

Changing Patterns of Pharmaceutical Innovation

A research report by
The National Institute for Health Care Management
Research and Educational Foundation



NIHCM
FOUNDATION

1225 19th Street, NW
Suite 710
Washington, DC 20036
TEL 202.296.4426
FAX 202.296.4319
WEB www.nihcm.org

CONTENTS

Executive Summary	2
Definitions: Types of Innovation	4
Findings: Changing Patterns of Innovation	7
Discussion and Analysis: Forces Promoting Incremental Technology	15
Conclusions: Implications for the Future	18
Credits	19
Appendices	20
Notes	22

I. Executive Summary

A. Introduction

In the last century, prescription drugs and vaccines have revolutionized medicine. They enabled physicians to prevent or treat most fatal diseases, thereby helping to increase average life expectancy by almost three decades. In addition, they have provided therapies for chronic diseases that enable patients to live more functional and productive lives.

Many of these gains were made before 1975. However, drugs have also provided some of the most significant medical advances made in the last generation. A recent survey of 225 leading internists asked them to consider 30 medical and health care innovations and identify those whose loss would have the most adverse effect on their patients. Four of the top 10 innovations and 11 of the top 20 were drug therapies.¹ Two types of medicines, ACE inhibitors used to treat cardiovascular diseases and statin drugs used to lower cholesterol, were among the top five.

Despite the enormous contribution these medicines have made to enhancing health, the quality of pharmaceutical innovation varies widely. It ranges from breakthrough treatments for life threatening diseases to minor modifications of drugs that have been on the market for some time. Because of this diversity, efforts to understand both the benefits and costs of new drugs need to be supported by an account of pharmaceuticals that distinguishes among levels of innovation. This is particularly important given the substantial contribution that new medicines have made to the rapid rise in prescription drug spending in recent years.²

This report characterizes the level of innovation of all the new branded medicines that entered the U.S. market from 1989 to 2000, excluding vaccines and other biologics products.³ It also assesses the specific contribution made to spending growth from 1995 to 2000 by new drugs at each level, from breakthrough technology to incrementally modified products providing no significant clinical improvement to older medications.

Finally, the report considers the structural forces that have shaped the direction of pharmaceutical innovation. In particular, it examines how modifying branded products approaching patent expiration can enable manufacturers to delay the threat of generic competition. Branded drug companies appear to be responding rationally to incentives created by the Drug Price Competition and Patent Term Restoration Act of 1984, generally known as the Hatch-Waxman Act.

B. Methodology

To assess recent levels of innovation, this report uses the U.S. Food and Drug Administration's (FDA) statistics on new drug application (NDA) approvals from 1989 to 2000. In addition, it uses the agency's classification system to define several major categories of new drugs, which fall on a continuum from very to slightly innovative.

The FDA classifies all NDAs on two dimensions: by chemical type and therapeutic potential. One measure of innovation is the newness of the compound forming the drug's active ingredient. The agency designates drugs relying on compounds that have never before been approved for the U.S. market as new molecular entities (NMEs). The FDA also approves many new medicines whose active ingredients are already available in a marketed product. In most cases, the manufacturer has altered the original medicine to produce a drug with different features, such as a new dosage form or route of administration. The FDA classifies these drugs according to the type of change made to the original product, and this report refers collectively to all such products as "incrementally modified drugs" (IMDs). Finally, the FDA approves a few NDAs for drugs whose active ingredients are available in identical marketed products, usually to allow a new manufacturer to make the drug. This report refers to these as "other drugs."

Clinical improvement is another measure of innovation. The FDA uses such improvement as the basis for assigning new drug applications either to a standard or swifter priority review track. The agency has a broad set of criteria to identify drugs that provide significant clinical improvement over currently marketed products. New products, including IMDs, can qualify for a priority review by demonstrating such improvement in one of four ways: evidence of increased effectiveness; reduced side effects and interactions; enhanced compliance; or use in a new subpopulation.⁴ Unlike biologics products, prescription drugs reviewed by the FDA's Center for Drug Evaluation and Research (CDER) may receive a priority rating even if they do not treat a serious or life threatening disease.

By combining these classification systems, this report defines five major categories of NDA approvals. In descending order of innovation, these are priority NMEs, standard NMEs, priority IMDs, standard IMDs, and other drugs, which are nearly all standard. The number of new drug approvals falling into each of these categories provides a profile of pharmaceutical innovation over the entire 12-year period. In order to assess changing patterns in innovation, the report compares the number of approvals in each category in the first half of the period examined (1989–1994) to those made in the second half (1995–2000). Appendix 1, Part 1 provides more information on this approach.

To analyze the contribution of different categories of new drugs to recent spending growth, the report uses retail sales data from Scott-Levin, a Pennsylvania-based pharmaceutical marketing firm. Its Source Prescription Audit (SPA) projects all outpatient prescriptions dispensed by U.S. retail pharmacy outlets.

The report defines total growth in spending from 1995 to 2000 as the difference in retail spending between these two years. It then identifies the contribution to spending growth made by each individual new drug approved by the FDA from 1995 to 2000. Since each drug belongs to one of the categories mentioned above, the report determines how much contribution the drugs in each group made to spending growth over this period. Appendix 1, Part 2 provides more information on this methodology.

C. Key Findings

In the 12-year period from 1989 to 2000, the FDA approved 1,035 new drug applications. Of these, 361 or 35% were for NMEs, or drugs containing new active ingredients. During this time, the FDA approved 674 medicines (65% of the total) containing active ingredients that were already available in marketed products. Of these, 558 drugs differed from the marketed product in dosage form, route of administration, or were combined with another active ingredient. These incrementally modified drugs, which can receive three years of market exclusivity under the Hatch-Waxman Act, accounted for 54% of all approvals. The remaining 116 other drugs (11% of approvals) were identical to products already available on the U.S. market.

From 1989 to 2000, the FDA gave a priority review to 24% of NDAs, which appeared to provide clinical improvement over the products available at the time of application. It assigned the remaining 76% to the standard review track, indicating that these drugs did not appear to provide significant clinical improvement over marketed products in one of the four recognized ways mentioned above. The vast majority (85%) of IMDs received a standard rating. This category included Oxycontin as well as versions of Claritin, Augmentin, Wellbutrin, and Zithromax. The FDA also gave a standard rating to 58% of NMEs. Prevacid, Zyrtec, Aciphex, and Detrol were among the drugs in this category. Although such medicines do not make important clinical advances, they increase physicians' prescribing choices, thus enabling them to match the drug to the needs of the patient. In some cases, modified drugs enhance patients' convenience.

Highly innovative drugs — medicines that contain new active ingredients and also provide significant clinical

improvement — are rare. Over the 12-year period examined, just 153 out of a total of 1,035 new drug approvals (or 15%) were for such drugs, priority-rated NMEs. Lipitor, Viagra, Fosamax, Avandia, Actos, and Plavix were among the drugs in this category. By contrast, drugs providing modest innovation are common. In 1989–2000, 472 new drugs or 46% of the total approved were standard IMDs.

Although many new drugs entered the market in the late 1990s, most of the growth came from less innovative products. Combined approvals of NMEs and IMDs grew by 219 products between the two six-year periods, from 350 in 1989–1994 to 569 in 1995–2000. However, standard-rated IMDs accounted for 62% of this increase, or 136 of the 219 additional new products. By contrast, priority-rated NMEs accounted for only 3% of the increase. As a result of this dynamic, standard IMDs comprised 50% of all new drug approvals, and priority NMEs just 13% in 1995–2000.

Standard-rated new products were the single most important driver of increased retail spending on prescription drugs from 1995 to 2000. Over this period, outlays more than doubled from \$64.7 billion to \$132 billion. Two-thirds of this increase, or \$44 billion, came from new drugs approved by the FDA in 1995 or later. New standard-rated medicines — those providing no significant clinical improvement over existing products — accounted for \$29.3 billion or 67% of the increase associated with new drugs, and 44% of the total increase in spending. Standard IMDs accounted for \$15.9 billion of the increase, or 36% of the amount associated with new drugs. Standard NMEs contributed an additional \$12.9 billion.

New priority NMEs, though relatively few, accounted for \$13.6 billion or 31% of the increase derived from consumption of new products. Priority IMDs, by contrast, contributed little (2%) to spending growth.

Drugs using new active ingredients tend to be much more expensive than older medicines. In 2000, the average cost per prescription for new priority NMEs was \$91.20, two and a half times the average for older branded and generic drugs, \$37.20. New standard NMEs cost only about 10% less, \$81.92 per prescription. This pattern suggests that when there are several new NMEs in a therapeutic class, price competition among them is limited.

Some modified versions of older drugs also command high prices. In 2000, the average price per prescription for standard IMDs was \$65.07, 75% more than drugs approved before 1995. For more innovative priority IMDs, the average cost was \$142. When some very expensive HIV antiviral drugs are excluded from this category, the average cost for priority IMDs was \$84.14. Though much lower, this amount is near the level for priority NMEs.

CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION

The increased emphasis on incremental drug development is not surprising. Large brand manufacturers have reached a scale at which they must generate several billion dollars in additional revenue each year in order to meet Wall Street growth targets. Yet only a handful of firms were able to bring 10 or more drugs with new active ingredients to market over the past decade, or at least one per year on average. To address the shortfall, companies have grown their franchises by adding line extensions: new products using the same active ingredient, but differing from the original in some way, such as more convenient dosing forms. Such enhancements can enable manufacturers to attract new patients and sustain or raise the prices of popular drugs.

FIGURE 1

Classification of FDA Approved Drugs

NEW MOLECULAR ENTITY (NME)

Drug whose active ingredient has never before been approved by the FDA for the U.S. market.

INCREMENTALLY MODIFIED DRUG (IMD)

Medicine that (1) relies on an active ingredient present in a drug already approved for the U.S. market, or a closely related chemical derivative of such an ingredient, and (2) has been modified by the manufacturer.

OTHER DRUG (OTHER)

Drug using an active ingredient that is already available in an identical marketed product.

PRIORITY DRUG

A product qualifying for the FDA's fast "priority review" because it appears to offer clinical improvement over available products and therapies in efficacy, safety, compliance, or use in a new sub-population.

STANDARD DRUG

A product that does not qualify for "priority review" because it does not demonstrate significant improvement over marketed products.

IMDs may also provide a high return on investment. The development of a medicine using an active ingredient whose safety and efficacy have already been established may be less time consuming, expensive, and risky than that of one using a compound about which little is known. The combination of high pricing potential for IMDs with a streamlined development effort probably makes modifying older products attractive.

The nation's framework of intellectual property protection, especially the Hatch-Waxman Act, rewards brand manufacturers for making even modest changes to their products. Large drug companies increasingly depend on blockbusters, or products with annual sales of at least \$1 billion. According to IMS Health, blockbusters accounted for 48% to 80% of the total prescription drug sales of the five largest pharmaceutical firms in 2001.⁵ As these drugs approach patent expiration, their manufacturers may be able to thwart generic competition by modifying them. If they do, they can often patent the new features and obtain three years of market exclusivity for the new version of the product. If physicians switch their patients to the new form of the drug, the franchise may be protected from market share erosion even if a generic copy of the drug's original form enters the market.

Against this background, it seems likely that brand manufacturers will continue to introduce many modified versions of older products. Such drugs may continue to contribute substantially to rising costs, both directly through their own relatively high prices and indirectly by reducing access to generics. Policy makers, as well as payers, consumers and others who wish to foster Americans' access to affordable prescription drugs, will be challenged to achieve more rational prescribing practices.

II. Definitions: Types of Innovation

Pharmaceutical innovation is manifold and falls on a continuum. At one end, it focuses on developing drugs about which relatively little is known at the time of their discovery. At the other end, innovation consists of enhancing drugs that have been on the market for some time by making minor changes to them. Between these extremes, manufacturers find numerous ways to increase the safety, effectiveness, and convenience of their products.

