The Clinical Research Enterprise
Time to Change Course?

Marya D. Zilberberg, MD, MPH

To keep up with the latest information, a physician needs to read 75 primary studies and 11 meta-analyses daily. Yet despite this avalanche of published research, solid evidence for everyday interventions remains scarce, and even available evidence has been called into question because of various ubiquitous threats to validity. As a result, despite the growth of available technologies and information, knowledge and understanding of the appropriate use of these tools is far from optimal. One possible manifestation of this lack of understanding is the death toll associated with medical interventions, particularly in hospitals. Iatrogenic events are the third leading cause of death in the United States, and unfortunately, despite a decade of focused interventions aimed at quality improvement in hospitals, these numbers have not changed. This is partly due to high barriers in the physician community to adoption of evidence-based practice guidelines, but other factors are likely at play. One such factor may be the paucity of individualizable evidence.

In the United States, multiple large stakeholders use a substantial proportion of clinical research output for making decisions and setting policy. Three of the largest are the Food and Drug Administration (FDA), Agency for Healthcare Research and Quality (AHRQ), and Centers for Medicare & Medicaid Services (CMS). Each has a unique mandate, informing the respective study designs. Because the FDA is charged with evaluation of new technologies’ safety and efficacy prior to market release, there must be a rigorous understanding of whether the new technology works. The sine qua non of answering this question is internal validity, or whether the technology is truly doing what it is intended to do. For this reason, the large, double-blind, randomized controlled trial (RCT) is the gold standard for gathering this type of information. However, a well-appreciated limitation of such rigorous investigation is the lack of generalizability. Furthermore, even in a large and potentially more representative trial of the relevant populations, the stringent statistical considerations by the FDA preclude investigation of appropriate subgroups of patients, in whom responses to the intervention may vary substantially from the mean or median calculated for the entire trial group. Such measures of central tendency, while reducing the noise in the data, at the same time may conceal important signals on either side of the center, both positive and negative.

Two other agencies in the Department of Health and Human Services are creators and consumers of clinical research. The AHRQ and CMS focus on effectiveness and efficiency of interventions in the real-world setting. Here, the data generated in an RCT are frequently irrelevant precisely because of their limited generalizability. Thus, research geared at quality improvement, translation, and coverage decisions requires a different set of data and methodologies. For the most part, these consist of before-and-after clustered studies, as well as other observational designs. While well describing what goes on in the real world, and thus providing better generalizability than an RCT, these data are limited by their ability to provide valid inferences of causality. Furthermore, they are rarely analyzed in a way to provide a granular enough picture for use at the bedside.

While there is a trade-off between internal and external validity in both interventional and observational study designs, neither type appears to provide the easily individualizable data every physician requires at the bedside. This represents a potentially critical, yet not well-articulated objection to evidence-based guideline implementation. This objection can be defined as the phenomenon of heterogeneous treatment effect. This is illustrated well by the fact that the majority of medicines on the market, having passed the efficacy test in a large and varied group of study participants, in reality works in a minority of the patients who qualify for them. It appears that in pursuit of valid and generalizable population knowledge, the most important constituency for the application of such knowledge, the physician-patient dyad, has been underrepresented and with dire consequences.

Therefore, what is the relevance at the bedside of the information contained in the daily dose of 75 primary studies and 11 meta-analyses, and is there a need to overhaul how most clinical research is designed, performed, and reported? There is a need for deep introspection and adjustment to the course. Although the approach of the last 40
years has brought much knowledge to the field of medicine, it has been unable to overcome its continued underperformance in terms of safety, effectiveness, and efficiency.

The way forward is far from clear. As computing capabilities continue to increase, they will facilitate a transition from the current approach to clinical characteristics that drive analyses today and a move to the more nuanced and realistic representation of the complexity of individual human physiology. As it becomes more feasible in the computing environment of the 21st century to manage and analyze massive naturalistic data sets without rapidly losing statistical power, knowledge gaps will be closed on how various combinations of multiple comorbidities may affect health interventions and outcomes of interest, making the evidence more relevant at the bedside.9 Another component in this progress will be better understanding of genetics. Because of the cognitive load this knowledge will bring, more robust decision-support systems will be critical as an adjunct to a physician’s hands-on evaluation.

