessary regulatory costs. These reforms will also let FDA better target its resources.

- o **Reducing or eliminating** many of the FDA requirements for companies to get approval for changes in their manufacturing facilities or processes for manufacturing drugs, biotech drugs, and other biologics;
- o **Allowing manufacturers of biological drugs to get licenses for pilot facilities** instead of making them build full-scale plants. Manufacturers will still have to show they can meet safety, purity, and potency standards;
- o **Permitting greater flexibility** in the appearance of distributors' names on biological product containers, package labels, and labeling;
- o **Eliminating** outdated requirements for insulin and antibiotics and allowing a private standard-setting body to establish testing and quality standards (thus 600 pages of Federal regulations will be eliminated);
- o **Excluding** drug and biologic manufacturers from requirements for most environmental assessments, which currently cost tens of thousands of dollars each time a new product is developed and provide no real benefit to the environment;
- o **Exempting** nearly 125 additional categories of low-risk medical devices from premarket review;
- o **Eliminating the "Reference List"** by clarifying that market clearances of low-risk devices will not be withheld unless FDA finds a reasonable relationship between the nature of current violations and the application under review;
- o **Developing a pilot program** for review of low-risk medical devices by outside review organizations to determine if such a system could be developed permanently;
- o **Speeding the marketing** of medical devices by seeking authority to charge industry user fees for device reviews, and committing FDA to meet certain strict performance goals;
- o **Expanding opportunities to export** drugs and medical devices to industrialized countries;

- o **Issuing a public statement clarifying how FDA determines the effectiveness of new drugs and devices;**
- o **Harmonizing FDA's drug and device approval requirements with those of other countries, thus expediting worldwide marketing of new products by reducing duplicative testing;**
- o **Expanding and standardizing the use of new information technologies for review of new products and to speed up import entries.**

Additional proposals for reforming the regulation of drugs and medical devices are being developed and will be announced in a later report. They will accompany recommendations related to the regulation of foods and veterinary products.

FDA'S PROPOSALS FOR REFORM

Drugs

New drugs must be approved by FDA prior to marketing. Under the provisions of the Federal Food, Drug and Cosmetic Act, they are tested first in animals, then in humans, and the data are submitted to FDA scientists for review via a New Drug Application.

Biologics include vaccines, blood products, and drugs made using biotechnology. They are licensed under a different legal authority than drugs, and are therefore subject to somewhat different requirements. Before marketing a new biological product, the sponsor must submit for FDA's approval a Product License Application, which presents safety and efficacy data. The facility making the product must submit an Establishment License Application demonstrating that the product can be accurately and safely manufactured.

Although full marketing of drugs must await FDA review and approval, in recent years the Agency has established ways for patients to gain early access to treatments for life-threatening diseases.

FDA also approves such changes as substituting different ingredients by reviewing a "supplement" to the original application for approval.

This section of the report describes reforms in the regulation of biologics and drugs. The reforms include: permitting biologics manufacturers to demonstrate their capability to make the product without first building a full-scale production plant; changing biologics labeling requirements to remove an impediment to flexible manufacturing, packaging and distribution arrangements; allowing manufacturing changes for both drugs and biologics to be made with less FDA prior approval; eliminating certain manufacturing requirements concerning antibiotics and insulin; and eliminating nearly all environmental impact statements for both biologics and drugs.

New Policy to Permit Use of Small-Scale and Pilot Facilities During Development of Biologics

Background: Lack of clarity about establishment licensure requirements has led some biologics manufacturers to make major capital investments in full-scale manufacturing facilities before initiating the large clinical trials necessary to demonstrate the safety and efficacy of their products. Such investments can result in significant financial losses if the product is not ultimately brought to market.

Proposal and Justification: *FDA will specifically state that manufacturers may use pilot and small-scale facilities to demonstrate safety and effectiveness and to support approval.* Under this reform, companies may immediately submit applications for clinical studies or approval of products manufactured in small-scale or pilot facilities.

Although the manufacture of biologics warrants a high degree of quality control and regulatory oversight, FDA believes that licensure of pilot and small-scale facilities provides industry with the flexibility it needs without diminishing public health protection. As a result, FDA will issue product and establishment licenses on the basis of demonstrated safety, purity, and potency of the product manufactured in the pilot or small-scale facility. Moving to a full-scale facility will require only a supplement to the manufacturer's product/establishment license applications.

Impact: Of 1,500 active and pending investigational new drug applications (INDs) (the manufacturer's application to begin testing a drug product in humans) for biologics, 100-500 current applicants need to decide whether to construct new facilities. Under this reform, a significant number of these companies may choose not to construct a new full-scale manufacturing facility. Instead, they may decide to use a pilot or small-scale facility, with potentially great cost savings. It has been estimated to cost \$25 million to construct a biologics manufacturing facility, and about \$15 million a year to operate.

Implementation and Timeline: Companies may apply immediately for licensure of small-scale and pilot facilities and their applications will be considered. FDA will issue a guidance document to clarify its policy on licensing small-scale and pilot facilities within the next three months.

Revision of Labeling Requirements for Biological Products

Background: Companies that develop a product sometimes find it advantageous to have their product manufactured by another company. Many small start-up companies, such as many biotechnology firms, prefer this option because they do not always have the manufacturing capabilities necessary to produce commercial quantities of a drug. However, FDA's current labeling regulations are a disincentive to such arrangements: the manufacturer's name must be displayed on the label more prominently than that of the developer's (which can be listed only as a selling agent or distributor).

Proposal and Justification: *FDA will allow the distributors' and selling agents' names to be displayed prominently on biological-product containers, package labels, and labeling.* This change will provide the biological products industry with the flexibility that it wants, and at the same time, maintain current label information on product manufacture and origin.

Impact: The change in labeling requirements will allow prominent display of the name of the distributor or selling agent, thereby removing an impediment to flexible manufacturing, packaging and distribution arrangements.

Implementation and Timeline: FDA will publish a proposal to revise its biologics labeling regulations within six months.

Drugs and Biologics: Eliminating Many Requirements for FDA Approval of Manufacturing Changes

Background: FDA regulations governing drugs and biologics require applicants to obtain FDA approval before implementing many manufacturing changes for those products. To obtain approval, manufacturers submit "supplemental" applications to FDA, of which the Agency receives several hundred each year. These changes range from the addition or subtraction of an ingredient, to using a different production facility or different equipment within the same facility, to changes in packaging or labeling. Manufacturers must often wait six to twelve months to receive FDA approval, during which time the manufacturer is prevented from making changes to the product or production facility that they believe are more efficient or otherwise necessary.

Proposal and Justification: *FDA will reduce the number of changes that require pre-approval.* Described below are the procedures for accomplishing this new policy for drugs and biologics.

DRUGS

FDA's Center for Drug Evaluation and Research (CDER), the Agency component responsible for oversight of human drug products, is developing a guidance for drugs in tablet and capsule form (other than those for controlled release). This document, designed to ease pre-approval requirements for certain manufacturing changes, would distinguish changes that are unlikely to have any detectable impact on a drug product's quality and performance from those that could have a significant impact. Examples of changes unlikely to have an impact include the deletion of a color from a product or changes from non-automated or non-mechanical equipment to automated or mechanical equipment for moving ingredients. The proposed FDA guidance would ease the pre-approval requirements for these and other manufacturing changes when the proposed manufacturing change does not affect the drug's quality or performance.