Despite the variety of innovation, the FDA's classification system provides a way to assign all new drug approvals to categories representing distinct levels of innovation. This is possible because the FDA's Center for Drug Evaluation and Research characterizes all the new drug applications it approves on two dimensions: chemical type and therapeutic potential.

- **Chemical type** refers to the compound forming the active ingredient of the product. It may be new, or form the active ingredient of another medicine that has already been approved, or be derived from the active ingredient of an approved drug.

- **Therapeutic potential** refers to the capacity of the drug, based on evidence available at the time of regulatory review, to improve on the clinical performance of products that are already available to diagnose, treat, or prevent the same disease or condition.⁶

In order to use the FDA's classification system, this report introduces a series of definitions (see Figure 1).

A. Chemical Type

1. New Molecular Entities (NMEs)

New Molecular Entities (NMEs) are medicines containing active ingredients that have never before been approved for the U.S. market. These drugs are intended to diagnose, treat or prevent a disease.

Because NMEs have active ingredients about which little is known at the time of discovery, manufacturers subject them to a lengthy process of testing in animals and humans in order to demonstrate that they are safe and effective. The manufacturer then submits this evidence to the FDA in a NDA, which the agency reviews before approving the drug for the U.S. market.

2. Incrementally Modified Drugs (IMDs)

Modified drugs are medicines that contain the same active ingredient as an approved product, but differ from the older medication as a result of changes made by the manufacturer. Branded drug companies often develop product line extensions by altering the original medication to develop a medicine that is safer, more effective, or convenient to use. After modifying the drug and performing any studies needed to demonstrate its safety and effectiveness, the manufacturer submits a NDA to the FDA for market approval of the new product. The FDA assigns these products to one of the three categories discussed below. This report introduces the collective term, "incrementally modified drugs" (IMDs), for drugs falling into these categories.

- **New formulations**

Manufacturers frequently make changes in dosage forms or routes of administration for their branded products. For example, they may introduce a popular drug in a different strength (e.g., 5 milligram tablets), or in an extended release form that can be taken less often than the currently available

product. They may also introduce a product that enables patients to take a drug that was formerly available only in oral form through an advanced delivery system such as an inhaler, transdermal patch, or implanted device. The FDA calls such products "new formulations" of older drugs.

- **New combinations of active ingredients**

Manufacturers may also combine the active ingredient of an approved drug with one or more other active ingredients to produce a single new product. Such drugs are called "new combination" medicines. For example, in August 2000 the FDA approved Bristol-Myers Squibb's Glucovance, a product containing metformin hydrochloride (HCl), the active ingredient in its anti-diabetic drug Glucophage, and glyburide, a generic drug also used to treat diabetes.

- **New salts or esters of approved compounds**

The pharmaceutical industry develops some new products whose active ingredients are chemical derivatives of previously approved drugs. The FDA classifies these medicines as "new salts or esters." For example, in recent years scientists have often tried to separate compounds that are mixtures of molecules in order to obtain the component of the mixture responsible for the beneficial pharmacological action of the drug and exclude the one responsible for most of the negative side effects and interactions with other drugs.

In some cases, the drug containing the purified compound is safer and more effective than the original medication. In others, the gains are marginal. For example, the FDA approved Nexium, the new antiulcerant drug based on a purified form of the active ingredient of Prilosec, as a new salt or ester. A recent comparative analysis found that Nexium increases treatment success in 8-week esophagitis healing by 3% to 8% compared with Prilosec, but shows no statistically significant difference in heartburn resolution.⁷

3. Other Drugs

The FDA approves NDAs for drugs that are already on the market in two situations. In the first, the approval allows a new manufacturer to make a drug that has been produced by another pharmaceutical company. In the second, the agency approves NDAs for certain drugs that were on the market before Congress enacted the Kefauver-Harris Drug Amendments in 1962.⁸ The Drug Amendments established the efficacy requirement for new medicines as a condition of market entry, and applied it retroactively to drugs approved after 1938. Drugs that had entered the market before 1938 were allowed to remain, and assumed to be safe and effective unless contradictory evidence emerged. Over time, manufacturers have submitted NDAs for some of these "grandfathered" medicines. Although the FDA classifies these

CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION

products as new drugs, they are generally not innovative in even an incremental sense. They contain active ingredients that are already available in an identical product, often one that has been on the market for many years. This report follows the FDA's usage by including these products with other new drug approvals, but distinguishes them by the collective name "other drugs."

B. Therapeutic Potential: Priority Versus Standard Rated Drugs

When a manufacturer submits a NDA, the agency determines whether the new drug offers improvement over marketed products (including non-drug products and therapies) in the diagnosis, treatment, or prevention of disease. If the drug can demonstrate even moderate clinical improvement, the FDA assigns it to the "priority review" track, where it can receive swift approval. If the drug fails to demonstrate an advantage, the FDA assigns it to the "standard" review track. Thus, standard rated medicines are those that the FDA views as providing no significant improvement over marketed products.

To achieve priority status, the new drug or indication can demonstrate significant improvement in one of four ways: (1) evidence of increased effectiveness in the diagnosis, treatment, or prevention of a disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness for a new patient subpopulation.⁹ Unlike biologics products, drugs reviewed by CDER can qualify for a priority review even if they are not intended for a serious or life-threatening disease.¹⁰

The FDA often gives priority reviews to NMEs that are breakthrough drugs: that is, the first medicines using a new mechanism of action to treat a certain disease.¹¹ For example, in May 2001 the FDA approved Novartis' Gleevec for chronic myeloid leukemia (CML). Gleevec is the first drug approved to treat cancer by interfering with the action of an abnormal protein that is produced in CML cells and enhances the growth of cancer cells.¹²

The FDA also gives priority reviews to some NMEs that are not breakthrough drugs, but offer superior safety or effectiveness to others in the same therapeutic class. For example, in 1999 the FDA gave priority reviews to two oral diabetes medicines, Actos, and Avandia, even though Rezulin, a drug using the same mechanism of action, was already on the market. Rezulin, the breakthrough drug of this class, raised safety concerns because of liver toxicity and was withdrawn from the market in March 2000. In clinical trials, Avandia and Actos lowered the blood glucose

levels of patients but did not show significant side effects. The FDA thus deemed them safer than Rezulin.

Finally, the FDA gives priority reviews to some new formulations and combinations of drugs whose active ingredients have been on the market for some time. In doing so, the agency recognizes that, in selected cases, enhanced versions of older medications can provide clinical advances. For example, in recent years the FDA has given a priority review to the following products:

- **Pulmicort Respules (budesonide inhalation suspension).** In 2000, the FDA approved AstraZeneca's asthma medication for young children and infants as young as 12 months. At the time of approval its active ingredient, budesonide, had been used for over 15 years in various anti-asthma formulations worldwide. However, inhaled corticosteroid therapy was previously administered with an asthma inhaler, which young children cannot use properly. Pulmicort Respules, by contrast, uses a jet nebulizer to convert the medication into a fine mist, which the child can inhale through a face mask or mouthpiece. The new product, as the first corticosteroid to be available in a nebulized formulation, was expected to improve the control of asthma in very young patients.¹³

- **Aggrenox (aspirin/extended release dipyridamole capsules).** In 1999, the FDA approved Boehringer Ingelheim's combination product Aggrenox to reduce the risk of stroke in patients who have had a previous stroke or a transient ischemic attack (a TIA or mini-stroke). Aggrenox combines aspirin, which has been on the market for many years, with dipyridamole, a NME. Aggrenox acts as an antiplatelet, preventing blood platelets from aggregating, or clumping, to form the blood clots that lead to stroke. The FDA based its approval on a study finding that Aggrenox reduced the risk of recurrent stroke by 37% compared to a placebo, and was 22% more effective than aspirin alone.¹⁴

As the examples above suggest, priority drugs may provide significant improvement in the treatment of prevalent life-threatening diseases. Nevertheless, the criteria for obtaining a priority rating are broad enough to include drugs that some observers would not regard as providing important therapeutic advances.¹⁵ For example, the FDA approved both Vioxx and Celebrex as priority drugs. These medications are not more effective against the pain and inflammation of arthritis than common nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen. They reduce the risk of gastrointestinal side effects associated with NSAIDs. Vioxx, however, has raised safety concerns because of evidence that it carries cardiovascular risk not shown by naproxen.¹⁶

FIGURE 2
Ranking System for New Drug Approvals Using FDA Characterizations as Criteria

NDA APPROVAL TYPE	LEVEL OF INNOVATION
Priority NMEs	Most Innovative
Standard NMEs	
Priority IMDs	To
Standard IMDs	
Other Drugs	Least Innovative

C. Ranking System for Innovation

Using the FDA characterizations of NDAs based on chemical type and therapeutic potential, it is possible to rank all new drugs from most to least innovative (see Figure 2).

Most observers would view priority NMEs as the most innovative type of new drug. These are medicines whose active ingredients are new compounds, and that appear to provide significant advances over products that are already available. As mentioned above, the FDA has also granted priority status to some IMDs, indicating that they provide therapeutic advances even though they are derivatives. For this reason, priority IMDs may also be considered moderately innovative.

The FDA rates many NMEs as standard products. Although based on new compounds, these drugs usually have the same mechanism of action¹⁷ as other drugs that are already on the market and achieve the same outcome. However, standard NMEs may have different safety and efficacy profiles from other marketed drugs in the same therapeutic class. These differences enable physicians to match drugs with the needs of different patients, so that a larger number can be treated with the type of therapy than would be the case if only one drug were available. For this reason, standard NMEs may enhance clinical outcomes even if they do not demonstrate significant improvement over other medicines already available. They are also moderately innovative.

Standard IMDs fall below standard NMEs and priority IMDs. These are typically product line extensions such as new dosage forms and combinations of active ingredients found separately in drugs that are already approved. The FDA views them as not providing significant clinical improvement over the parent drugs from which they are derived. However, they

can enhance patients' choice and convenience, and may make it easier for patients to comply with prescribed drug regimes. Hence, they are also somewhat innovative.

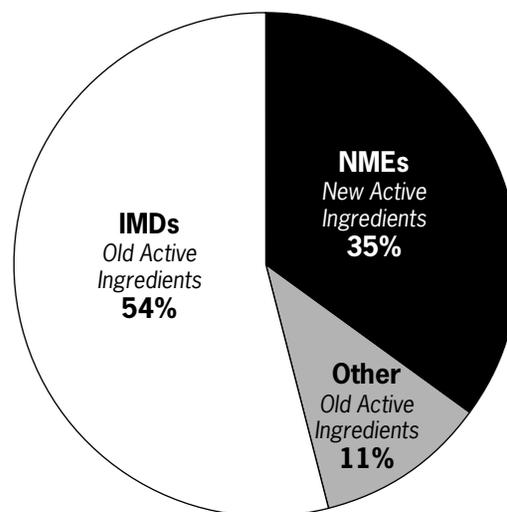
III. Findings: Changing Patterns of Innovation

A. New Drug Approvals from 1989 to 2000

From 1989 to 2000, the FDA approved 1,035 NDAs. Of these, a third (35%) were products with new active ingredients, or NMEs (see Figure 3). The other 65% used active ingredients that were already available in a marketed product. Over half (54%) were incrementally modified drugs (IMDs), or new versions of medicines whose active ingredients were already available in an approved product. The rest (11%) were other new drugs, which contained the same active ingredient as identical marketed products.

