NIHCM Report on Pharmaceutical Innovation:  
NIHCM Response to PhRMA Rebuttal is Silent on the Real Issues

On June 13, 2002, the National Institute for Health Care Management (NIHCM)—whose 12-member Board of Directors includes 11 Blue Cross and Blue Shield CEOs—responded to PhRMA’s critique of its report, “Changing Patterns of Pharmaceutical Innovation.” This response fails to rehabilitate NIHCM’s report.

In two respects, though, NIHCM’s response is revealing of the report’s lack of value in informing policy discussions. First, the response highlights the initial NIHCM report’s errors and omissions, since the response fails to meaningfully address—or even mention—the key points raised by PhRMA. Second, as discussed in greater detail below, portions of NIHCM’s response highlight its passages indicating that standard review drugs “enhance clinical outcomes.” To the extent that NIHCM’s response accepts our point regarding the significant clinical value of standard review drugs, it negates all other conclusions reached in the report.

This document briefly discusses the points raised—and neglected—by NIHCM’s attempt to salvage its flawed study.

NIHCM’s Erroneous Claim to Value Meaningful Evaluation of All Health System Issues

NIHCM concludes its report by stating, “NIHCM Foundation values meaningful evaluation of all issues that improve the effectiveness, efficiency, and quality of America’s health system.” However, as PhRMA’s rebuttal discussed, NIHCM’s agenda has been remarkably narrow in recent years. Its specialty increasingly is producing reports critical of the pharmaceutical industry\(^1\) while virtually ignoring meaningful patient care issues that involve its own industry. NIHCM’s response to PhRMA never addresses this point.

As one example of the type of issue that NIHCM ignores in favor of continuously attacking the pharmaceutical industry while proclaiming its interest

\(^1\) According to its website as of September 11, 2002, since February 1999, NIHCM had released 8 separate publications on pharmaceuticals. All can fairly be described as critical of the pharmaceutical industry. During the same time period, NIHCM issued no publications on medical necessity, Medicaid, Medicare, rural issues, state health care reform and individual market reform—all of which were the topic of reports prior to February 1999. The 16 non-pharmaceutical publications issued since February 1999 include 11 documents on children’s health issues (as noted on its website, NIHCM is under a five-year cooperative agreement with the U.S. Health Resources and Services Administration Maternal Child Health Bureau to produce these documents, most of which are quite brief) four brief “Expert Voices” essays, and a report that NIHCM describes as a “brief analysis” of Census Bureau data on health insurance coverage. Other than publications on child health, which NIHCM is under contract to produce, no other single health care issued has garnered as much attention from NIHCM as pharmaceuticals.
in “all issues that improve the effectiveness, efficiency, and quality of America’s health system,” PhRMA’s June 11 rebuttal pointed to NIHCM’s lack of interest in data showing apparent undertreatment of patients in its own member health plans. For example, the California Office of the Patient Advocate issues a health maintenance organization (HMO) report card that includes Blue Cross HMO – CaliforniaCare, which is part of Wellpoint, one of the NIHCM member companies. One measure of this report card provides a “quality score on making sure that children, adolescents and adults with asthma get the right medicine.” The measure shows the percentage of each group with asthma having a “prescription for anti-inflammatory medicine to reduce the severity of asthma symptoms and avoid asthma attacks.” Also according to the explanation of the scores posted on the Office of the Patient Advocate’s website:

Good asthma care means seeing that patients use medicines – called anti-inflammatories – regularly to reduce the effects of asthma including wheezing, coughing and shortness of breath. These medicines are part of the daily efforts of people with asthma to avoid the pain, anxiety or even death that results from asthma.

On this measure of “making sure that children, adolescents and adults get the right medicine,” Blue Cross HMO – CaliforniaCare (a NIHCM member-company), even after improving from the prior year, received 61% for children, 59% for adolescents, and 68% for adults, on a scale of 0% (worse) to 100% (best). Apparently issues such as “health care plan practices” that might reduce the large number of patients without the proper medicines to treat asthma, thereby improving “the effectiveness, efficiency, and quality of America’s health system,” have no meaningful place on a NIHCM research agenda devoted to attacking the pharmaceutical industry.