In all instances in which prior approval would no longer be required, FDA would still receive notification of the manufacturing changes from the drug manufacturer, either when the change takes effect or through annual reports on the drug application.

BIOLOGICS

The Agency will create a reporting process tailored to the severity and complexity of the change. Less stringent reporting requirements will apply when the changes do not pose demonstrable effects on product purity, potency or safety -- or when changes are readily amenable to on-site scrutiny during routine inspection of the production facility. FDA will

classify its oversight of manufacturing changes for biologics as follows:

Category I: Changes where no supplement submission will be required. The sponsor will generate and retain all relevant data defining (and validating, if necessary) changes being made. The firm may voluntarily notify the Agency of the changes and date of implementation.

Examples: Changes in the supplier of components (such as stoppers, vials, seals) that meet established specifications; changes which tighten existing specifications to provide greater assurance of product purity and potency; relocation of equipment in appropriate areas within approved facilities.

Category II: Changes for which the sponsor submits a standard supplement; unless the Agency objects, the sponsor can automatically implement the change in 30 days.

Examples: Expansion of existing manufacturing support systems (such as heating, ventilation, and air conditioning); modification of an approved manufacturing area which does not adversely affect safety, purity, or potency of product (such as adding new interior partitions or walls to increase control over the environment or replacing or adding new surfaces to enhance cleaning); replacement of equipment with that of similar but not identical design and operating principle that does not change the manufacturing process.

Category III: Changes requiring Agency approval prior to implementation.

Example: Change in processing conditions (such as process time, process temperature, or filtration process); change in dosage form (such as a change from a liquid to a powder); extension of dating period; use of a previously unapproved manufacturing area or facility.

Impact: These changes will benefit industry by: (1) saving resources that would have been spent on preparing supplemental applications; (2) permitting changes to occur without waiting for prior FDA approval; and (3) encouraging certain manufacturing improvements. Under the new procedures, the manufacturing site changes described above for drugs could be carried out--and the new site could begin operating--in a matter of weeks, and with significant cost savings. And the new policy will permit a manufacturer to change automated equipment without prior FDA approval, an improvement that will make newer facilities and equipment available to manufacturers much more quickly. Similar changes for biologics manufacturers will speed their ability to change production facilities or make other manufacturing improvements.

FDA will also benefit from these changes. The Agency estimates that this reform will eliminate its current review of more than 800 supplemental applications for drug and 500 for biologics annually. [For biologics, approximately 25 percent of supplemental applications (250) will fall into Category I, 25 percent will fall into Category II, and 50 percent will fall into Category III.]

Implementation and Timeline: For drugs, FDA will issue a guidance for most products sold in tablet form by the end of the year that will describe how these requirements will be relaxed. By the end of 1996, FDA will extend this guidance to other dosage forms, including controlled release drugs, liquids, and semi-solids.

For biologics, FDA will immediately issue a guidance document to implement the new three-category plan. The document will identify the types of changes in manufacturing procedures and establishments that may be carried out without prior approval. This guidance document will clarify which changes will not require a supplement. Within nine months, in a second step, FDA will propose amending its regulations to reduce further the instances requiring an FDA approval before products may be marketed. In an examination analogous to this for manufacturing changes, the Agency will also be reviewing its policy toward lot release of some biologics (i.e., a procedure whereby the Agency approves each batch of biologics prior to distribution), to determine how those requirements can be relaxed as well.

Antibiotic and Insulin Standards and Insulin Certification

Background: Section 506 of the Federal Food, Drug, and Cosmetic Act requires FDA to certify individual batches of drugs containing insulin as meeting standards of identity, strength, quality, and purity that are described by FDA regulations.

Section 507 of the Act imposes similar requirements for antibiotic drugs. The regulatory specifications for antibiotic drug products occupy more than 600 pages in the Code of Federal Regulations.

Antibiotics and insulin are subject to more stringent requirements than those applied to other drug products. For example, section 505 of the Act, which applies to most human drugs does not require FDA to certify individual batches of drug products or to issue product specifications prescribed in regulations. Moreover, in some cases, the insulin and antibiotic regulations known as "monographs" are outdated, reflect old technology or methodology, prescribe standards for products that are no longer marketed, or conflict with the standards found in the United States Pharmacopeia (USP). The USP, a compendium of standards of strength, quality, and purity for drug products, is published by the United States Pharmacopeial Convention, a private entity. Because the FDA can change its standards for insulin and antibiotic products only by regulation, the USP standards are often more up to date. The existence of conflicting standards can be confusing to the industry and to FDA staff who must determine whether a particular product meets the correct specifications.

Proposal and Justification: *FDA proposes to support the repeal of the certification requirement for insulin.* Congress enacted this statutory requirement decades ago, when insulin products were new and manufacturing and testing technology was rudimentary. Since then, the Agency and industry alike have become much more sophisticated and experienced with insulin manufacturing, so that certifying each batch of insulin is no longer necessary. Moreover, only two firms currently market insulin in the United States, and in the past 8 years, FDA has found no failures in more than 500 batches of insulin that it tested for certification purposes.

FDA also proposes to support the repeal of the statutory requirements for the FDA monographs that are now issued for insulin and antibiotics. In the 1940's, when Congress enacted those sections of the Federal Food, Drug and Cosmetic Act, detailed regulations setting forth standards and tests were thought to be necessary to ensure the quality and the safety of these products. At that time, Congress also expressly recognized, at least with respect to antibiotics, that a time would come when manufacturing technology would overcome the need for certification of such detailed regulation.

FDA also supports the repeal of the statutory provisions which allow for the certification of antibiotic drugs. The ability to control antibiotic drug quality is also well-established. For

example, a GAO study published in 1981 reported that from 1977 through 1980, less than one percent of all antibiotic products did not comply with monograph standards. FDA therefore concludes that the additional controls are no longer necessary to ensure the safety and efficacy of insulin and antibiotic drug products.

The Agency therefore proposes to regulate the approval of new insulin and antibiotic drug products, and generic antibiotic drug products, much as it deals with other human drug products. Concerning tests and methods of assay, the USP will maintain the standards for insulin and antibiotics in the same way that it maintains such standards for other drugs.

Impact: Under this reform, insulin manufacturers would no longer be required to submit applications and samples to obtain batch certification. And because the insulin industry is subject to certification fees under section 506 of the Act, the change would eliminate those fees.

Eliminating the statutory requirement for FDA to issue antibiotic monographs that set forth standards for tests and methods of assay for particular drugs would benefit antibiotic drug product manufacturers. This change would eliminate the confusion created by actual and potential differences between FDA regulatory standards and the USP.

Eliminating the regulations specifying insulin and antibiotic drug standards and tests will remove over 700 pages from the *Code of Federal Regulations*.

[INSERT CHART ON ELIMINATING 600 PAGES CFR]

Implementation and Timeline: The Administration will promptly propose legislation to repeal section 506 of the Act (which pertains to insulin) and to repeal section 507 of the Act (which pertains to antibiotic drug products). FDA would continue to approve new insulin products under section 505 of the Act, and would also seek to have antibiotic drug products and generic antibiotic drug products approved under section 505 of the Act.