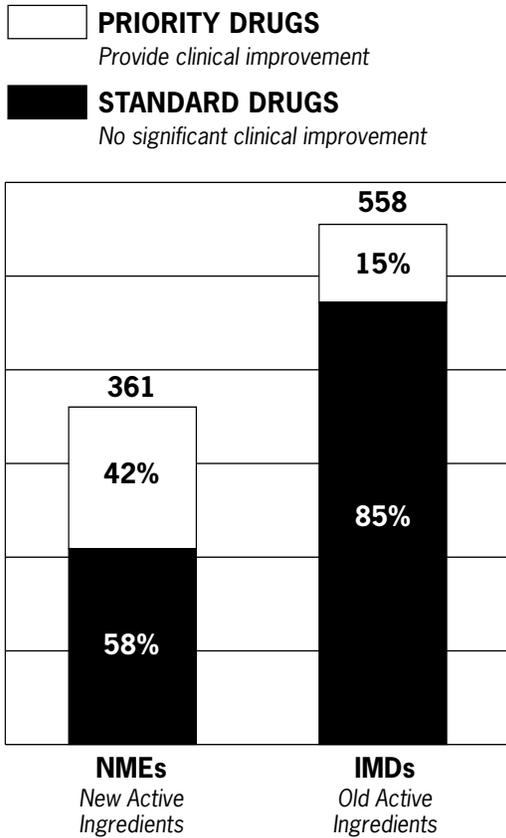
The FDA viewed the vast majority of IMDs as providing no significant clinical improvement, and rated 85% of them as standard drugs (see Figure 4). However, the agency also

FIGURE 3
Two-thirds of new drugs approved in 1989–2000 used active ingredients already on the market.



SOURCE: FDA 2001
NOTE: "Other" drugs include those for which the manufacturer has changed, and certain other drugs.

FIGURE 4
New Drugs Approved in 1989–2000 by Chemical Type and Therapeutic Potential



SOURCE: FDA 2001
 NOTE: In addition, the FDA approved 116 “Other” new drugs, nearly all of them through a standard review.

gave a standard rating to 58% of NMEs, as well as to nearly all (96%) other drugs.

As a result, 76% of all the new drugs approved in 1989–2000 were standard rated (see Figure 5). The FDA viewed 24% as providing sufficient clinical improvement to warrant a priority review.

Innovation, as mentioned earlier, falls on a continuum. Priority NMEs, the most innovative type of new drug, are comparatively rare. Over the 12-year period 1989–2000, just 153 or 15% of all new drug approvals were medicines that used new active ingredients and provided significant clinical improvement (see Figure 6). Drugs providing

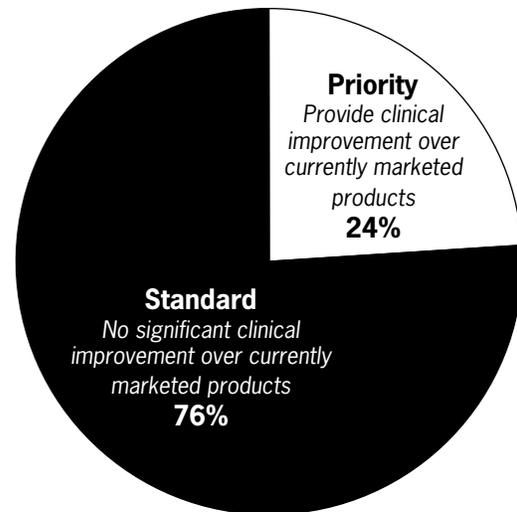
moderate innovation — standard NMEs or priority IMDs — comprised another 28% of approvals. However, 57% of approvals were for drugs showing only modest innovation, at best. Of these, 46% made some modification to an older product containing the same active ingredient, while the remaining 11% were identical to marketed products.

B. Change From First to Second Half of the Period

In order to assess changing patterns in NDA approvals, this report divides the 12 years from 1989 to 2000 into two six-year periods, extending from 1989 to 1994 and from 1995 to 2000, respectively. From the first to the second period, total new drug approvals grew from 430 to 605 as many new products entered the U.S. market. In the first period, the FDA approved 350 NDAs for drugs that were either NMEs or IMDs. In the second period, the agency approved 569 such applications, an increase of 219 new products that could be considered innovative to some degree. Approvals of other new drugs actually declined.

Examination of specific categories of new drugs reveals the following patterns of change:

FIGURE 5
NDAs Approved in 1989–2000 by Therapeutic Potential

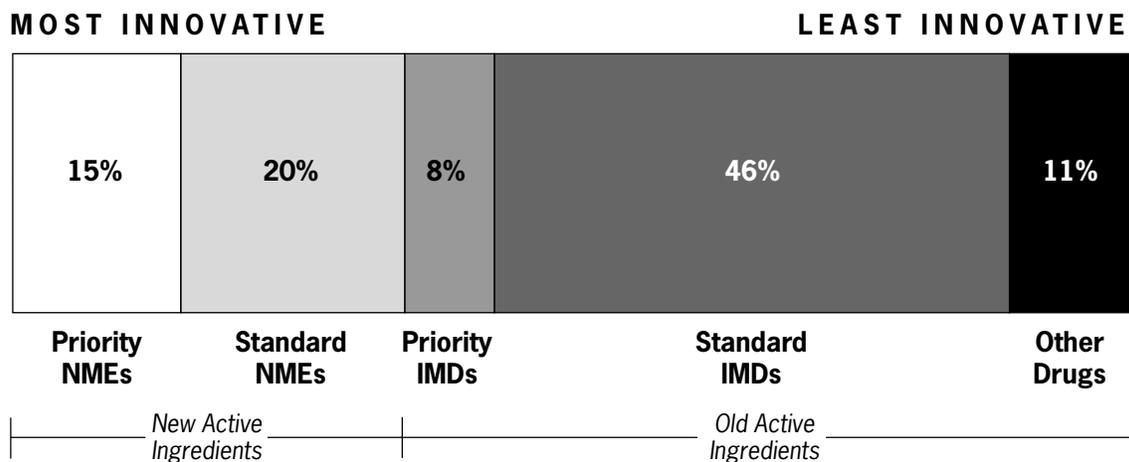


SOURCE: FDA 2001
 NOTE: Clinical improvement can be shown in safety, efficacy, compliance, or use in a new subpopulation.

FIGURE 6

Only 15% of new drugs approved in 1989–2000 were highly innovative priority NMEs.

*Distribution of NDAs, 1989–2000
TOTAL = 1,035 NEW DRUGS*



SOURCE: FDA 2001

- **Priority NMEs, the most innovative drugs, contributed little to the increase in new products.** From the first to second periods, priority NME approvals grew slowly. Thus, of the 219 total increase in new drug approvals mentioned above, priority NMEs accounted for just seven approvals or 3% (see Figure 7).

- **Most growth came from products that did not provide significant clinical improvement, especially modified versions of older drugs.** Standard-rated IMDs surged from 168 approvals in the first period to 304 in the second period, an increase of 136 new products. As a result, 62% of the increase in NDA approvals came from product line extensions that, in the FDA's view, did not provide significant clinical improvement over existing medications. Standard NMEs, the second most important source of growth, rose from 76 to 132 approvals, or by 56 new drugs. These drugs accounted for another 26% of the increase. Thus, standard rated products (IMDs and NMEs combined) accounted for 88% of the growth in product introductions seen in the second period.

- **Standard-rated drugs increased their dominance of the new product mix.** In the period 1995–2000, 50% of new product introductions were standard rated modifications

of older drugs, up from 39% in the earlier period. Standard NMEs expanded from 18% to 22% of the total mix of NDA approvals. Thus, despite the contraction in other drugs from 18% to just 6% of total approvals, standard-rated products accounted for 78% of NDA approvals in the later period.

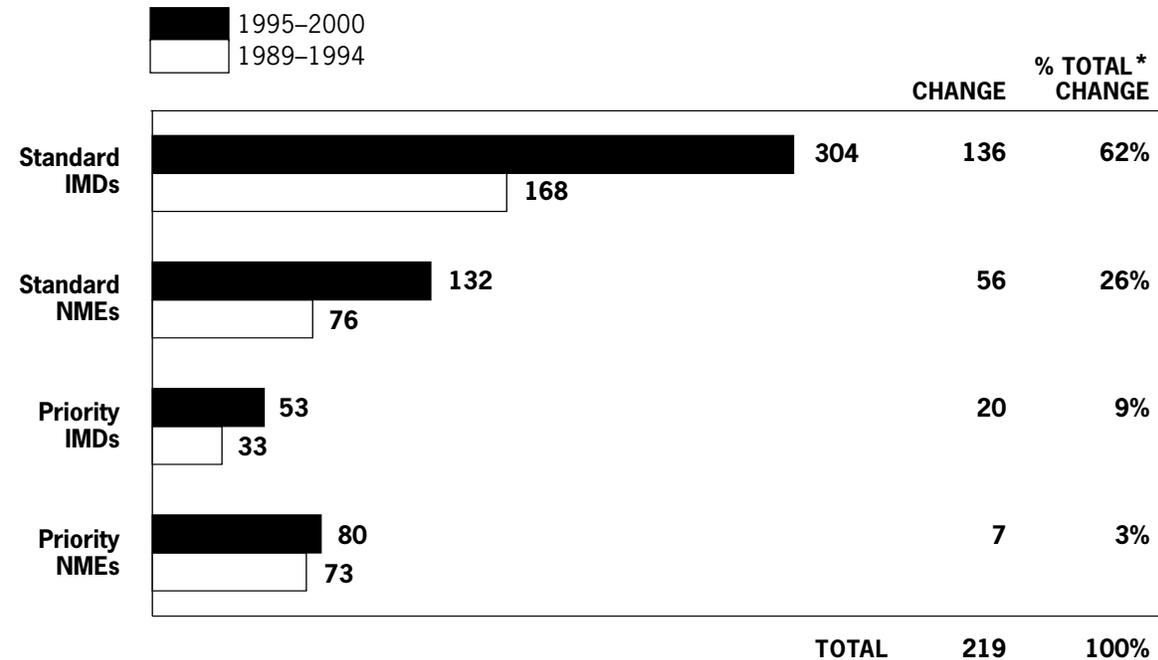
- **Priority NMEs, which were rare in the first period, have become a smaller part of the mix of new drug technology.** Although they represented 17% of total NDA approvals in the earlier period 1989–1994, they accounted for 13% in 1995–2000. If “other drugs” are excluded, the change is more dramatic. In the earlier period, priority NMEs accounted for 21% of combined NME and IMD approvals, versus 14% in the later period.

- **IMDs contributed more than NMEs to the increase in priority drugs.** In 1995–2000, the FDA approved 53 priority IMDs, versus 33 in 1989–1994. As a result of this rapid growth, IMDs became a more significant source of products offering improvement over available therapies. The FDA approved a total of 27 more priority NMEs and IMDs in 1995–2000 than in 1989–1994. IMDs accounted for 20 of these, while NMEs accounted for just seven.¹⁸

FIGURE 7

Most of the growth in product introductions has come from standard IMDs.

NDA's Approved



*Category Change divided by Total Change (219)

These patterns suggest that clinical improvements increasingly derive from technologies focused on refining older drugs or their delivery systems. In addition, research on currently marketed drugs may reveal that they are safe and effective for other diseases or conditions. The FDA has approved an increasing number of such new indications of approved drugs over the past few years, as discussed in Appendix 2.

C. Innovation and Prescription Drug Spending Growth

1. Sources of Growth from 1995 to 2000

From 1995 to 2000, total retail prescription drug spending more than doubled from an estimated \$64.7 billion to \$132 billion. Almost two-thirds of the \$67.3 billion increase came from new products, namely those approved in 1995 or later. Most of the increase attributable to new drugs involved standard rated products. Although standard IMDs contributed the most to overall spending growth, both prior-

ity and standard NMEs accounted for significant shares as well. All categories of new drugs were priced significantly higher than older drugs, with priority drugs commanding the largest premiums. (The methodology used for these estimates is explained in Appendix 1, Part 2.)