NIHCM’s Exclusion of Vaccines and Biologics from its Analysis

NIHCM’s analysis of patterns of pharmaceutical innovation arbitrarily excluded vaccines and biologics. As PhRMA’s rebuttal points out, it is easy for NIHCM to report any results it desires by arbitrarily excluding large numbers of medicines from the data it presents. In its response, NIHCM argues that it is

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2 For a statement of the importance of inhaled corticosteroids, see National Institutes of Health, Expert Panel Report 2, “Guidelines for the Diagnosis and Management of Asthma. “Thus, EPR-2 continues to emphasize that the most effective medications for long-term control are those shown to have anti-inflammatory effects. For example, early interventions with inhaled corticosteroids can improve asthma control and normalize lung function, and preliminary studies suggest that it may prevent irreversible airway injury.”

3 For the California Office of Patient Advocate HMO report card, see www.opa.ca.gov/report_card. In addition to the asthma measure discussed above, the report card also includes data on controlling diabetes and hypertension, among other measures.

4 Ibid.

5 Ibid.

6 Ibid.
justified in excluding all biotechnology drugs and vaccines from its analysis since biotechnology and pharmaceuticals are separate industries, with the biotechnology industry “responsible for developing” biologics and vaccines. It also argues that because most biotechnology medicines have come on the market within the last six years, a retrospective analysis is unlikely to be revealing of any sustained pattern.

First, NIHCM’s “separate industry” and “biotechnology industry develops biologics and vaccines” rationales for excluding biotechnology medicines from its study is wrong. Biologics are researched and developed in the private sector through a variety of arrangements, including by biotechnology companies alone, by pharmaceutical companies alone, and by pharmaceutical and biotechnology companies jointly. In some, but not all, instances, a biotechnology company researches a drug—often with backing by pharmaceutical companies—and then jointly develops it (i.e., moves the drug through the clinical trials phase that accounts for a large majority of total R&D expenditures) with a pharmaceutical company. At least thirteen pharmaceutical companies have approved biotechnology medicines and/or vaccines on the market (with research and/or development done in-house). Even more pharmaceutical companies currently have new biotechnology medicines in development.

Second, pharmaceutical companies often provide the capital that biotechnology companies need to research and develop medicines. In some cases, this is on a drug-specific basis. In other cases, it is through investment in a company. For instance, one major biotechnology company is majority-owned by a pharmaceutical company. NIHCM may erroneously claim that drugs developed through such collaborations should not be counted as having pharmaceutical industry involvement. Yet NIHCM’s own June 13 response claims (page 4) that the original NIHCM report “suggests the kinds of R&D projects that have received support in pharmaceutical firms for more than a decade.” When evaluating the kinds of R&D projects that have received pharmaceutical company support, there is no basis for distinguishing support of in-house biotechnology projects from support for projects located in biotechnology companies.

Third, the June 13 response’s claim that a retrospective analysis is unlikely to be revealing makes no sense. Elsewhere in its response (page 4), NIHCM emphasizes that it ignored new medicines in development because “[t]he study is a retrospective one, designed to assess the actual output of the originator pharmaceutical industry....” Thus, NIHCM chooses to ignore retrospective results when doing so supports its desired conclusion, but then reverses course and emphasizes retrospective results when that supports its desired conclusion.

Fourth, FDA approval statistics show that nearly as many new biologics (22) were approved from 1989-1994 as were approved from 1995-2000 (26).
The approval of nearly as many biologics during the 1989-1994 period as during the 1995-2000 period reflects the long-term commitment of scientific and financial resources of the industry—not a passing fad or temporary aberration as NIHCM’s response would have readers believe. But somehow, according to NIHCM, the 1995-2000 results indicate “biotech innovation falls outside the scope of a retrospective study.”