Environmental Assessments for Human Drugs

Background: The National Environmental Policy Act (NEPA) requires all federal agencies, including the FDA, to assess the environmental impact of their actions which may significantly affect the quality of the human environment. A drug cannot be approved without a manufacturer having submitted an acceptable Environmental Assessment (EA). On the basis of FDA analysis of the EA, the Agency can either issue a "finding of no significant impact" (FONSI), or decide that a full environmental impact statement (EIS) must be prepared. An EA test is usually quite expensive; yet, in virtually every case, a FONSI is issued.

Each year, the pharmaceutical industry submits approximately 50-60 full EAs and about 50 abbreviated EAs to the Center for Drug Evaluation (CDER). Pharmaceutical firms also send 20-25 EAs annually to the Center for Biologics Evaluation and Research, some in abbreviated form. And yet, in recent years, FDA has identified only one product, Taxol, as presenting any potentially significant environmental concerns. In the case of Taxol, the environmental impact was due to harvesting of Pacific yew trees, an endangered species.

In Taxol's case, CDER incorporated by reference the EIS prepared by the U.S. Forest Service to address the resource question; the manufacturing process and use were addressed through the routine EA and were found to have no significant impact. It can take up to six months to review the EA, obtain additional information from the firm to correct any deficiencies, and issue a FONSI.

Proposal and Justification: *FDA proposes to increase the number of categorical exclusions from the EA and EIS requirements.*

FDA proposes to reduce the number of EAs required to be submitted by industry and, consequently, the number of FONSI's prepared by the Agency under NEPA by increasing the number of categorical exclusions based upon little or no impact of the use of the drug on the environment. Based upon its experience to date in reviewing environmental assessments, FDA believes that nearly all product approvals will qualify for categorical exclusion. For example, virtually all drug approvals would result in only minute releases of the drug into the environment as a result of human use and that such releases would not be environmentally significant. FDA will provide for extraordinary circumstances in which a normally excluded action may have a significant environmental impact--circumstances that would require at least an EA. Taxol is an example of such an extraordinary circumstance.

Impact: These changes will substantially benefit industry and will improve regulatory efficiency without having any adverse impact on public health or the environment. Industry would save from \$40,000 to \$150,000 on each EA.

Implementation and Timeline: These changes will be implemented by amending FDA regulations, in consultation with the President's Council on Environmental Quality (CEQ), to increase the number of categorically excluded actions for which an EA or EIS is not required. New regulations will be proposed in consultation with CEQ in six to nine months. Policy guidelines clarifying current procedures will be published sooner.

Medical Devices

There are three classes of medical devices. Class I devices, such as tongue depressors, are subject only to general regulatory controls and receive little Agency oversight. Class II devices, such as infant incubators, are subject to special controls such as performance standards to ensure their safe and effective use. Class III devices, such as implantable pacemakers, are generally life-sustaining or life-supporting, are implanted in the body, or present potential unreasonable risk of illness or injury.

New devices enter the market in one of two ways: (1) through a premarket notification process, known as a "510(k)" because it is authorized under section 510(k) of the Federal Food, Drug and Cosmetic Act; and (2) through a more extensive premarket approval application (PMA).

Under the 510(k) process, FDA must determine whether a device is "substantially equivalent" to a device that is already legally marketed. A manufacturer using the premarket notification process informs FDA about the device and why any changes in its device can be made safely. (Some low-risk devices have been exempted from premarket notification.) If FDA finds the device to be "substantially equivalent," the manufacturer may market the device and must then comply with good manufacturing practice (GMP) requirements to ensure that the device is properly made. More than 90 percent of all devices enter the market under the premarket notification process. The more extensive premarket approval application is targeted toward Class III devices.

The reforms below are: additional exemptions from premarket notification; elimination of the current reference list program which link GMP inspections to new device approvals and replacing it with a process that focuses on serious GMP problems and how they may be applicable to individual premarket notification actions; a pilot program for external review of new devices; and a user fee program to speed device approvals.

Medical Device Exemptions from Premarket Notification

Background: Currently, the Federal Food, Drug and Cosmetic Act requires that manufacturers of most medical devices submit information to the FDA and receive FDA clearance before putting the device on the market, even if the device has an extremely low risk. Review of low-risk devices is not necessary to protect the public health and places an unnecessary regulatory burden on device manufacturers.

FDA currently regulates about 1700 types of medical devices. Of these, 441 categories of low-risk devices (such as stethoscopes, hernia supports, and surgical microscopes) have already been exempted from the requirement of premarket notification, including 148 exempted in December 1994.

Proposal and Justification: *FDA will exempt up to an additional 125 medical device categories from premarket notification requirements. As a result, about 580 categories, or more than 1/3 of all categories of devices, will be exempt from premarket notification requirements.*

Public health will not be compromised by the exemption of these devices from premarket review. These devices will remain subject to good manufacturing practice requirements, which include regular factory inspections, record keeping and device problem reporting.

[INSERT CHART ON EXEMPTIONS]

Impact: The device industry will no longer have to prepare and submit--and the Agency will not have to process and review--510(k) premarket notification submissions for the exempted device categories. FDA receives about 700 submissions each year for devices in these 140 categories and will be able to redirect the resources for the review of these products to more complex products.

Implementation and Timeline: FDA Device Advisory Panel Chairs are now reviewing the proposed exemptions and will complete their review by the end of this month. The majority of the device categories are currently in Class II, and under the law, must be reclassified to Class I before being exempted from FDA review. By June 1995, FDA will propose to reclassify these devices from Class II to Class I and to exempt them from premarket notification requirements.

Elimination of the Reference List

Problem: Under a program known as the "Reference List," FDA tracks medical device manufacturers found by FDA field inspections to have serious GMP violations. GMP violations are flaws in the manufacturing process that have the potential to affect the safety or efficacy of the product. If a firm is on the list, FDA may defer authorization for the firm to market a new product under section 510(k) of the FD&C Act.

The basis for placing a firm on the list has been an inspectional finding of serious GMP problems. In issuing the manufacturer a warning letter about its GMP violations, the FDA has advised the manufacturer that the Agency may not give marketing clearance to pending applications until the violations are corrected. A company is removed from the list only after FDA has re-inspected the firm and found that all serious GMP violations have been corrected. This process can take up to 6 months.

Industry has criticized the list as not needed to protect the public health. Industry views the list as a "blacklist" because it feels that the Agency does not make clear which firms are placed on the Reference List or when they are removed from it. Moreover, because it takes time to re-inspect after violations are found, manufacturers may be delayed in marketing their products.

Proposal and Justification: *FDA will eliminate the Reference List and instead focus attention on the appropriate linkage between serious GMP deficiencies and individual pending 510(k) applications.* FDA will also clarify that market clearances of Class I and II devices will not be deferred unless FDA finds a reasonable relationship between the nature of the current GMP violations and the application under review. A reasonable relationship will be found only if there are GMP violations that are directly related to the product under review or if there are systemic violations that are generally applicable. FDA will not defer 510(k) applications if no such reasonable relationship is found.