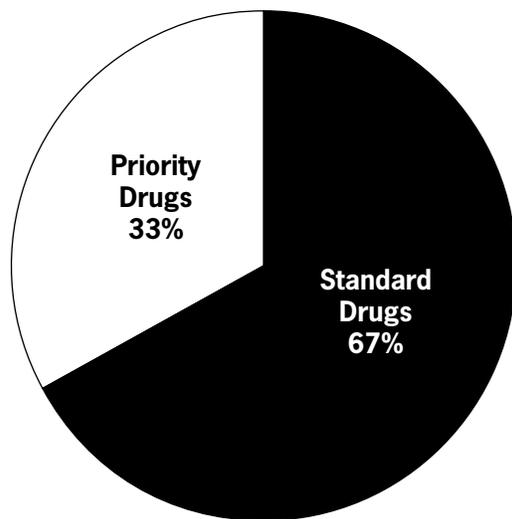
- An estimated \$44 billion or 65% of the total spending increase from 1995 to 2000 resulted from spending on new drugs. The rest, about \$23.3 billion or a third (35%) of the total, could be attributed to increased spending on older medicines, those approved by the FDA before 1995.

- Of the \$44 billion in increased spending attributable to new drugs, standard-rated drugs accounted for \$29.3 billion or 67%. Priority-rated drugs accounted for the remaining \$14.7 billion or 33% (see Figure 8).

- Standard IMDs contributed the most to increased spending on new drugs: \$15.9 billion or 36% of the total. Priority NMEs, with the second largest share, accounted for \$13.6 billion or 31%. Standard NMEs accounted for nearly as much, \$12.9 billion or 29%. Priority

FIGURE 8

Two-thirds of the increase in new Rx drug spending came from standard rated medicines.



PERCENT OF \$44 BILLION IN INCREASED Rx DRUG SPENDING 1995–2000 DERIVED FROM NEW:

STANDARD DRUGS (*no significant clinical improvement*)

IMDs	36%
NMEs	29%
Other	<2%
TOTAL	67%

PRIORITY DRUGS (*some clinical improvement*)

NMEs	31%
IMDs	2%
TOTAL	33%

SOURCE: FDA 2001, Scott-Levin data, AIR analysis

IMDs, by contrast, accounted for only about \$1 billion, just 2.3%. “Other drugs,” mostly standard, contributed the remaining \$0.6 billion, or 1.4%.

2. Variation Across Different Therapeutic Classes

Five therapeutic classes of drugs jointly accounted for an estimated \$23.4 billion in increased spending from 1995–2000, about 35% of the total increase. Priority NMEs had the greatest impact on overall spending growth for the top five classes, although their effects were uneven across different therapeutic areas.

From 1995 to 2000, combined sales of antidepressants, cholesterol reducers, antiulcerants, antiarthritics, and oral diabetes medications rose from \$15.1 to \$38.5 billion. Priority NMEs accounted for \$8.7 billion or 37% of the total increase in spending for the top five categories. Higher sales of older drugs accounted the next largest amount, \$7.9 billion, or 34% of spending growth. Standard NMEs contributed \$4.7 billion, or 20%, and standard IMDs \$2 billion or 9%. The impact of priority IMDs and “other drugs” was negligible for this group.

The disproportionate impact of priority NMEs on the top five categories’ spending growth is not surprising. In the late 1990s, the FDA approved several drugs as priority NMEs

that were heavily promoted to consumers and physicians and grew rapidly to blockbuster status. For example, Celebrex and Vioxx were approved as priority NMEs in December 1998 and May 1999, respectively. They reached total combined retail sales of over \$3.5 billion in 2000. Lipitor, a cholesterol lowering drug, was approved as a priority NME in December 1996 and reached annual sales of \$3.7 billion in 2000. In the oral diabetes category, the FDA approved Avandia and Actos as priority NMEs in May and July 1999. In 2000, they achieved combined sales of \$1.2 billion.

Among the top five categories the contribution of different types of drugs to increased spending varies widely. Priority NMEs accounted for nearly all of the increase in spending for antiarthritic medications, for 65% of the increase in spending on cholesterol lowering drugs, and 44% of the increase in oral diabetes drugs. By contrast, priority NMEs accounted for none of the increased spending on antidepressant and antiulcerant medications. These variations reflect a difference in maturity in the major drugs used across therapeutic categories. For example, anti-depressants are dominated by the class of drugs known as selective serotonin reuptake inhibitors, such as Prozac. Although these are considered advanced medications, they were often originally approved before 1995.

VALUE OF NEW TECHNOLOGY

Several studies have found that a shift to expensive new products contributed to rising drug costs in recent years.¹⁹ The benefits obtained by this shift are less clear. Some have argued that new drugs lead to better clinical outcomes and reduced non-drug costs. Of course, the question of interest to payers and consumers is: which new drugs improve outcomes and reduce costs, and which do not?

Some evidence suggests that drugs using new active ingredients outperform those using older ones. In a retrospective analysis of the 1996 Medical Expenditure Panel Survey data, Professor Frank R. Lichtenberg of Columbia University found that patients consuming newer drugs were less likely to die or to experience work-loss days by the end of the survey than those on older medications. Further, the use of new drugs was found to lower all types of non-drug medical spending, thereby reducing the total cost of treating a given condition.²⁰

Professor Lichtenberg measured the drug's age from the date when the FDA first approved the product's active ingredient. Thus, the new drugs related to better outcomes and reduced costs were recently approved NMEs. The older drugs included both the original forms of drugs approved as NMEs and modified versions of them, or IMDs. Thus the study suggests that recently approved NMEs tend to outperform older branded drugs, generic medications equivalent to these older branded drugs, and some IMDs.

The impact of drugs using new active ingredients varies for different medical conditions. Because of data limitations, Professor Lichtenberg tested his models on just 13 out of about 500 medical conditions treated with prescription drugs. Newer drugs showed a statistically significant impact on mortality for two of these conditions (ill-defined heart disease and disease of lipid metabolism). They also showed a positive effect on total non-drug medical expenditure for two conditions (ill-defined heart disease and arthropathies). Newer drugs reduced lost work days for four conditions (chronic sinusitis, disease of lipid metabolism, allergic rhinitis, and diabetes mellitus). This suggests that a relatively small number of NMEs may be responsible for much of the beneficial effects of new drug use on mortality, morbidity, and lost productivity.

3. Therapeutic Categories with Intensive Spending Patterns

A small group of therapeutic categories showed significantly increased spending on new IMDs. A somewhat larger group of different categories exhibited similar increases in spending on new NMEs.

• **There were five therapeutic categories with increased spending from IMDs of \$1 billion or more in 1995–2000, and 12 with \$500 million or more.** These included broad spectrum antibiotics with \$2.36 billion in increased spending from new IMDs; antidepressants (\$1.81 billion); inhaled respiratory steroids (\$1.37 billion); narcotic painkillers (\$1.21 billion); combined antibiotics (\$1.15 billion); anti-hypertensives (\$0.83 billion); oral cold preparations (\$0.80 billion); oral antihistamines (\$0.69 billion); non-narcotic painkillers (\$0.65 billion); fungicides (\$0.61 billion); sex hormones (\$0.60 billion); and HIV antivirals (\$0.53 billion).

• **There were eight therapeutic categories with increased spending of \$1 billion or more from NMEs in 1995–2000, and fifteen with \$500 million or more.**

Four of the top five categories for increased NME spending were mentioned above: cholesterol reducers (\$3.92 billion); antiarthritics (\$3.68 billion); antiulcerants (\$3.25 billion); and oral diabetes (\$1.57 billion). Other top categories for NME spending growth included antipsychotic drugs (\$1.65 billion); oral antihistamines (\$1.34 billion); bone density regulators (\$1.12 billion); antidepressants (\$1.00 billion); HIV antivirals (\$0.97 billion); and treatments of sexual function disorders (\$0.81 billion).

4. Spending Growth Concentration

Spending growth attributable to new IMDs was concentrated in a small number of therapeutic categories, with the top five responsible for about half of the total increase. The case is similar for NMEs, although the growth is concentrated in a different set of categories.

- Taken together, IMDs from the top five categories mentioned above jointly accounted for an estimated \$7.9 billion, almost half of the total \$16.9 billion increase in spending derived from IMDs from 1995 to 2000. The top ten categories accounted for \$11.5 billion or 68%, and the top 12 categories for an estimated \$12.6 billion, or 75%.
- The top five categories for NME spending accounted for a total of \$14.1 billion in increased spending from NMEs, over half (53%) of the total of \$26.5 billion in increased spending attributed to NMEs in 1995–2000. The top ten contributed \$19.4 billion to increased spending from NMEs, or 73% of the total from NMEs.

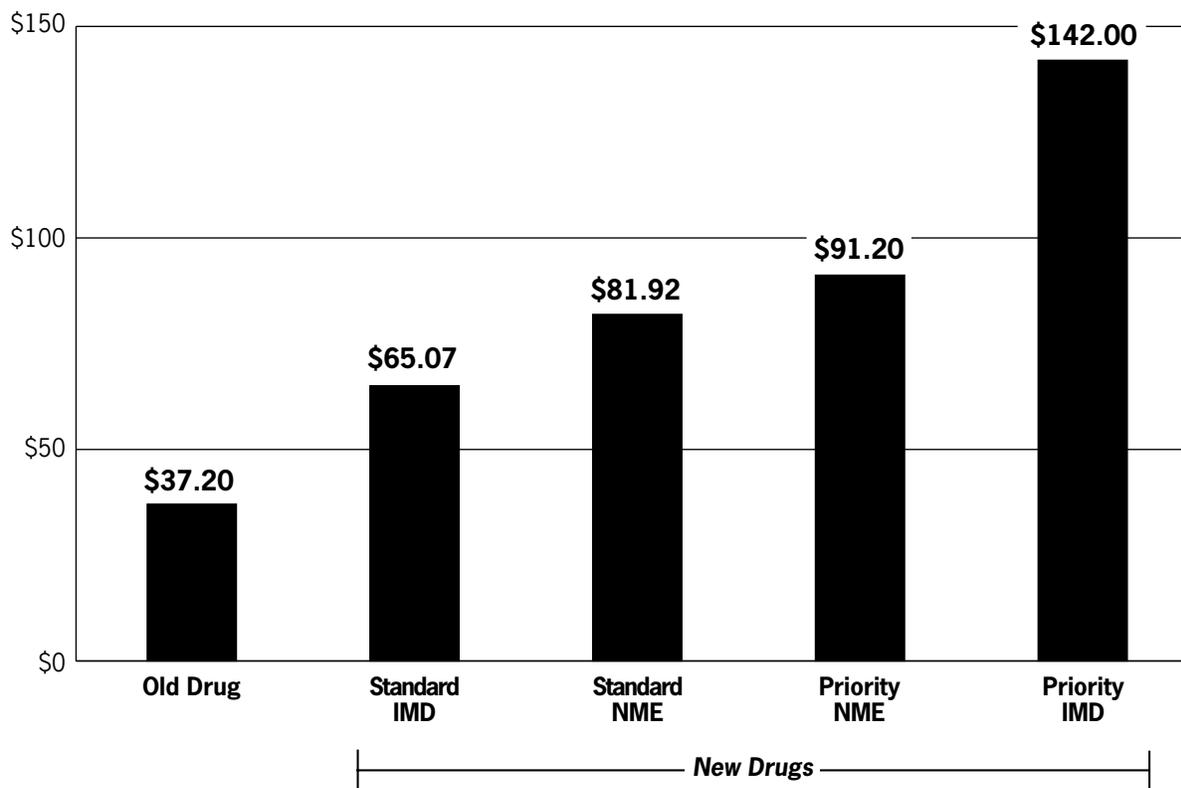
Although individual IMDs may be less conspicuous contributors to spending growth, in aggregate they may be major drivers of spending growth in specific therapeutic categories, as well as overall.

D. Innovation and Relative Pricing

In 2000, the average price per prescription varied widely by the age and class of drug (see Figure 9). Older medications, including a mix of branded and generic drugs, cost much less than products approved in 1995 or later. New priority-rated drugs commanded the highest prices. However, new standard drugs were also significantly more expensive than older medicines.