Although much of this is still far in the future, some of the more relevant methods already in existence need to be used more consistently, and new methods need to be developed and vigorously debated by all of the constituencies involved.7,10 Clinicians and payers need to agree on the importance of such studies in order to build appropriate and sustainable infrastructures to make them feasible. Given the low-level use of heterogeneity testing in the current literature,7 much room exists to augment its use by adding a few simple steps to analyses already performed, again extending their usefulness and validity to the critical end-user constituency.7 As for implementation of evidence, the explosion of information over the last decade in behavioral sciences has provided valuable insights on how to influence human behavior, underscoring the need for collaborations not only within the medical profession, but also across disciplines that can accelerate the diffusion of evidence into practice.

It is likely that the current research enterprise, having provided much insight into the science of human diseases, diagnostics, and therapies, may have exhausted its usefulness. The harm in the health care system today requires rapid, drastic, and creative ways of stemming the problem. In the context of resource constraints, the usability of generated data must be streamlined and optimized. This agenda must be moved forward if the primary obligation of medicine is to be fulfilled: primum non nocere.

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With tighter deadlines for the launch of new trials, new technology to increase transparency and streamline data management, and plans to consolidate the number of groups in its Clinical Trials Cooperative Group Program, the National Cancer Institute (NCI) has moved swiftly to implement some of the changes recommended by the Institute of Medicine (IOM) in April 2010. But questions remain about whether recommended funding increases and other changes will occur.

STATE OF CRISIS

The Clinical Trials Cooperative Group Program plays a key role in conducting trials unlikely to be undertaken by industry. In a report commissioned by the NCI, the IOM cautioned that the 55-year-old program was reaching “a state of crisis.” The report (http://www.iom.edu/nicancertrials) outlined how a cumbersome structure, poor reimbursement for those conducting the trials, and other problems were making it difficult for the program to adapt to changes in cancer research.

The program is organized into 10 groups, which work with more than 14,000 investigators and enroll more than 25,000 patients in trials each year. The report noted that it took more than 2 years of planning to start a trial and that half of the trials initiated were never completed. To remedy these problems, the IOM called for reducing the number of groups in the program, consolidating administrative functions, streamlining the process for approving trials, and increasing reimbursements for participating centers and physicians. In response to the report and previous recommendations from the NCI’s Operational Efficiency Working Group, last spring the NCI began implementing some changes to increase the efficiency of the program.

Among the changes implemented in the past 8 months were the establishment of new scheduling targets that dramatically cut the suggested timeline for moving a trial from conception to approval. Previously, the median time to take a trial from conception to launch was 800 days, explained James H. Doroshow, MD, director of the NCI Division of Cancer Treatment and Diagnosis. Now, investigators will have 300 days to usher a large phase 3 trial through this process, and 210 days for a phase 2 trial. The NCI also instituted a limit on the length of time for planning a trial, calling for a trial to be dropped if it takes more than 2 years of planning for a phase 3 trial or a year and a half for a phase 2 trial. These targets are now being met, but, Doroshow noted, “we need to get a year to a year and a half of experience to see if we will be able to hold to the targets.”

APPROVAL PROCESS CHANGED

To achieve this efficiency, the NCI has made several changes to the approval process, Doroshow explained. For example, when a trial proposal is submitted, contractors for the NCI will make any formatting changes necessary for the document to meet NCI requirements rather than sending back a list of suggested changes for the investigators to complete. Also, once a panel of experts has reviewed the proposal and identified any scientific issues that need to be addressed, a teleconference is arranged within a week to allow the investigators, statisticians, and NCI staff to either work out the issues or decide not to pursue the study. A similar teleconference is held to address issues identified by the NCI’s national institutional review board (IRB). These changes have greatly reduced the amount of time investigators and NCI staff spend corresponding about a proposed trial. For example, the IRB teleconferences have helped cut the time to receive IRB approval from 120 to 40 days.