Fifth, NIHCM is comfortable with characterizing the pharmaceutical industry’s output in six-year increments where it suits its purpose to do so, making the claim that biotechnology drugs should be excluded because most have come on the market within the last six years simply ludicrous. In the simplest terms, when claiming to characterize output over a defined period, it is illegitimate to exclude a large portion of output during that period on the basis that it may not represent a sustained pattern. It is difficult to find any legitimate rationale (rather than a rationale based on achieving desired results) for this selective exclusion of retrospective results from a retrospective study.

Sixth, Amgen, the biotechnology company named by NIHCM in the press as a contrast to the pharmaceutical industry, is a member of PhRMA’s Board of Directors, and PhRMA’s Board and membership include many other biotechnology companies.

Finally, to date, nearly all vaccines have been developed by pharmaceutical companies. Neither NIHCM’s report nor its June 13 response provide meaningful explanation for its exclusion of vaccines.

NIHCM’s Misuse of the FDA’s Priority Review Classification System

NIHCM’s report uses the Food and Drug Administration’s (FDA) Manual of Policies and Procedures 6020.3, which defines “standard” and “priority” review drugs, to justify its conclusion that standard rated medicines provide no significant improvement over marketed products. PhRMA’s rebuttal pointed out that NIHCM selectively cited the FDA manual, failing to note that this same manual also states:

The priority determination does not take into consideration any information or estimate of price and is based on conditions and information available at the time the application is filed. It is not intended to predict a drug’s ultimate value or its eventual place in the market. (Italics added).

Although this was clearly stated in PhRMA’s rebuttal, NIHCM’s response is silent about this portion of FDA policy. In light of NIHCM’s continuing claims that its
research is “objective,” it is difficult to understand why this crucial passage was left out of both its original analysis and its response.

Moreover, FDA classification is necessarily based only on evidence available before a drug is reviewed and on the market. The value of a drug often is not fully known until it has been on the market for a few years. NIHCM could have examined evidence that developed after the drug reached the market, since it chose to conduct a retrospective study. Yet it chose not to do so, thereby ignoring a large body of evidence that sheds light on important issues it purports to address.

PhRMA’s rebuttal also noted that the FDA itself publishes a list of what it labels “Notable Drugs” receiving approval each year (PhRMA’s rebuttal lists these drugs for each of the last three years), and that many of these drugs received standard reviews. NIHCM’s response was silent on this point as well.

Additionally, PhRMA’s rebuttal pointed out that many standard review drugs represented the first drug in their class. These include, for instance, among many others:

- Cozaar®, the first in a new class of antihypertensive agents that block angiotensin-II receptors;
- Accolate®, the first leukotriene receptor antagonist for asthma treatment;
- Remeron®, the first in a new class of antidepressants;
- Vistide®, the first in a new class of antivirals (nucleotide analogues) for treatment of cytomegalovirus retinitis in AIDS patients; and
- Tasmar®, the first in a new class of drugs (catechol-O-methyltransferase inhibitors) for the treatment of Parkinson’s disease.

NIHCM’s response to PhRMA is silent on this point, too.

PhRMA’s rebuttal also pointed out the striking inconsistency between the NIHCM report’s methodology and the practices of NIHCM’s own Blue Cross and Blue Shield members. While the NIHCM report claims that drugs accorded a standard review by the FDA “are those that the FDA views as providing no significant improvement over marketed products” and “those providing no significant clinical improvement over existing products,” NIHCM fails to explain that the Blue Cross and Blue Shield companies that make up almost the entire NIHCM Board frequently select standard review drugs for the formularies that largely determine which medicines are accessible to patients. Most notably, they do so under policies that emphasize the value of the medicine they have chosen. NIHCM’s response to PhRMA’s rebuttal on this point is—once again, complete silence.

As one example of the inconsistency between its report and its Board members’ practices that NIHCM has chosen not to address, Blue Cross of
California (a subsidiary of a NIHCM Board member Wellpoint) states, “Formulary revision is based on objective evaluation of the efficacy, safety and value of reviewed medications.”