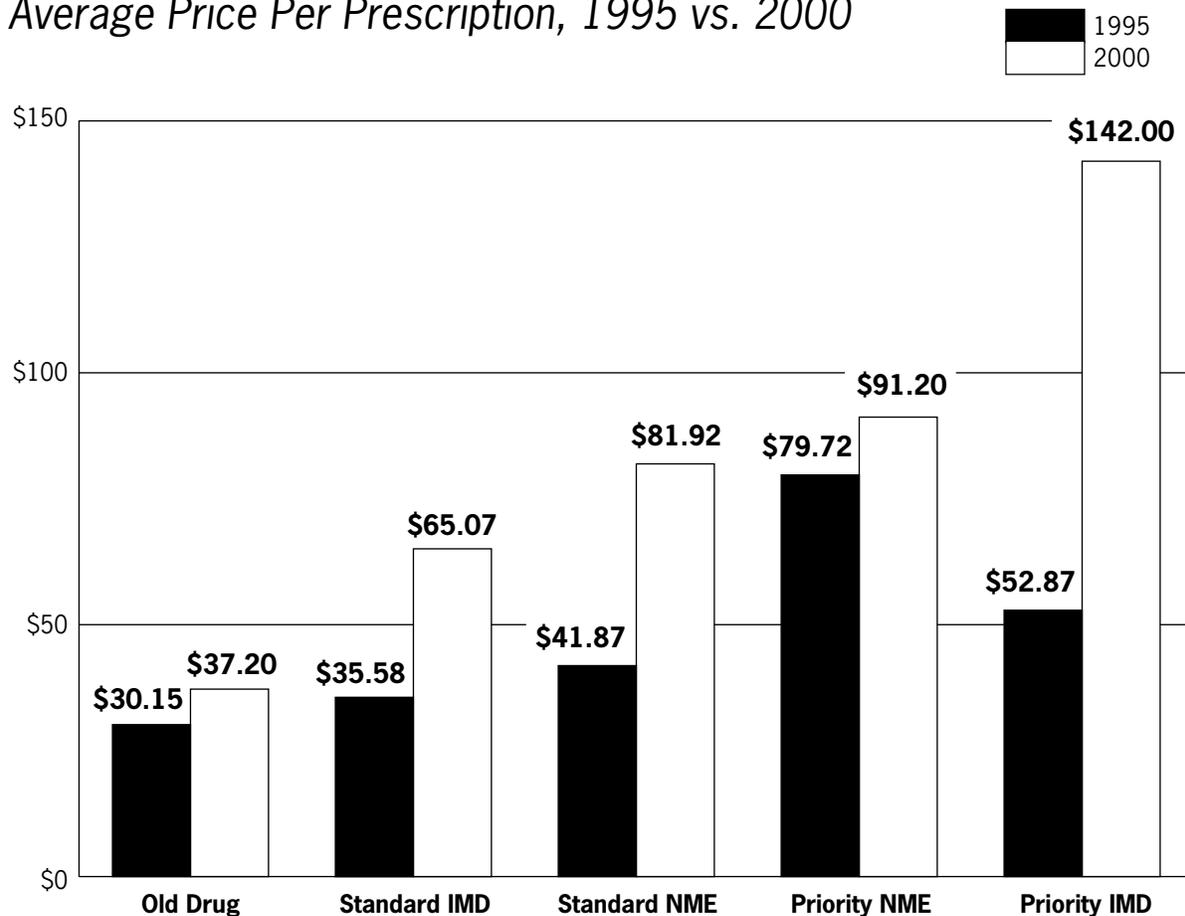
• **Priority IMDs were the most expensive drugs in 2000.** With an average price per prescription of \$142, they cost almost four times as much as older drugs and 56% more than priority NMEs. However, their high average price resulted in part from the presence of some very expensive HIV antiviral drugs in this class. COMBIVIR, a combination product containing lamivudine and zidovudine, accounted for 87% of HIV antiviral sales in the priority IMD group and

FIGURE 9
Average Price Per Prescription in 2000 for Old vs. New Drugs



SOURCE: Scott-Levin SPA data; AIR analysis
NOTE: Old drugs are those approved before 1995

FIGURE 10

Average Price Per Prescription, 1995 vs. 2000

SOURCE: Scott-Levin SPA data; AIR analysis

NOTE: Old drugs are those approved before 1995.

had an average price per prescription of \$551.58. Without these expensive HIV antiviral drugs, the average price for priority IMDs would have been \$84.14. This is a little less than the average price of priority NMEs and 2.3 times the average price for older drugs.

• **Priority NMEs, the most innovative class, cost two and half times as much as older drugs (\$91.20 vs. \$37.20).** Standard NMEs, with an average price of \$81.92, cost only 10% less than priority NMEs, however. This pattern suggests that when there are several new NMEs in a therapeutic class, price competition among them may be limited.

• **Standard IMDs, though not as expensive as other classes of new drugs, cost 75% more than older drugs in 2000: \$65.07 versus \$37.20.** This suggests that brand manufacturers can maintain relatively high prices for aging products by making incremental changes to them.

Between 1995 and 2000, the relative prices of standard and incremental technology rose (see Figure 10). In 1995 three classes of new drugs — standard NMEs, standard IMDs and priority IMDs — were priced within a close range of one another and well below priority NMEs. By 2000 priority IMDs (excluding HIV antivirals) and standard NMEs cost about as much as priority NMEs. Even standard IMDs, which cost less than half of priority NMEs in 1995, cost about 71% as much in 2000.

IV. Discussion and Analysis: Forces Promoting Incremental Technology

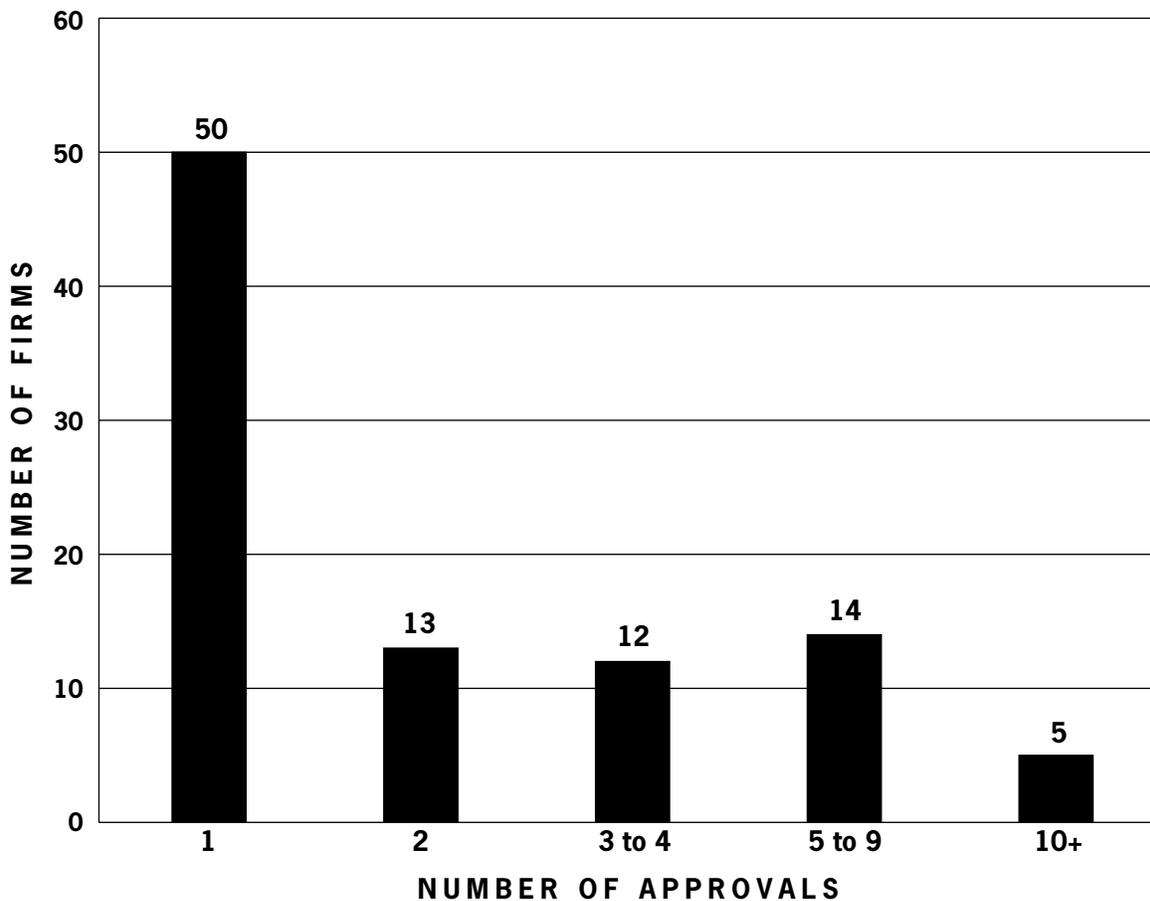
Numerous forces have joined in recent years to encourage brand manufacturers to modify drugs that are already on the market. Because these forces are structural and persistent in nature, they are likely to continue fostering the development of product line extensions that are IMDs. The rest of this section will briefly consider the financial, legal, technological, and regulatory incentives for innovator

companies to invest in the development of IMDs, as well as examine the competitive advantages provided by such drugs in more detail. In particular, it will examine the legal and regulatory mechanisms that manufacturers use to reduce the threat of generic competition to their franchises.

A. Financial: The Drive for Revenue Growth

Pharmaceutical manufacturers are under pressure from the investor community to grow sales and profits, an increasingly difficult task. In 1989, Merck & Co., Inc., and Pfizer, Inc., needed to generate approximately \$350 million and

FIGURE 11
*Distribution of Firms by Total Approvals of Drugs with
New Active Ingredients, 1990–1999*



SOURCE: Drug Information Journal 2000 based on Tufts CSDD Analysis

\$200 million in new prescription drug sales to achieve a 10% growth rate over the prior year's annual revenues, respectively.²¹ In 2002, Merck needs to generate \$4.7 billion and Pfizer \$3.2 billion in incremental sales to achieve 10% growth over their respective 2001 revenues.²² This level of sales growth is equivalent to growing three to five products into blockbusters each year.

In the past, blockbusters have often been drugs based on new compounds treating prevalent diseases that previously lacked effective therapies. However, few major manufacturers, if any, are able to meet today's sales targets by the introduction of products based on new compounds alone. Only five pharmaceutical firms introduced 10 or more drugs based on new active ingredients in the decade from 1990 to 1999, or an average of at least one per year (see Figure 11).²³

Modifying a drug whose active ingredient has already been proved safe and effective may be less expensive, time consuming, and risky than developing a new medicine from a compound about which little is known at the time of discovery. Moreover, a new version of the drug may benefit from physicians' and consumers' familiarity with the brand. Thus, it is natural that manufacturers would develop new versions of established drugs in order to achieve sales growth.

B. Legal: Expiration of Patents on Branded Products

Large brand manufacturers increasingly depend on blockbusters, or products with annual sales of at least \$1 billion. According to IMS Health, blockbusters accounted for 48% to 80% of the total prescription drug sales of the five largest pharmaceutical companies in 2001.²⁴

Over the next few years, some important drugs with combined sales of tens of billions of dollars will lose patent protection.²⁵ With expiration dates looming, branded manufacturers are aggressively seeking ways to protect their most valuable franchises from generic competition.

C. Technological: Advances in Drug Delivery Systems and Production of Single Isomer Compounds

Technological advances have increased the ability of manufacturers to develop new versions of popular products offering greater convenience, less prevalent or severe side effects, faster onset of action, and enhanced efficacy. Specialty pharmaceutical firms focused on extended release and unique delivery systems have joined long established

pharmaceutical manufacturers in the development of improved versions of already marketed drugs. In addition, companies such as Massachusetts-based Sepracor, Inc. are using technological breakthroughs made in the early 1990s to develop purified drugs from older products containing molecular mixtures as their active ingredients.