Second, if market clearance of the application is deferred because of GMP violations, FDA will either reinspect the firm within 60 days after being notified that corrective actions have been taken, or clear the 510(k) application without a reinspection.

Finally, FDA will prepare clear written policies and procedures so that companies know if they have an outstanding GMP violation, understand when their 510(k) applications may be held up due to GMP violations, and the procedures to follow to correct the problems and obtain the device application clearance.

Impact: The proposed changes benefit industry by providing assurance that no market clearance will be deferred unless a clear linkage between GMP violations and the device

under review is found. In addition, by clarifying FDA's procedures, any industry fear of indiscriminate delay in the clearance of a 510(k) application will be eliminated. Finally, the fixed time frame for reinspection benefits manufacturers by removing uncertainty about when they will be able to market their products after they correct GMP violations.

Implementation and Timeline: The Agency will implement these new policies and procedures by publication of a notice in the Federal Register by May of 1995. FDA will immediately review all deferred applications to determine if the GMP violations are reasonably related to the pending applications. Firms with GMP violations unrelated to the pending applications will have their applications cleared unless there are other problems.

Medical Device External Review Pilot Program

Background: Almost all medical devices enter the market by an application process in which the manufacturer demonstrates that the device is "substantially equivalent" to a device already marketed. The device industry contends that this process inhibits innovation and competitiveness because, due to limited resources, FDA takes too long to review these applications. (A comprehensive assessment of FDA's device review resource needs, conducted by FDA and audited by the device industry, documented an annual shortfall of about \$24 million and more than 200 staff positions.)

Industry recommends that FDA adopt an approach similar to that used in the European Community, in which device firms have their device applications reviewed by a third-party scientific organization accredited by the government. Under this approach, manufacturers pay third-party organizations for their review, the third-party organization notifies the government of the results of their review, the device is marketed without government review, and the government monitors the device after it is on the market for subsequent safety problems. This concept has not been tried in the United States, so its applicability in this country is unknown.

Proposal and Justification: *FDA proposes to create a pilot program for external reviews of devices.* This pilot program will contain several key elements of the European model to test whether that model is appropriate the United States. The program will have the following elements:

- o At least ten categories of devices, comprising at least 100-400 device applications annually, will be identified for eligibility in the program;
- o Those categories of devices will have a low to moderate risk profile, which have clear standards for market clearance, and which do not require clinical data as part of the application (e.g., applications which principally raise engineering issues);
- o The outside reviewers will be accredited by FDA as capable of assessing the design, performance, and safety of devices;
- o The accredited review organization will be responsible for conducting the entire review of the device application, producing a written review document, and making a recommendation to FDA. The review will be checked by FDA and the final decision will be made by FDA and communicated to the company;
- o The program will be funded by the manufacturer's payment to the reviewer for its services. Participation by manufacturers will be voluntary; and

- o The accredited reviewing organization will be expected to demonstrate independence from device manufacturers for whom they will be doing reviews, and conflict of interest standards will be adhered to.

Impact: The pilot program will allow FDA and the device industry to determine the feasibility of third-party reviews of devices. It will answer questions such as whether private groups can conduct a thorough, rapid review; whether such groups exist or will need to be created; whether safeguards against improper influence of non-government reviewers can be established; and how much groups will charge for these services.

Implementation and Timeline: The pilot program will begin early in the next fiscal year. The pilot program will operate for two years, and during the second year FDA will evaluate its success and potential for expansion and permanent continuation.

Device User Fees

Background: Even if the medical device external review pilot program and other streamlining efforts detailed in this report are successful in reducing resource demands upon FDA's device program, the Agency will still lack sufficient resources to ensure timely action and review of device applications. Each year, FDA receives approximately 40-60 Premarket Approval Applications (PMAs), 400 PMA supplements, and 6000 premarket notification actions for marketing devices under section 510(k) of the Federal Food, Drug and Cosmetic Act. In fiscal year 1994, the average review times were about two years for PMAs, one year for PMA supplements, and 215 days for premarket notification [although premarket notifications, which have been the most controversial, were down to a median time of 98 days in January 1995]. Compare that to fiscal year 1990, when the average review times were ten months for PMAs, six months for PMA supplements, and 100 days for premarket notifications. These lengthy review times delay the introduction of devices into the market. FDA can reduce these review times, without diminishing the public health protections it provides, if it had adequate resources to review applications.

Proposal and Justification: *The FDA proposes to authorize user fees for applications.* FDA will collect fees for reviewing PMAs, PMA supplements and premarket notification actions (510(k)s) and dedicate them to funding premarket review and related activities. In addition, FDA will commit to specific performance goals.

FDA will agree to performance goals of (1) eliminating the backlog of applications within 24 months; (2) completing a comprehensive, substantive review for 90 percent of PMAs in 180 days; and (3) taking a final action on 95 percent of 510(k)s in 90 days. These performance goals were negotiated with the industry as part of legislation proposed last year, and major segments of the device industry supported them.

Impact: The proposed solution will address a major complaint about federal premarket review times for devices. The device industry will benefit from increasingly faster review and approval times, will be able to market new and innovative products faster, and will become more competitive in foreign markets. Consumers inside and outside the United States will benefit from easier access to new and improved products.

[INSERT CHART]

Implementation and Timeline: User fees will require statutory changes to the Federal Food, Drug and Cosmetic Act. The Administration has proposed these changes in the budget for fiscal year 1996. Device user fees would account for \$23,740,000 of the Agency's budget for the entire fiscal year, and the funds would include associated start-up costs and the hiring of over 200 staff people over the first two years.

Cross-Cutting

Several issues confronting FDA cut across product lines and affect both the pharmaceutical and medical device industries. Exports involve two such issues. One of them is the different mandatory requirements that the Agency must follow in approving exports of drugs and medical devices. The other export issue stems from the varying standards for regulated health care products in the U.S. and in many of its trading partners. FDA plans to ease some of the current export restrictions. Also, the Agency will intensify its efforts to bring into harmony international standards for health care products, so that firms developing new products will have to deal with only one set of requirements.

Another issue raised by both the drug and device industries is whether FDA requires new products to be shown to be superior, as opposed to equal, to products that are already on the market. An upcoming policy statement will clarify the Agency position. FDA also proposes to take steps to advance the development of an electronic information system to support the review processes, and to implement the second phase of an automated system for the processing of imports.

Drug and Device Exports

Background: Drugs and medical devices not approved for sale in the United States are now exported under different statutory requirements.

Drugs may be exported only to the 21 developed countries listed in the statute if, among other things, (1) the sponsor has an investigational new drug (IND) exemption in effect that permits testing in humans; and (2) the drug is approved in the importing country.

Devices may be exported if FDA determines, based on information supplied by the exporting company that: (1) export of the devices does not harm public health and safety, and (2) the device is approved for importation by the importing country.

Manufacturers have contended that these requirements place them at a competitive disadvantage and that FDA review of exportation to foreign countries is both time-consuming and unnecessary.

Proposal and Justification: *It is proposed to allow the export of drugs to any of the statutorily-listed countries without an IND.* In addition, the Administration proposes to work with Congress on changes in the current law based on an examination of whether to amend the present list of 21 countries, and whether to adopt other changes.