“We’re just not allowing the process to be bogged down,” Doroshow said.

Investigators can also now monitor the status of their proposal in much the same way delivery companies enable customers to track packages. The NCI has created a Web site that allows investigators to check which stage their proposal has reached and whether it is meeting the targeted schedule, Doroshow said. Additionally, the NCI has purchased a clinical trials software system for use by all the groups; currently, each uses its own. The system is similar to those used in the pharmaceutical industry, and it can collect enough information to satisfy Food and Drug Administration requirements, if necessary. Doroshow said the NCI has begun installing the software but that it will take about 2 years to get it fully operational.
In December, the NCI also announced that it planned to consolidate from 10 groups to 5. One of the groups will be the existing pediatric group, which was created by combining 4 groups several years ago. There will also be 4 groups focused on adult cancers. The NCI will review each group's performance individually and also create more incentives for groups to work cooperatively with one another. Doroshow said having fewer groups should make it easier to implement the changes already under way. To determine the composition of the new groups, the agency will solicit proposals from the existing groups.

While the changes have been well received so far, much work remains to be done.

Allen S. Lichter, MD, chief executive officer of the American Society of Clinical Oncology (ASCO), noted that ASCO supports the recommendations of the IOM and the work done so far by the NCI. However, he cited other existing roadblocks to swift completion of trials. For example, he said, it will be important to boost interagency cooperation and to better coordinate oversight of trials by multiple federal agencies to prevent trials from being caught up in prolonged back-and-forth between agencies.

Additionally, Lichter said, it will be important to implement the IOM’s recommendations in their entirety. ASCO and the National Cancer Policy Forum are holding a workshop March 21 to discuss with a range of stakeholders how to best implement the IOM’s recommendations.

Of particular concern is the need to increase reimbursements for investigators and centers participating in trials. He noted that reimbursements for investigators haven’t increased in a decade, despite increased regulatory burdens, more stringent reporting requirements, and a corresponding need for more investigator time to meet such demands. ASCO calls for doubling the current reimbursement rates, although Lichter acknowledged this may be difficult in the current economic and political environment.

“We understand the complexities of this,” he said. “Yet if funding stays flat, inflation and other requirements mean that the reimbursement is being cut every year.”

Doroshow said that as a former investigator in the program, he is well aware of the need for increased reimbursement rates, and that the NCI is working to determine “how we can change the way we operate to provide additional resources to investigators, even in the face of difficult economic times.”

Lichter emphasized the increasing importance of the trials conducted by the cooperative groups, noting that studies comparing drugs or assessing combinations of compounds or treatment modes will simply not be conducted by industry.

“With all the emphasis on value and comparative effectiveness, these studies are the bedrock on which we base cancer treatment,” he said.

### IDSA Creates MRSA Treatment Guideline

Bridget M. Kuehn

A NEW GUIDELINE ON THE TREATMENT of methicillin-resistant *Staphylococcus aureus* (MRSA) infections issued by the Infectious Diseases Society of America (IDSA) provides physicians with detailed recommendations on how to treat various types of MRSA infections, including information on dosing of antibiotics when necessary.

The guideline was published January 5 and provides a detailed resource for physicians treating MRSA infections, ranging from uncomplicated skin infections to infective endocarditis, and provides specific recommendations on the care of pediatric patients with such infections (Liu C et al. *Clin Infect Dis*. 2011;52[3]:285-322). The guideline was drafted by a panel of infectious disease experts, including individuals with expertise in emergency department care and pediatrics, and reviews the evidence on each covered topic.

The Pediatric Infectious Diseases Society, the American College of Emergency Physicians, and the American Academy of Pediatrics endorse the guideline.
A Historical Perspective on Clinical Trials Innovation and Leadership
Where Have the Academics Gone?