D. Regulatory: Swifter Development and Regulatory Review

The FDA, recognizing that new versions of older drugs are sometimes safer and more effective than the original product, has established policies to promote their development. The agency's "505(b) pathway" enables manufacturers to bring such drugs to market more quickly and less expensively than would be the case for the typical new compound. It is available to a broad array of new formulations of products with previously approved active ingredients: e.g., purified drugs derived from molecular mixtures, extended release dosing forms, and new routes of administration.²⁶

E. Competitive: Mechanisms to Prevent Generic Entry and Utilization

Modifying older products enables manufacturers to extend the intellectual property protection of their franchises in two ways. The company may be able to (1) patent new features of the modified drug; and (2) obtain three years of market exclusivity for the new version or use of the product. Under provisions of the Hatch-Waxman Act, these protections may enable the brand manufacturer to delay the entry of generic competitors. In addition, state pharmacy laws generally prevent the substitution of a generic form of the original branded medication for the new version of the drug.

The rest of this section examines the primary mechanisms used for these purposes in detail. Appendix 3 contains case histories of several branded drugs whose manufacturers used these and other mechanisms to delay the entry of generic competitors.

1. New Patents

Drug manufacturers patent a wide range of inventions connected with incremental modifications of their products, including minor features such as inert ingredients and the form, color, and scoring of tablets. In some cases, these patents may discourage generic companies from trying to develop a competitive product. In others, the generic

company may be able to “design around” the new features.

However, provisions of the Hatch-Waxman Act can enable branded manufacturers to postpone the entry of even such carefully designed generic products by recourse to a mechanism known as the “30-month stay.”

2. Triggering the 30-Month Stay

When a brand manufacturer submits a NDA, the application must contain information about any patents protecting the drug. Upon approval, the FDA lists all of these patents in a publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly called the “Orange Book.” The brand manufacturer may obtain additional patents related to the product, either in original or modified form, after it has been approved. When it does, the firm submits the new patents to the FDA and the agency, in turn, lists them in the Orange Book. Only patents that claim the brand product or its use are to be listed. However, the FDA relies on NDA holders for this information, and thus always lists the submitted patents.

When a generic manufacturer submits an abbreviated new drug application (ANDA) to the agency, the applicant must certify to the branded product’s patent information in one of the following ways: (1) no patent information has been submitted by the brand manufacturer; (2) the applicable patent has expired; (3) the patent is valid but the generic firm will not market its product until the patent has expired; or (4) the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug. The latter is often referred to as a “Paragraph IV” certification and must be provided not only to the FDA, but also to each owner of the patent and to the NDA holder.

Once the patent owner and NDA holder receive(s) a notification, he has 45 days to sue the generic firm for patent infringement. The lawsuit triggers a statutory delay of 30 months under provisions of the Hatch-Waxman Act. The FDA cannot approve the generic unless the court decides that the patent is invalid or not infringed, or decreases or lengthens the 30-month period. Because the typical patent infringement suit takes many years to resolve, the 30-month stay is almost automatic, regardless of the merits of the lawsuit.

The framework established by the Hatch-Waxman Act raises three particular issues for the generic drug approval process.

• Scope of patents subject to Paragraph IV certification
Generic companies submitting an application for a drug copying a branded product must provide Paragraph IV

certifications not only for the patents originally listed for the drug, but also for those added later to the Orange Book. These patents may be irrelevant to the original form of the product that the generic copies.

• Ineligible or improperly listed patents

The FDA generally refuses to review new patents that manufacturers request to have listed in the Orange Book on the ground that it lacks the expertise to determine their validity. The agency’s role has thus been limited to an administrative one of accepting and listing any patents presented by the companies. Some have claimed that the lack of an effective gatekeeper enables brand companies to list ineligible patents in the Orange Book.²⁷

• Late listed or “submarine” patents

Pharmaceutical companies are sometimes able to time the grant of a patent to coincide with the date when the FDA is about to approve a generic drug. Such “late listed” or “submarine” patents — so-called because they are kept invisible until just before the generic is scheduled to go to market — can scuttle the attempts of generic companies to introduce competing products.²⁸

The Federal Trade Commission has opened a formal inquiry into patent and Orange Book abuse, with a view to determining whether the practices of late and improper listing of patents are hindering competition in the pharmaceutical market.²⁹

3. Incrementally Modified Drugs and Generic Substitution

Under provisions of the Hatch-Waxman Act, if the FDA approves a modified version of the branded drug on the basis of new clinical studies, its manufacturer receives three years of market exclusivity on the “new use” of the product, beginning on the date of approval. New use, in this context, encompasses not only new indications but also other changes, such as those made to the older drug’s dosage form, route of administration, and incorporation into a new combination product. During these three years, no generic company can market a product directly competitive with this new use. Thus, by modifying the same product repeatedly, a brand manufacturer may be able to keep directly competitive generics off the market for a decade or more after the compound patent on the original drug expires.

Market exclusivity does not prevent generic companies from seeking and obtaining FDA approval for copies of the original form of the drug: i.e., the one lacking labeling for the

new use. However, the FDA will not rate such a generic as therapeutically equivalent to the new use, but only to the original form of the drug. In order to receive the agency's therapeutic equivalence rating, a generic must have the same dosage form as well as be bioequivalent³⁰ to the branded product.³¹

The FDA publishes a list of all approved drugs with their therapeutic equivalence ratings in the Orange Book and its monthly Cumulative Supplements.³² The agency provides this information as a reference source, but does not require pharmacists to follow its evaluations. State governments, which regulate the practice of pharmacy, have developed their legal and regulatory frameworks with guidance from the FDA, however. Most encourage pharmacists to follow the Orange Book's therapeutic equivalence ratings either by requiring them to consult it, or by using it to develop statewide formularies or substitution criteria. As a result, if the FDA has not rated a generic as therapeutically equivalent to a branded drug, state pharmacy laws usually prevent its substitution for that product. For example, a pharmacist will generally not be able to substitute a generic version of a drug that must be taken every 4 to 6 hours for a branded drug containing the same active ingredient that must be taken every 12 or 24 hours.

As a result, brand manufacturers sometimes introduce a new version of an older drug and aggressively promote it well in advance of the patent expiry date on the original drug. If doctors can be persuaded to switch their patients to the new product, pharmacists will not be able to substitute a generic copy of the older form of the drug. If successful, such conversion efforts can shield the brand franchise from competition before the date of generic entry.

4. Success in Reducing Generic Market Penetration

Generic drugs cost an estimated 30 to 60% less than their brand name equivalents.³³ Over the past two decades, public and private payers have attempted to encourage appropriate generic substitution in order to control costs. Despite these efforts, the use of generic drugs has stalled. Generic market share, as measured by the percentage of total prescriptions written in the United States, rose to 41.6% in the 1996, and remained within one percentage point of this level through 2000, with minor fluctuations up and down.³⁴ Although 1,505 new generic products were approved between 1994 and 2000, they had virtually no effect on utilization share after 1997.

Several demand side factors may have contributed to this stagnation, including rapid market penetration by new brand drugs with patent protection,³⁵ consumers' unfamiliarity with

generic drugs,³⁶ physicians' limited knowledge of prescription drug prices,³⁷ and massive promotion of branded products to both professionals and consumers.³⁸ However, the entry of many IMDs in the late 1990s, as discussed above, has probably contributed to the leveling off in generic utilization as well.

V. Conclusions: Implications for the Future

Economists expect total national health spending to continue rising over the next decade. The Centers for Medicare and Medicaid Services (CMS), formerly known as the Health Care Financing Administration, have projected that total national health expenditures (NHE) will double from \$1.4 trillion to \$2.8 trillion between 2001 and 2011.³⁹ Although the economy will grow, NHE will outpace Gross Domestic Product (GDP). Thus in 2011 NHE will represent 17% of GDP, versus 14% in 2001 and less than 11% in 1988.

Prescription drug spending will contribute significantly to the growth in costs. The CMS estimate that between 2001 and 2011, prescription drug spending will nearly triple, rising from about \$142 billion to almost \$414 billion. Over the next decade, drug spending growth will exceed total health spending growth by almost 5 percentage points per year on average. As a result, CMS estimates that prescription drugs will account for 14.7% of total NHE in 2011, versus 10.0% in 2001.⁴⁰

As a result, pressures on access to health care will grow over the next decade. Private insurers face the dilemma of reducing benefits or raising premiums to levels that will induce some employers to reduce coverage or pass more of the cost to employees. Consumers not covered by employer plans may reduce or drop their health insurance altogether. Adding a prescription drug benefit to Medicare appears ever less feasible as the states struggle to manage deficits due to runaway Medicaid spending, especially for prescription drugs.

Against this background, physicians and consumers will be challenged to make more rational choices among alternative drug therapies. This report has shown a disparity between spending and clinical value, with a large increase in recent spending attributable to line extensions providing no significant clinical improvement over older medications. To make cost effective decisions, they will need to increase their understanding of the relative value of pharmaceutical alternatives: the relationships among price, clinical outcomes, effect on non-drug forms of medical spending as well as on non-medical costs such as lost work productivity. Integrating

the information into prescribing behavior and consumer awareness will be essential to taming prescription drug costs.

At the same time, Congress needs to examine the special forms of intellectual property protection given to branded drug manufacturers. The Hatch-Waxman Act provides incentives for these companies to invest in modifying older products and patenting their new features. Acting rationally in response to these incentives, brand manufacturers have flooded the market with product line extensions that, in 85% of the cases, do not provide significant improvement over currently marketed therapies. These line extensions contribute substantially to rising costs, however. Standard IMDs accounted for 36% of the spending growth attributable to new drugs in 1995–2000. The current incentive structure offers opportunities for reform that could, over time, help restrain the growth in drug spending and promote access to needed medications.

Credits

Michie Hunt, Ph.D., President of Michie I. Hunt and Associates, wrote this report. Dr. Hunt is a leading expert on pharmaceutical intellectual property protection. Nancy Chockley, MBA, President of the NIHCM Foundation, edited the report. Dan Sherman, Ph.D., of the American Institutes for Research, analyzed the Scott-Levin data.

About the NIHCM Foundation

The National Institute for Health Care Management Research and Educational Foundation is a non-profit organization whose mission is to promote improvement in health care access, management and quality.

Relevant NIHCM Foundation Publications

- *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs* — April 2002
- *Prescription Drugs and Mass Media Advertising, 2000* — November 2001
- *Prescription Drug Expenditures in 2000: The Upward Trend Continues* — May 2001
- *Prescription Drugs and Mass Media Advertising* — September 2000
- *Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation* — August 2000
- *Factors Affecting the Growth of Prescription Drug Expenditures* — July 1999

VI. Appendices

A. Appendix 1: Methodology

1. Part 1: Analysis of NDA Approvals 1989–2000

The analysis uses NDA approval statistics for 1990–2000 accessible from the U.S. Food and Drug Administration's (FDA) website at www.fda.gov/cder/rdmt/pstable.htm, as well as efficacy supplement approval statistics published in the *Center for Drug Evaluation and Research 2000 Report to the Nation: Improving Public Health Through Human Drugs*, which is also accessible from the FDA website. The FDA supplied 1989 NDA approval and 1989–1992 efficacy supplement approval information directly to the author. In addition, the analysis relies on annual reports on efficacy supplement (ES) approvals for 1998–2000, which are published on the website and provide detailed information on the type of approval granted: e.g., of a new indication, dosing form change, labeling change and so forth.

From 1989 to 1993, seven FDA approvals of new indications for drugs that had already been approved were counted as NDA rather than ES approvals, even though the majority of new indications approved during this period were counted as supplemental approvals. Beginning in 1994, the FDA has counted all approvals of new indications as ES approvals, not NDA approvals. To maintain consistency in reporting categories, the author has subtracted the seven approvals mentioned above from the FDA's reported NDA approvals in the 1989–1994 period, and added them to the reported ES approvals.

