NIHCM Foundation stands by its report 100%. The report uses objective data and a robust methodology to address issues of broad concern to policy makers and the public.

“Changing Patterns of Pharmaceutical Innovation” examines all of the drugs approved by the U.S. Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) from 1989 to 2000. By analyzing FDA data, the report found that relatively few of the new drugs approved during this period were highly innovative, and that modified versions of older medications became increasingly dominant over time. It also found that a significant share of the growth in retail prescription drug spending from 1995 to 2000 could be attributed to modified versions of older drugs that, according to the FDA, were similar in clinical value to drugs that were already available.

PhRMA, the trade association of the pharmaceutical industry, attacked the report in a paper released on June 11, 2002. The material below is a point-by-point response to PhRMA’s criticisms.

PhRMA begins by claiming that NIHCM Foundation’s report never disclosed its sponsorship. In fact, NIHCM Foundation published “Changing Patterns” through its website, www.nihcm.org, which lists its Board of Directors and funding sources. In addition, NIHCM Foundation has an Advisory Board of senior health policy experts, including: John Iglehart, Health Affairs; Uwe Reinhart; Princeton University; Robert D. Reischauer, the Urban Institute; John Cogan, Stanford University; James Mongan, Massachusetts General Hospital; and Gail Wilensky, Project HOPE. NIHCM Foundation provided “Changing Patterns” to the Advisory Board for review before its publication. The NIHCM Foundation’s Board of Directors were not provided copies of the report prior to its release.

1. “NIHCM Arbitrarily Excludes All Vaccines and Biotech Drugs From Its Purported Objective Analysis.”

“Changing Patterns” analyzes all of the 1,035 new drugs approved by the FDA’s CDER over the twelve-year period from 1989 to 2000. It excludes biologics drugs and vaccines because the FDA regulates and approves them under a separate system and through a separate organization, the Center for Biologics Evaluation and Research (CBER). CDER and CBER have different regulations and policies.

These differences reflect the fact that biotechnology is a separate industry, different in many respects from the traditional pharmaceutical industry. It consists of a group of companies using a specialized set of technologies under a unique regulatory and legal framework, different from that used for conventional drugs.

Some large pharmaceutical companies have diversified into biotechnology by acquiring or investing in biotechnology companies, or by entering into agreements to market products developed by
biotechnology firms. However, analysts generally recognize that the industry consists of a group of firms specializing in biotechnology or maintaining significant biotech operations, including Amgen, Biogen, Chiron, Genentech, Medimmune, Immunex, and IDEC Pharmaceuticals.

As noted in the report, biotechnology is only now emerging from its infancy and beginning to bring a significant number of new products to market. According to the Biotechnology Industry Association (BIO), 70% of all the biotech medicines now on the U.S. market were approved within the last six years. For this reason, a retrospective analysis of biotechnology is not likely to be revealing of any sustained pattern. To the contrary, most of the interest in biotechnology focuses on its promise of bringing new medicines to market in the future (see footnote 3 in the report).

Some significant biologics drugs and vaccines have already come to market, as the PhRMA paper states. What PhRMA neglects to say is that the biotechnology industry, not the traditional pharmaceutical industry, was responsible for developing them. According to a recent Standard & Poor’s industry report, the top ten biotechnology products in terms of 2001 global sales were all developed by biotechnology firms, although some of them are marketed by leading pharmaceutical firms (see Figure 1 below).

### Figure 1
**Top Ten Biotechnology Drugs**

<table>
<thead>
<tr>
<th>Product</th>
<th>Indicated Use</th>
<th>2001 Sales in $Millions</th>
<th>Developer</th>
<th>Marketer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procrit</td>
<td>Red blood cell enhancement</td>
<td>3,430</td>
<td>Amgen</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Epogen</td>
<td>Red blood cell enhancement</td>
<td>2,109</td>
<td>Amgen</td>
<td>Amgen</td>
</tr>
<tr>
<td>Intron A/Rebetron</td>
<td>Hepatitis C, certain forms of cancer</td>
<td>1,447</td>
<td>Biogen, ICN</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Neupogen</td>
<td>Restoration of white blood cells</td>
<td>1,346</td>
<td>Amgen</td>
<td>Amgen</td>
</tr>
<tr>
<td>Humulin</td>
<td>Diabetes mellitus</td>
<td>1,061</td>
<td>Genentech</td>
<td>Genentech, IDEC</td>
</tr>
<tr>
<td>Avonex</td>
<td>Relapsing multiple sclerosis</td>
<td>972</td>
<td>Biogen</td>
<td>Immunex, American Home Products</td>
</tr>
<tr>
<td>Rituxan</td>
<td>B-cell non-Hodgkin’s lymphoma</td>
<td>819</td>
<td>IDEC</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Rheumatoid arthritis</td>
<td>762</td>
<td>Immunex</td>
<td>Immunex, American Home Products</td>
</tr>
<tr>
<td>Remicade</td>
<td>Rheumatoid arthritis, Crohn’s disease</td>
<td>721</td>
<td>MedImmune</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Cerezyme</td>
<td>Enzyme replacement therapy</td>
<td>570</td>
<td>Genzyme</td>
<td>Genzyme</td>
</tr>
</tbody>
</table>

Source: Standard & Poor’s “Biotechnology,” May 2002
2. “NIHCM Misuses FDA’s Priority Review Classification System.”