Anthem, another Blue Cross and Blue Shield plan that is a NIHCM Board member, is even more explicit about how it selects medicines for its formulary:

A Formulary (or Preferred Drug List) is a list of brand-name and generic medications that have been rigorously reviewed and selected by a committee of practicing doctors and clinical pharmacists for their quality, cost savings and effectiveness.

Anthem goes on to state that:

First, the Clinical Review Department reviews the medication’s profile or its significant features and the treatments for which it will be used. Pharmacists evaluate the benefits of the new medication and compare them to existing therapies.

Next, they evaluate research studies that assessed the effectiveness of the medication and may perform a cost benefit analysis of the medication. Finally, the Anthem Prescription and Therapeutics Committee discusses the findings and vote on whether to add or remove the medication on the formulary. When determining which drugs to approve, committee members consider medical literature and studies of each drug’s effectiveness, safety, and cost, compared with other drugs in the same category. (italics added)

PhRMA does not endorse the formulary choices of any particular health plan, nor do we know whether health plans adhere to the principles stated above. Nonetheless, it is not possible to reconcile the self-proclaimed practices of NIHCM’s member companies that lead to inclusion of many standard review drugs on formularies with the NIHCM report’s premise that standard review drugs lack significant value. NIHCM member companies’ decision-making processes and choices directly contradict the methodology used and conclusions reached in the NIHCM report.

NIHCM Ignores Benefits of Standard Review Drugs

PhRMA’s rebuttal included a section titled, “NIHCM Ignores Benefits of Standard Review Drugs.” This section states “While paying lip service to the possibility that standard review drugs (which often include drugs that are not the

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7 See “Formulary,” at Blue Cross of California’s website (under Visitors, Individuals and Families, Pharmacy) at www.bluecrossca.com/pharmacy/indexPhar.asp?brand=b&role=v&businessUnit=ind&command=introduction&browser=IE.
8 See “Anthem Rx Clinical Questions,” at Anthem’s website at www.anthemprescription.com.
first in a class) offer significant clinical benefits, [NIHCM’s] entire analysis is premised on the notion that standard review drugs provide no significant clinical improvement for patients.”

In its response to PhRMA, NIHCM cites the relevant section heading of the PhRMA critique and then quotes brief passages from its report that pay lip service to the possibility that standard review drugs offer clinical benefits. Based on any reasonable reading of the entire report, PhRMA’s characterization of the NIHCM report is accurate. **However, to the extent that NIHCM’s response accepts our point—that standard review drugs provide important clinical value for patients—it negates all other conclusions reached in the report. We applaud NIHCM’s recognition of the value of standard review drugs for patients.**

**NIHCM Ignores New Medicines in Development**

NIHCM states that its report is retrospective, suggests the kinds of R&D projects that have received support in pharmaceutical firms for more than a decade, and that NIHCM does not “have access to detailed information about the pharmaceutical industry’s R&D investments.”

As discussed above, NIHCM’s report is **selectively retrospective**—retrospective **results that do not support the report’s predetermined conclusions are excluded.** Also as discussed above, the report **selectively examines** the kinds of R&D projects supported by pharmaceutical companies—those **projects that were supported by the pharmaceutical industry but that do not confirm the report’s predetermined conclusions are excluded.**

Additionally, information regarding new medicines in development is easily available from PhRMA’s New Medicines in Development series, which describes the research pipeline for various populations and diseases. This information can be obtained by NIHCM or any member of the public at PhRMA’s website, [www.phrma.org](http://www.phrma.org).

**NIHCM Report Claims But Does Not Demonstrate A Changing Pattern of Innovation**

NIHCM claims to have identified a changing pattern of innovation over the course of the 1989-2000 period. During the first half of this period (1989-1994), 34% of NDA approvals were for new molecular entities (NMEs). In the second half of this period (1995-2000), 39% of total NDA approvals were for NMEs. Moreover, in the second half of this period (1995-2000), the average number of NMEs approved per year (35) was markedly higher than in the first half (1989-1994) of the period (25).  