The analysis uses the FDA's classification of all NDAs by chemical type and by therapeutic potential, as explained in the text. Three of the FDA's classifications — new formulations, new combinations, and new salts or esters of currently marketed drugs — are grouped into one combined category, called incrementally modified drugs. Similarly, the analysis groups NDAs approved for new manufacturers and for certain drugs that were on the market before Congress enacted the Drug Amendments of 1962 into a single combined category, called "other drugs."

2. Part 2: Analysis of Prescription Drug Spending Growth

The retail spending analysis is based on data from Scott-Levin, a Pennsylvania-based health care market research firm. Its annual Source Prescription Audit projects all outpatient prescriptions dispensed by U.S. retail pharmacy outlets, accounting for an estimated 65% of outpatient

drug sales. The SPA does not include sales of prescription drugs by mail order or through nursing homes, hospitals, HMOs, or other health facilities. The Scott-Levin data are not adjusted for discounts on individual drugs, but do include manufacturers' discounts at the wholesale and retail level.

The spending analysis, performed by the Washington, D.C. office of the American Institutes for Research (AIR), uses SPA data to estimate total retail sales by individual drug for 1995 and 2000. Spending growth is defined as the difference in retail sales between these two years. New drugs are defined as those approved by the FDA from 1995 to 2000, while older drugs refer to those approved prior to 1995.

Because sales data are available for individual drugs, and the FDA approval categories are known for all new drugs, it is possible to attribute 2000 sales to one of seven sources: (1) older drugs approved before 1995; (2) new Priority NMEs; (3) new Standard NMEs; (4) new Priority IMDs; (5) new Standard IMDs; (6) new Priority other drugs; and (7) new Standard other drugs. The AIR found that all 2000 sales could be traced to one of these seven categories of drugs except for about \$1.2 billion, less than 1% of the total of \$132.0 billion in total sales for that year.

Drug sales were grouped into major therapeutic categories such as antidepressants, cholesterol reducers and oral diabetes medications. For each category, the sources of spending growth were identified in order to determine the relative contributions of older drugs versus new drugs characterized as either priority NMEs, standard NMEs, priority IMDs, standard IMDs, or "other drugs."

Finally, the 1995 and 2000 average retail price per prescription was calculated for each major category of drug by dividing the total sales for the drug category by the total number of prescriptions dispensed. The average price per prescription is not adjusted for differences in the number of units (such as tablets or capsules), dosage strength, or dosing regime.

B. Appendix 2: Growth in New Indications for Approved Drugs

Research performed on drugs that are already on the market may reveal that they provide safe and effective treatments for diseases or conditions other than the indication(s) for which the product was originally approved. Manufacturers discovering such new uses for approved products may submit a supplemental application, usually called an efficacy supplement, to the FDA in order to receive approval of the new indication.⁴¹ Once the agency grants approval, the manu-

facturer can legally promote the drug for this new use.

Efficacy supplement approvals more than doubled in the late 1990s, rising from 251 in the 1989–1994 period to 650 in the 1995–2000 period. On average, the FDA approved about 108 supplemental applications per year in the later period, versus fewer than 42 in the earlier one.

In recent years, the majority of ES approvals have been for new indications, labeling changes, or new dosage forms. Over half (55%) of ES approvals made in 1998–2000 were for new indications of already approved drugs. In addition, 21% of these approvals authorized changes in the labeling of drugs, and 12% were given to new dosage forms of drugs that are already on the market.

Efficacy supplements have contributed significantly to priority approvals in recent years. In the three-year period 1998–2000, the FDA made 40 ES approvals under the priority review system, versus 44 approvals for NMEs, and 29 for IMDs. The surge in supplemental approvals and the number receiving priority review suggest that new indications may have become an important part of pharmaceutical innovation.

C. Appendix 3: Brief Case Histories

There are numerous examples of the use of product line extensions, late and improperly listed patents, and the 30-month stay to defend brand franchises against generic competition. The following illustrate the breadth of tactics available.

1. Cardizem (Diltiazem)

Hoechst Marion Roussel (HMR), formerly Marion Merrell Dow and now Aventis, combined product line extensions with lawsuits leading to the 30-month stay to thwart generic competition for over a decade. When the FDA finally approved Andrx' generic form of Cardizem CD in 1997, HMR sued Andrx and entered an agreement under which Andrx, in exchange for quarterly payments of \$10 million, would not market the product commercially until the litigation was settled. Finally, when the lawsuit was settled in 1999, a generic version of the CD product reached the market.

2. Eldepryl (Selegiline)

When Eldepryl, Somerset Pharmaceutical's treatment for Parkinson's disease, was about to lose its market exclusivity and generic tablets were already in development, the manufacturer withdrew the tablet and substituted a capsule form of the drug, citing safety concerns. When the FDA

approved the generic in tablet form anyway, Somerset sued the agency. It lost the suit, but in the meantime the FDA has decided that tablet and capsules are not the same dosage form and cannot be substituted for each other as therapeutic equivalents.

3. Premarin (Conjugated Estrogen)

Premarin, introduced in 1942 in what was thought to be an immediate release form, is manufactured from the urine of pregnant mares. It is still the treatment of choice for hormone replacement therapy (HRT) beginning at menopause. Premarin is one of the most prescribed drugs on the U.S. market, and part of a franchise "family" of HRT drugs with about \$2.2 billion in 2001 retail sales and substantial growth prospects as more baby boomers reach 50 years of age. Its manufacturer Wyeth-Ayerst Pharmaceuticals, a subsidiary of Wyeth (formerly American Home Products, Inc.), has protected this franchise by introducing numerous new dosage forms and combination products, including a modified release form of the drug. In addition, Wyeth was able to get the FDA to rescind the approval of the generic products by questioning the bioequivalence of the generic. Wyeth persuaded the agency that the generics were not safe and effective because their rate of absorption differed from that of the modified release form of Premarin.

When generic companies developed a reformulated product, the company campaigned to have the FDA add one of Premarin's concomitant components, on which it held a patent, to the list of its active ingredients. Duramed Pharmaceutical's synthetic conjugated estrogen product Cenestin was not approved until 1999, and then through the 505(b) pathway rather than the less burdensome ANDA route designed for generic drugs. Moreover, because Cenestin is a synthetic product whereas Premarin is a natural product derived from horse urine, the products are not considered to be therapeutically equivalent, and thus are not substitutable.

4. Paxil (Paroxetine)

In 1998, Apotex Corporation filed an ANDA for approval of a generic form of Paxil, a leading antidepressant worth \$2.1 billion in 2001 retail sales. Paxil's manufacturer, GlaxoSmith-Kline (GSK) sued Apotex for infringement of its patent on crystalline paroxetine hydrochloride hemihydrate, a patent that Apotex claimed its ANDA did not infringe. Subsequently, GSK listed eight patents in the Orange Book for Paxil, and brought several lawsuits against Apotex for infringement. The 30-month stays associated with newly listed patents could

keep the generic off the market until 2003.⁴² The FTC is currently investigating GSK's tactics to protect Paxil.⁴³

5. BuSpar (Buspirone)

In November 2000 Bristol Myers Squibb (BMS), facing the expiration of its patent on the lucrative anti-anxiety drug BuSpar, announced that it had received a patent on a metabolite of buspirone and, in an eleventh hour attempt to block generic entry, had the FDA list this patent in the Orange Book. In March 2001, the U.S. District Court for the District of Columbia ordered the FDA to "delist" the patent and approve Mylan Laboratories' generic version.

BMS appealed the delisting decision, and on October 12, 2001 the Federal Circuit reversed the district court decision. The Federal Circuit did not address the merits of the case, and instead held that the trial court did not have jurisdiction over BMS.⁴⁴

In December 2001, New York and 28 other states filed an antitrust lawsuit against BMS in the U. S. District Court in Manhattan. According to the complaint, BMS violated federal and state antitrust laws by obtaining a new patent extending BuSpar's exclusive hold on the market, and knowingly made false statements to the FDA about its new patent to prevent generic manufacturers from introducing a copy of the drug. The states said that these improper actions kept a generic off the market for nearly four months.⁴⁵

BMS filed a motion to have the antitrust complaint dismissed. In January 2002, the FTC filed an *amicus curiae* brief in the court opposing the company's motion to dismiss the case. The commission's brief reflected its continuing interest in ensuring that competition between the manufacturers of generic and branded pharmaceuticals is not impeded by potentially anticompetitive acts or practices.⁴⁶

On February 14, the court denied BMS' motion to have antitrust claims dismissed, thus making it possible for litigation of these claims to proceed.⁴⁷ The court ruled that listing a patent in the Orange Book was not an activity immune under existing antitrust law. The court decided that listing a patent which a reasonable person would know does not and cannot cover the approved product under Hatch-Waxman may be an antitrust violation.⁴⁸ This ruling allows consumer groups, makers of generic drugs, and states to proceed with antitrust suits against Bristol. Some believe that if they win, the company could be liable for millions of dollars in damages.⁴⁹

Notes

1. These included ACE inhibitors for the treatment of cardiovascular disease; the statin drugs used to lower cholesterol; proton pump inhibitors and H2 blockers for the treatment of gastrointestinal disorders; and selective serotonin reuptake inhibitors (SSRI) and recent non-SSRI antidepressants. Cf. V.R. Fuchs and H.C. Sox, Jr., "Physicians' Views of the Relative Importance of Thirty Medical Innovations," *Health Affairs* (Sept/Oct 2001): 30–42.
2. Cf. Kaiser Family Foundation and the Sonderegger Research Center, School of Pharmacy, University of Wisconsin — Madison, *Prescription Drug Trends: A Chartbook Update* (Menlo Park, California: Kaiser Family Foundation, November 2001). The Kaiser Family Foundation found that the types of drugs used accounted for 33% of the growth in prescription drug spending in the 1993–1997 period, and 28% in the 1997–2000 period. Cf. also National Institute for Health Care Management Foundation, *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs*, (Washington: NIHCM Foundation, March 2002). Cf. also National Institute for Health Care Management Foundation, *Prescription Drug Expenditures in 2000: The Upward Trend Continues* (Washington: NIHCM Foundation, May 2001). Cf. also National Institute for Health Care Management Foundation, *Factors Affecting the Growth of Prescription Drug Expenditures* (Washington: NIHCM Foundation, 1999).
3. Historically, the U.S. Food and Drug Administration has regulated conventional drugs and biologics products under different frameworks and separate administrative units. More importantly, the biotechnology sector has only begun to fulfill its promise. Over half of the 133 biotech medicines available today were approved over the past five years. Thus biotech innovation falls outside the scope of a retrospective study, even though some observers expect it to provide major advances over conventional drug therapies in the future. Cf. Biotechnology Industry Association, "FDA Approves 16 New Biotech Products, Eight New Indications in 2001," Press release (February 2002), accessed April 5, 2002 from <http://www.bio.org>.
4. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "Review Management: Priority Review Policy," (Rockville, MD: FDA, 1996): 1–2.
5. IMS Health, "IMS HEALTH Data Reveal Dramatic Growth in Megabrands," no date, accessed March 25, 2002 from <http://www.imshealth.com>.
6. The FDA initiated its therapeutic rating system in 1976 to prioritize its reviews, and until 1992 used a three-tiered system, with A, B and C ratings used to represent a significant gain over an existing therapy, a moderate gain, and little or no gain, respectively. Since then, it has converted to a two-tiered system under which drugs are rated either as "priority" or "standard." Drugs rated as A or B under the old system are designated as "priority" drugs under the new. Private communication with the FDA, June 22, 2001. Cf. also J.A. DiMasi, "New Drug Innovation and Pharmaceutical Industry Structure: Trends in the Output of Pharmaceutical Firms," *Drug Information Journal*, Vol. 34 (2000): 1169–1194.
7. Rx Intelligence, "Economic Comparison of Proton Pump Inhibitors in the Treatment of Mild to Moderate Acute GERD Symptoms," Executive Summary, prepared by RTI Health Solutions, Research Triangle Institute, Research Triangle Park, NC.
8. Cf. Food and Drug Administration, "The Evolution of U.S. Drug Law," accessible at <http://www.fda.gov/fdac/special/newdrug/benlaw.html>.
9. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "Review Management: Priority Review Policy," (Rockville, MD: FDA, 1996): 1–2.