FDA proposes two new criteria for allowing devices not approved in the U.S. to be exported for marketing abroad without prior FDA permission: (1) devices can be exported to advanced industrialized countries (the list of which would be determined in consultations with Congress) if the devices conform to the importing country's laws; (2) devices can be exported to countries not on the above-mentioned list if the exporter has an Investigational Device Exemption (IDE) permitting testing on humans in the U.S., if the importing country has given FDA a letter providing blanket import approval for IDE-type devices; and the device is in compliance with the importing country's laws.

This change from current procedures would significantly relax restrictions on exports to industrialized countries while leaving intact existing protections for countries that are not industrialized.

Impact: For drugs, companies will be able to export their products for marketing in the 21 developed countries listed in current law, even if they do not have an IND in the United States.

For devices, exports to the most significant markets--industrialized nations such as Japan and the European Community, will be exempt from FDA's oversight. The U.S. industry will be spared the expense of developing and submitting export requests to FDA and would not need to await FDA review, which now averages 16 days but can take as long as 150 days.

Furthermore, a firm with an appropriate IDE will be able to export the unapproved device to less developed countries which have agreed to such importation without going through FDA review, currently averaging 10 days. The U.S. device industry believes that these changes will encourage firms to remain in the U.S. rather than moving their operations abroad. FDA could redirect the resources used for the current export approval program to more pressing public health matters.

Implementation and Timeline: Discussions with Congress on both drug and device legislation could begin immediately. Permitting devices with an IDE to be exported without further FDA clearance to countries who have provided prior agreement can be accomplished administratively by FDA, and proposed regulations will be issued within four to six months.

Effectiveness of Drugs and Devices

Background: The pharmaceutical and medical device industries have argued that FDA requires a new drug or Class III device (highest risk) to be shown to be more effective for its intended use than comparable therapies that are already approved for marketing.

Representatives of these industries believe FDA's requirements for demonstrating efficacy presents unreasonable difficulties to the development of new therapies and bringing them to market.

New industry representatives also argue that the Food, Drug and Cosmetic Act should not be read to require multiple clinical studies when one pivotal study could suffice.

Proposal and Justification: *FDA proposes to issue a public statement to respond to this concern.* The statement will make the following points:

Comparative Effectiveness

Under the Federal Food, Drug and Cosmetic Act, new drugs and Class III devices must be shown to be safe and effective for their intended uses. In evaluating the safety of a new drug or Class III device, the Agency weighs the demonstrated effectiveness of the product against its risks to determine whether the benefits outweigh the risks. This weighing process also takes into account information such as the seriousness and outcome of the disease, the presence and adequacy of existing treatments, and adverse reaction data.

In evaluating effectiveness, as with safety, FDA reviews new drugs and Class III devices on their merits. The Agency does not require new drugs and Class III devices to be more effective than therapies for the same disease or condition that are already approved for marketing. In general, both new drugs and Class III devices must be shown to be effective through evidence consisting of well-controlled investigations that provide a basis on which it can be concluded that the drug or Class III device will have the effect it is represented to have.

For the majority of new drugs and Class III devices, i.e. new products intended to treat less serious illness or provide relief from symptoms, a showing of effectiveness is usually based on a clinical trial comparing the product to a placebo. Such a showing does not involve a comparison to any other product.

In certain circumstances, however, it may be important to consider whether a new product is less effective than available alternative therapies, when less effectiveness could present a danger to the patient or to the public. For example, it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when:

1. the disease to be treated is life-threatening or capable of causing irreversible morbidity (stroke or heart attack, for example); or
2. the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., venereal disease).

It should be noted that new products are often developed for particular subpopulations who either do not respond to or are not able to tolerate an existing approved therapy. FDA will generally approve for use in such a subpopulation a product that is shown to have effectiveness in this group, regardless of whether the product can be shown to be as effective in the broad target population as the alternative therapy. This is because, in effect, there is no available alternative therapy for the subpopulation. For example, a number of patients cannot tolerate a widely used therapy for an AIDS-related pneumonia. FDA approved the drug atovaquone for use in these patients, even though it had been shown to be less effective than the standard therapy when tested in a broad population.

Number of Studies Needed to Demonstrate Effectiveness

FDA believes that a showing of effectiveness in one study must be replicated to constitute an adequate demonstration of effectiveness for a new product. While a second study may well be needed to replicate the results of the first study, it is also possible to replicate the results within one, large, multicenter study.

The biotech drug Pulmozyme was recently approved to treat cystic fibrosis on the basis of one multicenter study with features that provided elements of replication. Similarly, the drug timolol was approved to treat hypertension following a demonstration of improved survival in a single study involving three different patient groups in three different hospitals; and a multicenter double-blind placebo-controlled trial led to prompt approval of zidovudine for AIDS in 1987 when it was found that 16 deaths had occurred in the placebo group, as opposed to one death in the group receiving the drug. FDA has also approved vaccines, including a vaccine for Hepatitis A, that have been studied for effectiveness in a single controlled study.

Impact: Placing such a statement in the public record would clarify for sponsors of drugs and Class III devices how FDA addresses and evaluates effectiveness in the context of overall review for product approvability. This clarification should be helpful to product sponsors in the planning and development of new products.

Implementation and Timeline: FDA will publish a statement in the Federal Register for comment within the next three months.

Harmonization of Standards

Background: Nations have differing requirements for approval of new drugs, biologics, medical devices, food additives, and animal drugs. This results in multiple tests on animals and humans and different applications for marketing approval. Nations also have differing standards for manufacturing practices and regulatory inspections. There is a substantial need to harmonize standards wherever possible, while retaining the U.S.'s high level of public health protection.

Proposal and Justification: *Seek common international standards.* FDA will work jointly with other countries, particularly the European Community, Japan, and North American Free Trade Agreement partners to harmonize product testing and development standards with those of the U.S. Work has already begun on drug development and should be expanded to other areas of FDA regulation.

In addition, where appropriate, FDA will adopt international standards developed by multilateral or private-sector standards-development bodies.

Impact: Increased harmonization offers clear benefits for U.S. public health. Since harmonization will not compromise FDA's high standards of public health protection through the harmonization process. It can also improve the safety and quality of products sold in foreign countries and may help increase the availability of new products.

Harmonization benefits industry by replacing many different standards with one international standard that industry must meet. In the long run, this brings cost savings to industry, enhanced opportunities for export of U.S. goods, and also may lessen the time needed to bring new products to market.

Harmonization permits FDA to make more efficient use of its resources, as other countries share the workload of developing new standards. Harmonization also may save future FDA resources by enabling cooperation with other countries in the assessment of new products. (However, it should be noted that a sizeable up-front investment of FDA resources is needed to reach harmonization.)