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NIHCM Report Ignores Evidence Indicating Multiple NMEs in a Class Does Lead to Price Competition

PhRMA’s rebuttal pointed out that NIHCM’s report—representing self-proclaimed “objective” research—suggests that having several NMEs in a therapeutic class does not lead to price competition and noted that the report did not present either in-depth analysis or the extensive research by Tufts Professor Joe DiMasi that contradicts its assertion. NIHCM only presents support for its own view (and reiterates “its own analysis,” which does not qualify as meaningful economic analysis) while remaining silent on the DiMasi research. Thus, one-sided advocacy is cloaked as “objective” research—excluding findings that contradict one’s own advocacy position could lead readers to erroneously conclude that there is no important counterevidence.

Notably, NIHCM need not have resorted to academic studies to address price competition among drugs within a therapeutic class. In a May 24, 2002 letter to the National Association of Insurance Commissioners, the Blue Cross and Blue Shield Association—which includes the Blue Cross and Blue Shield companies that make up 11 out of 12 members of NIHCM’s Board of Directors—and other managed care organizations, cited competition among “therapeutically similar drugs” as “creating the potential for driving down the cost of the class of drug.” While we do not endorse this letter’s proposals, its observations regarding the value of multiple drugs in a class clearly contradicts NIHCM’s claims.

NIHCM Report is Self-Contradictory in its Critique of Pharmaceutical Innovation

PhRMA’s rebuttal pointed out that NIHCM accuses the pharmaceutical industry of attempting to stifle competition while focusing too much effort on incremental improvements to drugs and follow-on drugs in a class. It is unreasonable to simultaneously criticize the pharmaceutical industry for stifling competition and for developing medicines that compete with one another.

NIHCM’s response on this point—which goes to the heart of its report—is complete silence. Instead, NIHCM’s responds by referencing the PhRMA rebuttal’s oversight of the NIHCM report’s one example of development of new formulations for specific patient populations. We agree that the NIHCM report offered this one example. But unlike NIHCM’s silence on its report’s self-contradictory critique, the oversight of this one example does not implicate any of the PhRMA rebuttal’s central points about the serious flaws in NIHCM’s study.

NIHCM Report Misleads by Blaming Standard-Rated Medicines for Cost Increases
PhRMA’s rebuttal cited the NIHCM report’s conclusion that “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.” The PhRMA rebuttal went on to state that “NIHCM’s analysis seemingly implies that spending would be lower if new drugs had been confined to ‘priority’ drugs. But this would be true only if all of the patients taking the second or third drug in a class would have gone untreated—particularly in light of the fact that tens of millions of patients remain untreated for serious illnesses.” NIHCM’s response is that its report “does not ‘blame’ any medicines for cost increases.”

PhRMA’s comment on the NIHCM report is accurate in light of the report’s content and claims that standard review drugs provide no significant clinical improvements for patients. (This claim is repeated in the very sentence providing the spending figures.) If the purpose is not to cast doubt on the value of spending on standard review drugs, then what is the analytic meaning or value of NIHCM’s analysis?

NIHCM’s protests also ring hollow in light of its body of work since early 1999. As described above, NIHCM’s work increasingly focuses narrowly on the pharmaceutical industry, is uniformly critical of the pharmaceutical industry, focuses on the costs of increased use of pharmaceuticals while providing little information about the value of pharmaceuticals in treating disease, and does not accord substantial attention to important issues such as undertreatment of patients in its own member health plans.

NIHCM Report Focuses on Price of New Drugs, Not Their Value to Patients

NIHCM replies that its report does not try to determine the value of individual drugs. This is an obvious smokescreen, as even a cursory review of the NIHCM report reveals. NIHCM’s entire report is based on assessing the “value” of drugs by classifying them by priority versus standard review status. Moreover, the report identifies standard review drugs as “providing no significant clinical improvement over existing products.”