10. *Ibid.* The FDA's Center for Biologics Evaluation and Research does require that the product be intended for a serious or life-threatening disease or condition to receive a priority review.
11. A mechanism of action is the way the drug affects a biological pathway by acting on a biological structure or system to achieve a desired outcome.
12. Doctor's Guide, "FDA Approves Gleevec (Imatinib Mesylate) for Leukemia Treatment," Washington, D.C. (May 10, 2001), accessed March 6, 2002 from <http://www.docguide.com>.
13. Doctor's Guide, "FDA Approves Pulmicort Nebulized Corticosteroid (Budesonide) For Asthmatic Children," Wayne, PA (August 2000), accessed January 21, 2002 from www.docguide.com. Cf. also www.fda.gov.
14. Doctor's Guide, "FDA Approves Aggrenox for Patients With Previous Strokes," Ridgefield, CT (November 23, 1999). Accessed March 5, 2002 from <http://www.docguide.com>.
15. As mentioned above, the ranking system used by the FDA until 1992 distinguished among three classes of new drugs. The present system, which the FDA began to use in 1992, recognizes only two classes of drugs, priority and standard. The priority class comprises both the (A) and (B) groups of the older ranking system, thus including medicines that would formerly have been viewed as offering moderate improvements.
16. In a September 17, 2001 warning letter to Raymond V. Gilmartin, President and CEO of Merck, the FDA notes that in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, "patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), Naprosyn (naproxen)." Accessed March 30, 2002 from www.fda.gov.
17. Drugs using the same mechanism of action affect the same biological pathway by acting on the same biological structure or system in a similar way, thus achieving the same outcome. Such drugs are often said to be in the same therapeutic class.
18. This number excludes an increase in three priority approvals for other drugs, which would bring the total increase in priority approvals to 30.
19. Kaiser Family Foundation and the NIHCM Foundation.
20. F.R. Lichtenberg, "Are the Benefits of Newer Drugs Worth Their Cost? Evidence From The 1996 MEPS," *Health Affairs* (Sept/Oct 2001): 241-251.
21. K.A. Getz and A. De Bruin, "Breaking the Development Speed Barrier: Assessing Successful Practices of the Fastest Drug Development Companies," *Drug Information Journal*, Vol. 34 (2000): 725.
22. Pfizer 2001 revenue is taken from the company's "2001 Fourth Quarter Earnings Release," accessed from www.pfizer.com. Merck's 2001 revenue is taken from Standard & Poor's Stock Reports, "Merck," (March 4, 2002), accessed from www.agedwards.com.
23. J.A. DiMasi, PhD, "New Drug Innovation and Pharmaceutical Industry Structure: Trends in the Output of Pharmaceutical Firms," *Drug Information Journal*, Vol. 34 (2000): 1169-1194.
24. IMS Health, "IMS HEALTH Data Reveal Dramatic Growth in Megabrands," no date, accessed March 25, 2002 from <http://www.imshealth.com>.
25. Estimates of the combined value of drugs going off patent vary, depending on the methodology and time horizon used. Last year, some industry analysts projected that the principal patents on branded drugs with collective sales of about \$35 billion would expire by 2005, and that about \$53 billion would do so by 2010. Cf. J.I. Treppel, "Generic Drugs: Where Are We Now? Where Are We Going?" Presentation given at the National Association of Pharmaceutical Manufacturers (NAPM) 2001 Annual Meeting and Educational Conference, January 2001.
26. U.S. Food and Drug Administration, "Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance," (Rockville, MD: FDA, 1999). Accessible at <http://www.fda.gov>.
27. A.Y. Tsien, "Orange Book Patent Listing Litigation," presentation given at the NAPM Annual Conference, January 29, 2001, Puerto Rico.
28. In recent years, the Patent and Trademark Office's (PTO) user fee system has fostered such surprises. The PTO typically grants a patent 60 days after the user fee is paid. Thus, branded companies can submit a patent application to the PTO well in advance of the expected date of generic approval, but withhold the user fee payment. This tactic enables the PTO to complete its review of the application, but prevents it from actually granting the patent. Sixty days before the company wishes to receive the patent, it pays the PTO user fee, thus timing the patent grant and ability to list the new patent in the Orange Book with some precision.
29. The Federal Trade Commission announced its proposed investigation and requested comments in a Federal Register notice in October 11, 2000. This notice may be accessed from <http://www.ftc.gov/os/2000/10/frngenericstudy.htm>. Cf. also Greenblum & Bernstein PLC, "Greenblum & Bernstein Update," Vol.5, No. 2 (February 2001). The commission is expected to release a study this summer on competition between generic and brand-name drug companies. Cf. G. Harris and C. Adams, "Drug Firm Taken To Task By FTC For Tactic To Keep Generic At Bay," *Wall Street Journal* (April 24, 2002), A3.
30. In order to be bioequivalent, the generic drug must use the same active ingredient, and the rate and extent of the active ingredient's absorption by the body must be the same.
31. A complete discussion of the background and basis of the FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which contained the FDA's responses to public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582).
32. The FDA uses a code based on letters to assign equivalence ratings to branded and generic drugs. In general, two letters are assigned to a drug. The first of the two letters indicates its bioequivalence status. Bioequivalence means that the body's rate and extent of absorption of the drugs' active ingredient are the same. The FDA's rating of "A" means that the drug has no unresolved bioequivalence issues; a rating of "B" that it has a potential or documented bioequivalence problem. The second letter designates the dosage form. For example, an "AA" rating means that the drug has no bioequivalence problems in conventional dosage forms. An "AP" rating means that the drug is an injectable solution meeting bioequivalence requirements, an "AT" rating that it is a topical drug meeting such requirements.
33. J.A. Jacob, "Michigan Blues Plan Pushes Generic Drugs," *American Medical News* (September 10, 2001), accessed September 20, 2001 from <http://www.amednews.com>.
34. J.I. Treppel, "Generic Drugs: Where Are We Now? Where Are We Going?" The market share estimates were derived by Bank of America from data provided by IMS Health.
35. In the late 1990s the FDA approved several new branded products that achieved rapid market penetration. These included the anti-cholesterol drug Lipitor; the COX-2 inhibitors Vioxx and Celebrex; and the anti-diabetic agents

CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION

Actos and Avandia. These drugs still enjoy patent protection and thus do not face direct generic competition.

36. A 1999 survey of over 1,000 adult consumers sponsored by Merck-Medco LLC, a New Jersey-based pharmacy benefit manager, found that nearly half (46%) of respondents reported that they were not knowledgeable about generic drugs. Further, knowledge affected other beliefs. Consumers who believe that generic drugs are safe and effective alternatives to branded drugs (56%) were significantly more likely than those who do not (40%) to be knowledgeable about them. Cf. Bruskin Goldring Research for Merck-Medco LLC, "Executive Summary: Generic vs. Brand Name," (Edison, New Jersey: March 1999): 3.

37. Physicians appear limited in their ability to make cost effective prescribing decisions, despite good intentions. A study of physicians' attitudes and knowledge conducted at New York's Mount Sinai Medical Center found that although 81% of physicians felt that the cost of medicine was an important consideration in prescribing decisions, 80% said that they often felt unaware of the actual costs of medicines. Further, only 33% of the doctors had easy access to drug cost data, and only 13% had been formally educated about drug costs. When they were asked to estimate the cost of a month's supply of 33 common medicines, their estimates were accurate in just 45% of the cases, too low in 40%, and too high in 15%. The costs of brand name and expensive drugs were most likely to be underestimated. Cf. S. Reichert, MD, T. Simon, MD, E.A. Halm, MD, MPH, "Physicians' Attitudes About Prescribing and Knowledge of the Costs of Common Medications," *Archives of Internal Medicine*, Vol. 160, No. 18 (October 9, 2000): 2799–2803.

38. National Institute for Health Care Management Foundation, *Prescription Drugs and Mass Media Advertising, 2000* (Washington: NIHCM Foundation, November 2001). Cf. also IMS Health, "IMS Health Reports Pharmaceutical Direct-to-Consumer Ad Investment in U.S. Reaches \$1.3 Billion in First-Half 2000," accessible at www.imshealth.com. Cf. also Michie I. Hunt, *Prescription Drug Costs: Federal Regulation of the Industry*, Executive Summary, (Washington: Blue Cross Blue Shield Association, September 2000): 6, accessible at <http://www.bcbshealthissues.com>.

39. S. Heffler, S. Smith, G. Won, M.K. Clemens, S. Keehan, and M. Zezza, "Health Spending Projections for 2001–2011: The Latest Outlook," *Health Affairs* (Mar/Apr 2002): 207–218. The CMS 2001 prescription drug spending estimates differ from the NIHCM Foundation's because CMS uses a different methodology. Cf. also discussion of CMS projections in C.D. Mullins, J. Wang, F.B. Palumbo, and B. Stuart, "The Impact of Pipeline Drugs on Drug Spending Growth," *Health Affairs* (Sept/Oct 2001): 210–215.

40. *Ibid.*

41. Under U.S. law, it is legal for a physician to use any FDA approved drug to treat diseases or conditions for which the drug has not been approved. However, it is not legal for the manufacturer to promote the drug for an unapproved use. If the market for a new use of the drug is sufficiently large, the manufacturer has an incentive to perform clinical studies and apply to the FDA for approval of the drug for the new indication. Once the agency gives its approval, the manufacturer can legally promote the drug for this use.

42. Apotex Corporation, Press Release, "Apotex Receives Tentative FDA Approval for Generic of GlaxoSmithKline's Paxil®," (Weston, Florida: May 30, 2001), accessed September 29, 2001 from <http://www.google.com/search?q+cache:itunOTc-DvE:biz.yahoo.com/prnews/010530/clw010.html>. Cf. also Apotex Corporation, Press Release, "Apotex Seeks Injunction Against GlaxoSmithKline and Food and Drug Administration (FDA) on Paxil®; Apotex Seeks Removal of Six Patents for Blockbuster Anti-Depressant from FDA's Orange Book." Both of these articles have expired but may be retrieved as cached material through the search engine at <http://www.google.com>. There is no guarantee that a generic version of Paxil will reach the market by 2003, however. Cf. "Fifty Ways to Keep Your Patent," *Business Week Online* (December 10, 2001): accessed May 21, 2002 from http://www.businessweek.com/magazine/content/01_50/b3761007.htm.

43. G. Harris and C. Adams, "Drug Firm Taken To Task By FTC For Tactic To Keep Generic At Bay," *Wall Street Journal* (April 24, 2002), A3.

44. Greenblum & Bernstein, P. L. C., "Greenblum & Bernstein Update," Vol. 6, No. 5, No. 10 (October 2001).

45. C. DeBoise, "New York, 28 Other States File Antitrust Suit Against Bristol-Myers," *Dow Jones* (December 12, 2001), accessed May 15, 2002 from <http://www.spancoalition.org/NewNews/12.12.01.htm>.

46. Federal Trade Commission, "Issuance of Two Amicus Curiae Memorandum of Law Briefs," January 9, 2002, accessed from www.ftc.gov/opa/2002/01/fyi0202.htm. The text of the brief can be accessed from www.ftc.gov/os/2002/01/busparbrief.pdf.

47. M. Petersen, "Bristol-Myers Held Culpable in Patent Move Against Rivals," *New York Times* (February 20, 2002) accessed May 15, 2002 from <http://www.spancoalition.org/NewNews/02.20.02.htm>.

48. Greenblum & Bernstein, P. L. C., "Greenblum & Bernstein Update," Vol. 6, No. 3 (March 2002).

49. M. Roman, "Bristol-Myers Has a Legal Headache," *Business Week* (March 4, 2002): accessed May 15, 2002 from <http://www.spancoalition.org/NewNews/03.04.02.htm>.