Implementation and Timeline: FDA will build on and expand efforts to achieve international harmonization by:

1. Launching work on new harmonization topics in the testing of human drugs, biologics, and devices related to clinical trials, biotechnology, medical terminology, and standards for the electronic transfer of regulatory information. Harmonized standards will be issued as guidelines for industry. Substantial progress on guideline development is expected within two years.
2. Accelerating work on harmonizing drug Good Manufacturing Practices, Good Laboratory Practices, and Good Clinical Practices standards and inspections. A number of proposals for harmonized guidelines should be completed within two years; however, harmonization of inspections will probably take longer.
3. Beginning an initiative to harmonize registration requirements for animal drugs. The first proposal for harmonized guidelines should be completed within three years.
4. Initiating work towards more harmonization with our NAFTA partners. Such harmonization efforts should become part of the work plans of existing technical working groups formed under the Canada/U.S. Free Trade Agreement.

Submission Management and Review Tracking (SMART) Program

Background: The current premarket review processes (preparation, handling and storage of information related to product applications) are paper intensive with limited electronic means of accessing, sharing or archiving product-related information within the Agency. Many applications consist of hundreds of volumes of detailed scientific information. The regulated industry is similarly affected by the need to generate an overwhelming amount of paper.

The Prescription Drug User Fee Act of 1992 (PDUFA) mandates significant reductions in the time required to review new drug applications. PDUFA funds the hiring of additional review staff to accomplish these goals. However, one of the longer term objectives is to improve the efficiency of the review process and to begin addressing ways to improve regulated industry's data handling efficiencies as well. FDA has begun to develop a comprehensive, standardized information management system (SMART) to support the review processes.

Proposal and Justification: *FDA proposes to proceed with the development of SMART by pursuing a series of information systems pilot projects which will directly support FDA's meeting the near-term PDUFA goals.* The Agency is already putting in place a system to identify, evaluate, and prioritize these pilots. A longer term SMART strategic plan has been developed which articulates how these pilots will serve as building blocks toward integrated drug development/review information management.

The pilots will focus on upgrading and interconnecting the hardware and software on the reviewer's desk, establishing standards, developing applications which will directly support the receipt, review, tracking and archiving of industry submissions, and provide analytical tools to support the review process. This proposed approach will provide the most immediate benefit to shortened review times and will be funded with PDUFA fees.

Impact: The drug and biotechnology industries will continue to see progress in meeting the PDUFA review time goals. Through information systems design, the review processes will be clarified and managed for greater consistency, better documentation, and improved efficiencies. As standards are developed and implemented, the regulated industry will achieve greater internal efficiencies in their development and formatting of regulatory submissions.

[INSERT AUTOMATION CHART]

Implementation and Timeline: Over the next 12 to 24 months, FDA's drug review programs will complete the upgrade of reviewer hardware and software and networking capability; and develop and implement a number of automated applications (e.g., electronic Establishment Licensing Applications (ELAs), electronic lot release testing, gene therapy

patient registry, pre-approval inspections, and other pilots). The program offices will also begin selecting and implementing electronic data interchange (EDI) standards which are acceptable to the regulated industry and to regulatory authorities in Europe and Japan. FDA plans to take a leadership role in defining international EDI standards, thereby contributing to the global harmonization of the drug development and regulatory processes. Data transport standards will be piloted between FDA, the EU, and Japan within the next six months.

Operational and Administrative System for Input Support (OASIS)

Background: FDA is responsible for ensuring that the imported products it regulates meet the same safety, efficacy, and quality standards as products produced domestically. Importers must have FDA clearance for each shipment before it can enter the U.S. The number of imported shipments of FDA-related products has doubled in the 1990s to more than two million per year.

FDA's traditional process for clearing import shipments required that importers prepare and submit a prescribed form, with invoices and any other documentation attached, for each shipment. FDA staff reviews the documentation, decides whether to admit the shipment in the country, and sends a paper response back to the importer. This paper process often takes days to complete, and delays in clearing shipments are a serious problem for importers. Reductions in government resources and increasing workload make it clear that FDA's traditional paper system for clearing imports must be improved. Automation of the process was essential.

Proposal and Justification: FDA has begun developing a phased information systems initiative to support automation of the import clearance process. Phase I was implemented nationwide in 1994. It operates in conjunction with the Customs Service, with whom import brokers are already on line.

The new FDA system enables the import broker to enter additional FDA-specific data, which passes through a screening process that recognizes what the product is, country of origin, producer, and shipper. FDA has developed a set of decision criteria based on its past experience with import risks and surveillance sampling techniques to determine whether the shipment is admissible, or whether FDA needs to look more closely at it.

Within minutes, the broker receives a return message, advising whether FDA has cleared the shipment, or further examination testing is needed. Shipments in which FDA has no further interest can move immediately into commercial channels.

FDA will proceed with implementing Phase II of the Operational and Administrative System for Import Support (OASIS). Whereas Phase I automated the initial submission and screening of import data from import brokers, Phase II will automate FDA's internal handling of those import transactions requiring FDA review beyond the initial screening. The Phase II system will provide automated links between FDA laboratories, inspection, and compliance units.

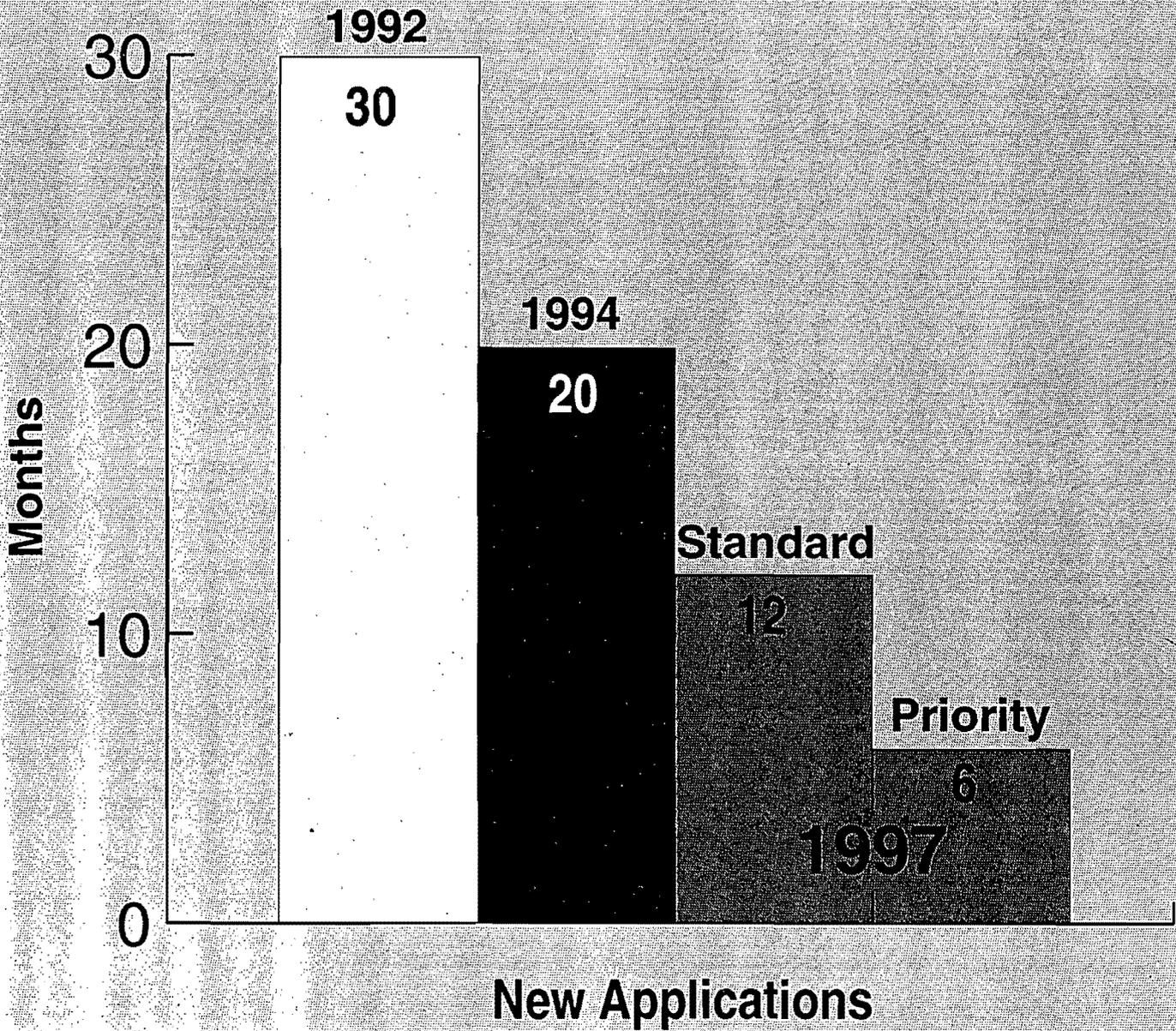
FDA will achieve national uniformity, tracking, and enforcement of suspect products and a more rapid final response to brokers on import disposition. In addition, full implementation of the OASIS system will permit electronic links with other FDA data bases that must be accessed during the import entry review process. For example, FDA must confirm that an imported drug has an effective NDA or an IND, that medical devices are approved and have been properly registered, and that manufacturers of low acid canned foods have registered.