As stated in the report, the FDA’s priority and standard designations are robust criteria for distinguishing drugs that make clinical improvements from those that are similar to those already on the market. The CDER uses four specific criteria for determining whether a new drug may receive a priority review. New drugs may qualify by:

(1) evidence of increased effectiveness in the treatment, prevention, or diagnosis of disease;
(2) elimination or substantial reduction of a treatment-limiting drug reaction;
(3) documented evidence of improved patient compliance; or
(4) evidence of safety or effectiveness for a new patient population.

They need not treat a serious or life-threatening disease to qualify, as do biologics products reviewed by CBER (see page 6 and footnote 10 in the report).

CDER gives the coveted priority designation to any drug that can show an advantage in one of the four ways mentioned above. Thus, as the report states on page 6, both Vioxx and Celebrex received priority reviews because they were believed to have less severe and prevalent gastrointestinal side effects than common non-steroidal anti-inflammatory (NSAID) drugs such as ibuprofen and naproxen. Gastrointestinal problems occur for only a small percentage of patients receiving NSAID drugs, which are safe enough to be sold over-the-counter. Nevertheless, the FDA viewed the small increase in safety as sufficient to warrant a priority designation.

CDER also gives a priority review to “me too” drugs if they can demonstrate improvement over a breakthrough drug that is already on the market. For example, the FDA gave priority reviews to both Avandia and Actos, two anti-diabetic drugs approved in 1999 for treatment of type 2 diabetes. Avandia and Actos were “me too” drugs using the same mechanism of action as Rezulin, which was already on the market at the time of their approval. However, they appeared to be safer than Rezulin, which raised concerns because of liver toxicity and was later withdrawn from the market.

Thus, drugs receive a standard review only if they fail to demonstrate a clinical advantage in any of the four accepted ways.

The FDA’s priority or standard designation at the time of review does not, of course, constitute final judgment on the value of the drug. A medicine’s full range of benefits and side effects and interactions with other medicines are usually not known until the drug has entered the market and been used by thousands of patients. Thus:

- Some medications prove effective for new indications after they have entered the market. New indications approved under efficacy supplement applications have emerged as an important source of priority rated new technology, as the NIHCM Foundation study notes in Appendix 2 on pages 20-21.
- On the other hand, some drugs eventually manifest side effects and interactions that were not known at the time of approval, and must be withdrawn from the market for safety reasons. In recent years the FDA has removed several medications approved since the mid-1990s, including four standard NMEs and two priority NMEs that were included in the report’s count of total NMEs.

What “Changing Patterns” actually says about standard drugs is the following, on page 7 under “C. Ranking System for Innovation.”

“The FDA rates many NMEs as standard products. Although based on new compounds, these drugs usually have the same mechanism of action 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.”

4. “NIHCM Ignores New Medicines in Development.”

The study is a retrospective one, designed to assess the actual output of the originator pharmaceutical industry and determine which types of medicines have been driving the rapid growth in prescription drug spending. Several studies have identified a shift toward the use of new drugs as a prime factor responsible for increased spending. However, “Changing Patterns” is the first study to address the question of how drugs with differing levels of innovation have affected spending growth.

By measuring actual output, “Changing Patterns” suggests the kinds of R&D projects that have received support in pharmaceutical firms for more than a decade. NIHCM Foundation does not have access to detailed information about the pharmaceutical industry’s R&D investments. However, the report’s analysis of the industry’s actual output and related spending growth patterns provides evidence that pharmaceutical firms have made significant investments in modifying older drugs and aggressively marketing them.

This shift toward modified drugs, in turn, enables policy makers to assess some of the effects of the Hatch-Waxman Act, which was intended to provide incentives to brand manufacturers to develop new medicines and promote access to affordable generic drugs. Many studies assessing the effect of the Act have focused on the development of medicines based on new compounds, or NMEs. However, Hatch-Waxman also provides strong incentives for manufacturers to develop incremental technology: three years of market exclusivity for “new uses” of older drugs, and the “30-month” stay provision, often used to delay market entry of generic drugs. Thus, the report’s retrospective
analysis provides a way to assess this often ignored effect of the Hatch-Waxman Act (see pages 16-18 of the report).

5. **“NIHCM Report Claims But Does Not Demonstrate Changing Pattern of Pharmaceutical Innovation.”**

As mentioned above, “Changing Patterns” focuses on a 12-year period, and examines the difference in drug approvals made in the first half, from 1989 to 1994, and the second one, from 1995 to 2000. The study found that as the 1990s progressed, the number of incrementally modified drugs (IMDs) the FDA approved grew at a faster pace than drugs based on new molecular entities (NMEs). In the six-year period 1995-2000, the FDA approved 304 new standard incrementally modified drugs versus 168 in the period 1989-1994, an increase of 81%. By contrast, approvals of priority new molecular entities increased by just 10%, from 73 between 1989 and 1994, to 80 between 1995 and 2000.