Modifications to Existing Drugs Do Not Preclude Generic Competition on Older Invention Once its Patent Expires, Contrary to NIHCM’s Suggestion

NIHCM states in its response to PhRMA’s rebuttal that “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.”
NIHCM’s response highlights its original objection to improvements in medicines. The last sentence in the paragraph above echoes the following claim from NIHCM’s initial report: “In some cases, these patents may discourage generic companies from trying to develop a competitive product.” Thus, the thrust of this claim is NIHCM’s apparent concern about the capacity of copies of older drugs to successfully compete against newer, improved medicines—an issue which has no relationship to allegations of patent abuse. If NIHCM opposes improvements to medicines, it should simply say that it believes today’s medicines are good enough for patients and should not be improved, rather than couching this position as one of patent abuse.

NIHCM also seems to suggest that when a new, improved version of a medicine is developed, the patents on the new medicine somehow prevent generic companies from copying the old medicine. In fact, once all patents on an older drug have expired, remaining patents only applying to a newer version of the drug do not block a generic from copying the older drug. That’s why there are brand name drugs on the market today that compete against a generic copy of an older version of the same drug. Of course, it is the innovator company that did the research needed to develop both the older version and the newer, improved version.

Further, NIHCM’s characterization of the 30-month stay as a tactic to delay generic entry is wrong. The Federal Trade Commission (FTC) examined whether or not the 30-month stay is a barrier to competition. In its July 2002 report, FTC concluded that the 30-month stay provides the opportunity to resolve patent disputes prior to generic entry and does not appear to delay generic entry:

The 30-month stay affords both the brand-name company and the generic applicant the opportunity to resolve patent disputes prior to commercial marketing, and in tandem with FDA review of the ANDA for approval. (FTC, “Generic Drug Entry Prior to Patent Expiration,” July 2002, 36.)

One 30-month period to resolve disputes over patents listed in the Orange Book prior to the ANDA’s filing date appears unlikely to delay generic entry, however, because it historically has approximated the time necessary for FDA review and approval of the ANDA and the duration of a patent lawsuit. (FTC, “Generic Drug Entry Prior to Patent Expiration,” July 2002, 36.)

“Changing Patterns” further mischaracterized patent law in ways that, tellingly, advance rather than cast doubt on its advocacy position on pages 17–18. The report claims 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.

The market exclusivity granted to innovators who conduct additional clinical trials to identify new uses or enhanced safety and effectiveness profiles is a reward for the additional research and clinical trials to support these incremental innovations. A generic that wishes to market a copy of the original drug without labeling the drug for the new use does not even have to file a paragraph IV certification on the new use. The ANDA filer may file a “section VIII statement” – a simple statement to FDA that the filer is not seeking approval to market its drug for that specific use. FDA will rate the generic as therapeutically equivalent to the drug for the uses for which the generic is approved and labeled.

NIHCM’s report incorrectly characterizes other aspects of patent law, also in ways that advance rather than cast doubt on its advocacy position. For instance, it claims that 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.” According to footnote 28, this is fostered by a Patent and Trademark Office user fee system that grants patents 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…. 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.” NIHCM’s allegation is simply wrong—the patent statute requires payment of fees within three months after the PTO has completed its review. If the applicant does not pay the fee before the three-month period expires the patent application is abandoned, i.e., the patent is not issued.

Conclusion

NIHCM is presenting pure advocacy as objective research. It has continued to do so in the face of criticism pointing out serious errors and omissions in its analysis. Selective citing of the evidence—hardly a hallmark of “objective” research—is continued rather than corrected, even after pointed out. Its assertion that it is interested in “all issues that improve the effectiveness, efficiency, and quality of America’s health care system” is belied by its body of work emphasizing attacks on the pharmaceutical industry and its failure to meaningfully discuss issues such as health plan practices that could help undertreated patients receive needed medicines. NIHCM’s interest in obscuring rather than highlighting useful information is demonstrated by its silence on the contradiction between its own member companies’ publicly stated practices and the content of its report. And its failure to identify in its report its role as an
organization of Blue Cross and Blue Shield plans is misleading. We hope that future NIHCM studies include objective and balanced research so that we can engage in a healthy, fact-based debate, instead of an ever more acrimonious and intense exchange unlikely to contribute to better health policy for patients in the United States.