Impact: In February 1995, 67 percent of all shipments processed in FDA's electronic system received final clearance within minutes. Import brokers need not prepare and submit to FDA any paperwork for these shipments that are cleared electronically. Importers' costs for holding up shipments awaiting FDA clearance are reduced markedly. Perishable shipments no longer risk spoilage from clearance delays.

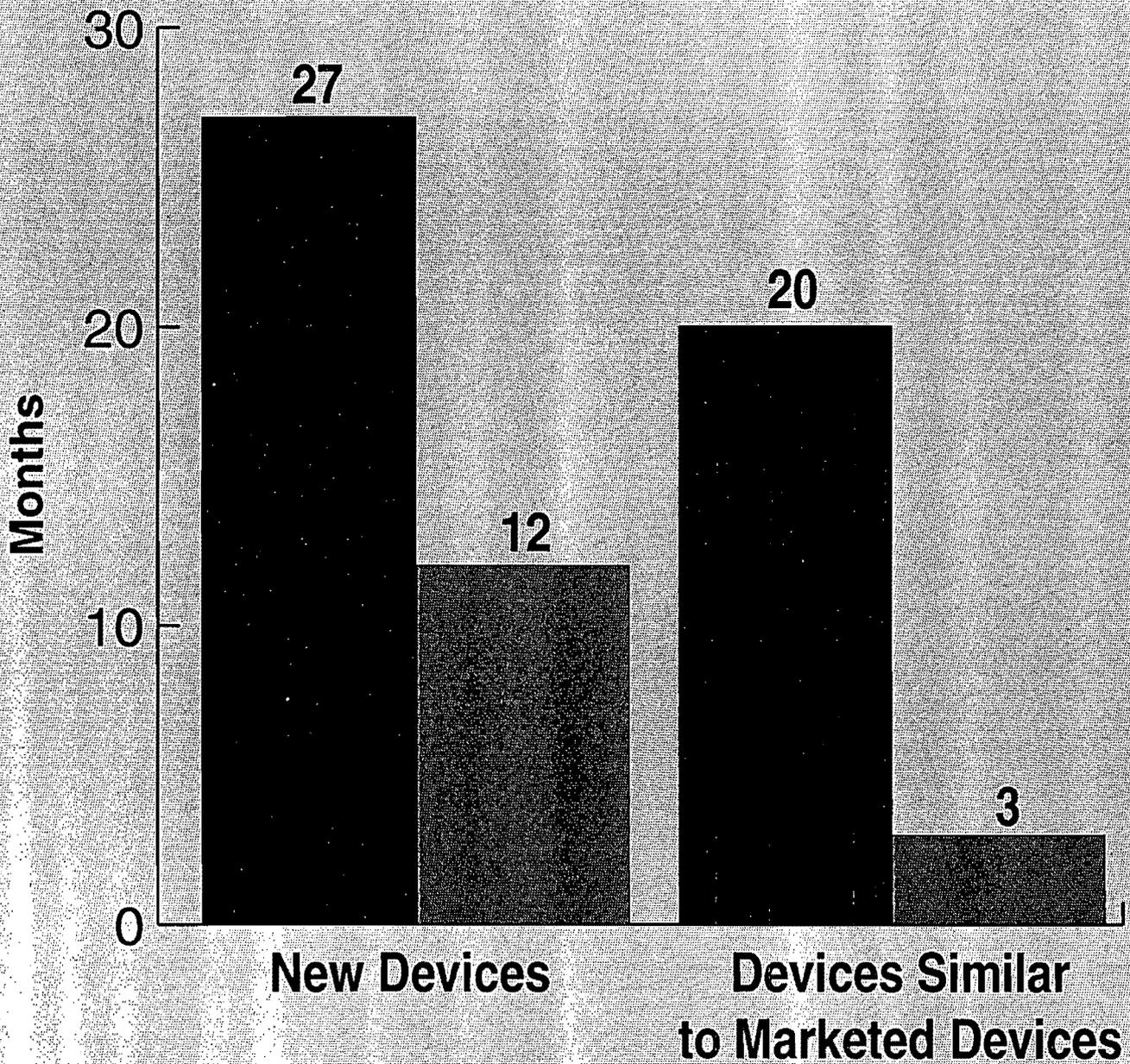
The American consumer is the major beneficiary. The freeing up of FDA resources that would have been required to handle and review the paperwork submitted by importers for all shipments allows the Agency to focus its attention on those shipments that may not conform to required standards. Implementation of the full OASIS system will speed the clearance of the third of shipments which require some form of FDA detailed review. FDA can target its resources on those import shipments that are suspected of not meeting quality requirements.

Implementation and Timeline: The full system, will take several more years to complete, assuming funding is available. FDA is seeking user fees, to be paid by the importers, to fund full development and implementation of the OASIS system.