Of the 219 more IMDs and NMEs approved in the period 1995 to 2000 compared to the period 1989 to 1994, 156 (71%) were incrementally modified drugs and 63 (29%) were new molecular entities.

NIHCM Foundation chose the 1989 – 2000 period because it is recent and revealing of the impact of several laws enacted in the early 1980s and 1990s, particularly the Hatch-Waxman Act.

6. **“NIHCM Report Ignores Evidence Indicating Multiple NME’s in a Class Does Lead to Price Competition.”**

“Changing Patterns” presents evidence from its own analysis that there is only about a 10% difference between the average price per prescription for a priority NME and a standard NME: $91.20 versus $81.92 versus in 2000. By contrast, the average cost per prescription for drugs approved before 1994 was $37.20, less than half of either the standard or priority NME. These findings suggest that the primary price competition in prescription drugs occurs between older drugs (brand and generic) and new drugs, not among the new drugs themselves.

The study’s findings are consistent with earlier studies that have also found that there is only limited price competition among drugs in a given therapeutic class. In 1998, the Congressional Budget Office released a report examining the list prices of breakthrough versus me-too drugs in five therapeutic classes. The study found that in four of the five, the list price of the breakthrough drug continued to rise above the rate of inflation after the entry of one or more me-too products. Similarly, a University of California study found that the average list price of brand-name drugs continues to rise faster than inflation after the introduction of a me-too competitor.

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7. “NIHCM Report is Self-Contradictory in its Critique of Pharmaceutical Innovation.”

“Changing Patterns” raises no objection to modifying older drugs to produce better medications. Contrary to the PhRMA’s claim that “NIHCM fails to acknowledge that companies develop new formulations for specific patient populations,” especially children, the report cites AstraZeneca’s asthma medication Pulmicort Respules as an example of a modified drug that extended the benefits of inhaled corticosteroid therapy to children and infants as young as 12 months old (see “Changing Patterns,” page 6). The report notes that this drug received a priority rating from the FDA because it extended the benefits of an established therapy to a new class of patients.

“Changing Patterns” does argue that incremental modification of older drugs provides brand manufacturers with access to several mechanisms that may be used to prevent the entry of generic competitors. In particular, it notes the listing of new patents in the Orange Book as a means of triggering the 30-month stay, which delays generic entry. The Federal Trade Commission is currently investigating brand manufacturers’ use of tactics mentioned in the report to prevent or delay generic competition.


“Changing Patterns” does not “blame” any medicines for cost increases. It analyzes the sources of increased retail spending on prescription drugs from 1995 to 2000, and finds that 67% of the $44 billion increase that could be attributed to new drugs came from standard-rated medications. Moreover, 36% of the increase could be attributed to standard-rated modified drugs (IMDs), typically product line extensions. It further analyzes the average price per prescription for new versus older drugs, and finds that older drugs are on average much less expensive than new drugs, whether these are standard or priority-rated.

9. “NIHCM Report Focuses on Price of New Drugs, Not Their Value to Patients.”

“Changing Patterns” assesses the level of innovation of several broad classes of drugs; it does not try to determine the value of individual drugs. However, the report endorses efforts to measure value. On page 18, it notes that in order to make cost-effective choices among drug therapies, physicians and consumers “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.”

10. “Modifications to Existing Drugs Does Not Preclude Generic Competition on Older Invention Once its Patent Expires, Contrary to NIHCM’s Suggestion.”

Modifications of drugs do not, by themselves, prevent generic versions of the older form of the drug from entering the market. They do, however, provide brand manufacturers with access to the 30-month stay provision of the Hatch-Waxman Act, which can be used to delay generic entry. They
also enable brand manufacturers to shield the franchise from competition from generic copies of the older version of the drug.

What “Changing Patterns” actually says on this subject on pages 16 and 17 is the following:

“Drug companies patent a wide range of inventions connected with incremental modifications of their products … 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 manufacturers to postpone the entry of even such carefully designed products by recourse to a mechanism known as the ‘30-month stay.’”

On pages 17 – 18, “Changing Patterns” says the following with respect to market exclusivity given to “new uses” of older drugs:

“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.”

**Conclusion**

NIHCM Foundation invites you to read the report, accessible from [www.nihcm.org](http://www.nihcm.org), and to visit the FDA’s website at [www.fda.gov](http://www.fda.gov). The FDA provides summary information on all drug approvals made from 1990 to 2001, broken out by chemical type and therapeutic potential, in a table accessible at [www.fda.gov/cder/rdmt/pstable.htm](http://www.fda.gov/cder/rdmt/pstable.htm). The report is an objective analysis of a critical component of health care. NIHCM Foundation values meaningful evaluation of all issues that improve the effectiveness, efficiency, and quality of America’s health care system.