Drug Review Times



Device Review Times



 Current  Proposed

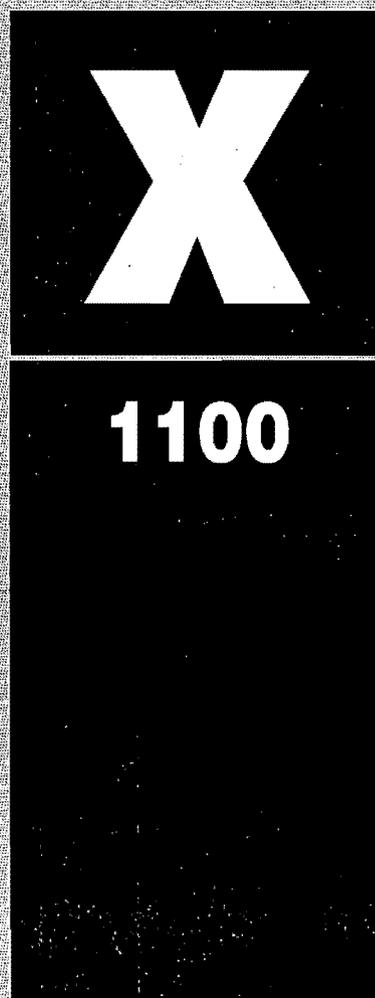
Device Premarket Reviews

Categories Being Reviewed



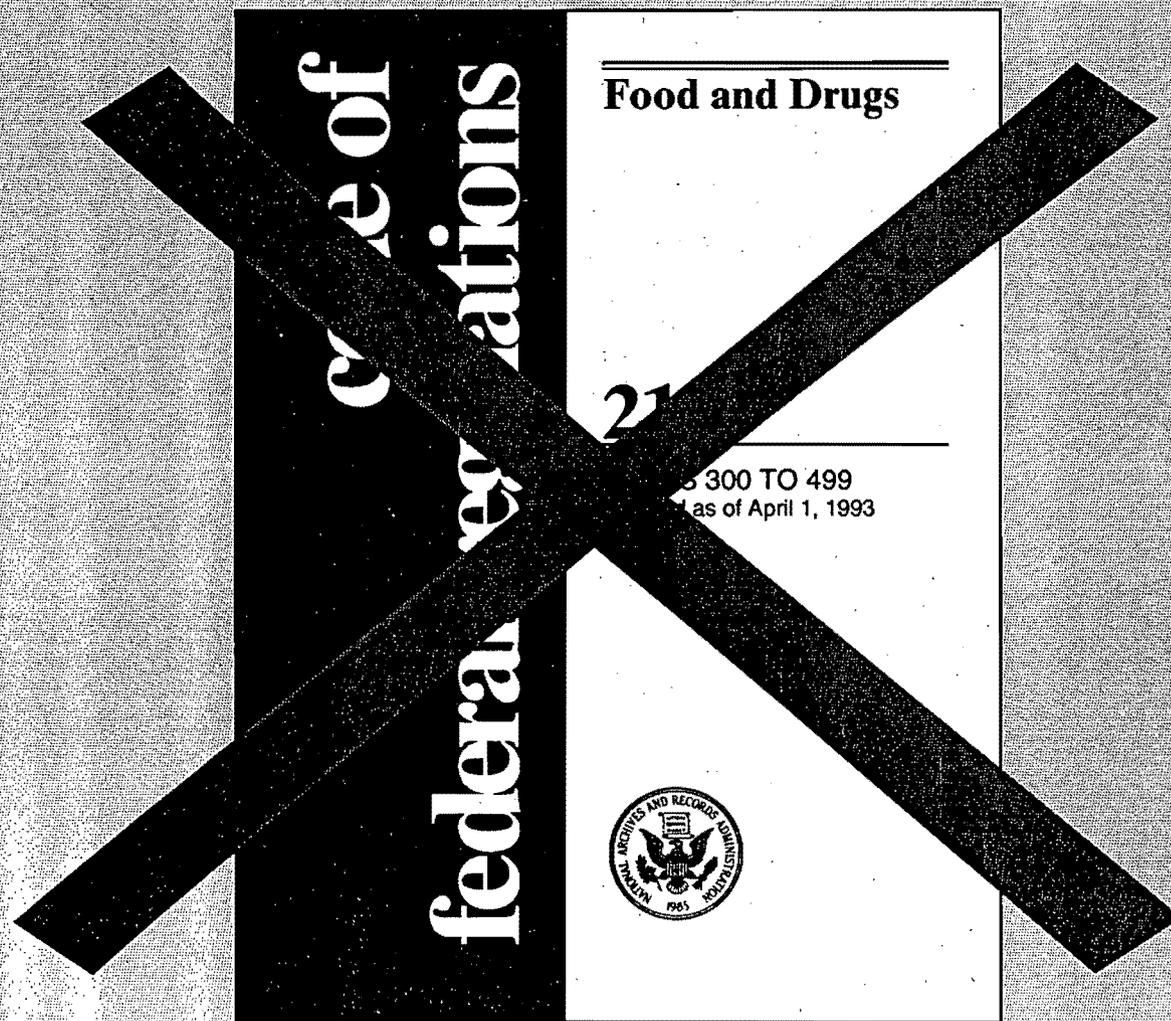
Before Exemptions

600
Exempted



After Exemptions

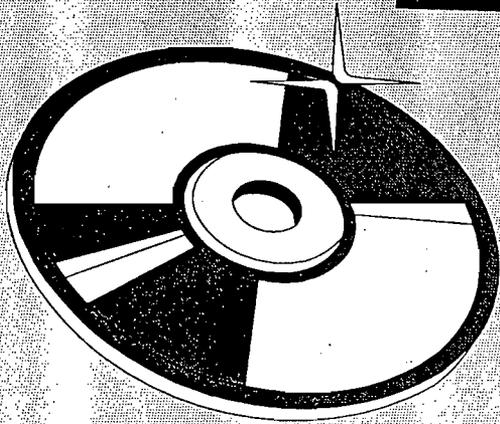
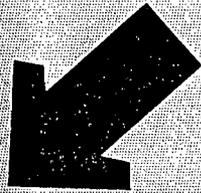
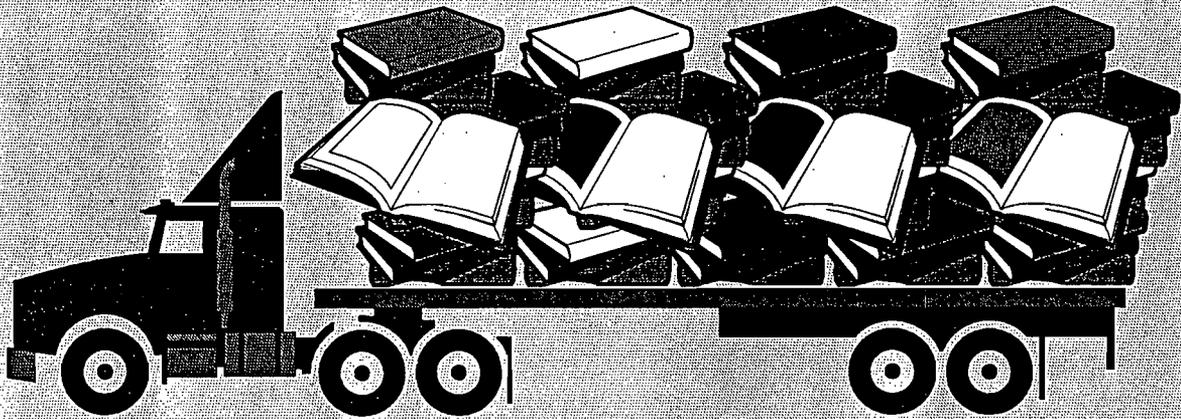
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\$50 Million**

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