David L. DeMets, PhD
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The randomized controlled trial (RCT), the gold standard for evaluating the balance of risk and benefit in medical therapies, first emerged as a key clinical research tool in the mid-20th century thanks to visionary leadership of agencies such as the US National Institutes of Health (NIH), the UK Medical Research Council, and academic research institutions. Since then, clinical trials activity has shifted from the NIH and academia into the purviews of the medical products industry and regulatory authorities. Recent emphasis on evidence-based medicine, patient-centered outcomes research,¹ and learning² and accountable³ health care systems underscores the fact that most clinical trials fail to provide the evidence needed to inform medical decision making. However, the serious implications of this deficit are largely absent from public discourse, and a better balance between commercial interests and public health is critically needed.

In this context, the word “academic” describes a diverse group of individuals exploring scholarly questions, with motivations arising not from pursuit of profit but from an interest in the public health. The wellsprings of such activity should reside in the NIH and other federal research agencies, coupled with external grantees—most of whom work in the nation’s academic health and science systems. The primary mission of academic health and science systems, as required by their not-for-profit status, places public health interests above return on investment to specific investors. This in no way disparages the motivations of the many excellent scientists working in industry or in the US Food and Drug Administration (FDA) that regulates its products. On the contrary, the development and appropriate use of medical technologies are vital to the public health. However, it is important to remain mindful that decisions affecting for-profit research will reflect fundamentally different priorities than those of academic researchers. In a sense, the academic enterprise seeks a “return on investment” for taxpayers who grant (and support) its nonprofit status. Thus, while all researchers are bound by the same standards when conducting human studies, the fundamental questions addressed will differ, and failure on the part of academia to increase its involvement will have predictable consequences.

When fundamental trials methodologies were being developed at the NIH in the 1960s, an NIH-commissioned task force delineated recommendations for organizing and conducting RCTs.⁴ One significant early example is the Coronary Drug Project,⁵ a joint effort among NIH sponsors, an academic coordinating center, and a steering committee of academic leaders. In the 1970s and 1980s, the NIH often convened academic leaders to identify knowledge gaps and prioritize and conduct specific trials as funding permitted.

During the 1960s, there was scant statistical literature examining clinical trials methodologies. Researchers learned by doing trials, noting successes and failures, and iterating to advance the field. In a series of discussions in the 1970s, ideas were debated and solutions to immediate problems were proposed.⁶ Throughout the 1970s and 1980s, NIH and academic biostatisticians developed many methods now in routine use, including sample size estimation, interim data monitoring, and repeated measure methods for analysis.

At the outset of this era, few large randomized clinical outcomes trials were sponsored or conducted by industry. Meanwhile, the FDA was developing biostatistical teams to support review of new drug and device applications and increasingly demanded RCTs, often with clinical outcomes end points, as the standard for approval and labeling. By the early 1990s, academia was working with industry to lead and conduct clinical trials, using a modification of the NIH organizational structure.⁷ While some fields developed this hybrid model of academic leadership in industry-sponsored RCTs, most industry trials evolved in a different direction and were designed by industry scientists in concert with regulators, often with little or no independent academic input.

As the clinical trials enterprise grew, statistical principles mandated adequate sample sizes to provide power for detecting typically modest differences in clinical outcomes. Concurrently, the enterprise’s rapid expansion, coupled with egregious instances of fraud or lapses in quality, resulted in the implementation of auditable data systems. This confluence of factors spurred massive increases in clinical trial costs.⁸
Research agendas in the pharmaceutical industry were also evolving during this period. In the 1980s, an alignment of interests between science and industry meant that pharmaceutical research typically focused on diseases lacking adequate treatments, assuming that this would translate into commercial success. However, ever-increasing drug development expenses, driven partly by trial costs, drove companies to seek “blockbuster” drugs with enormous earnings potential. This in turn yielded an emphasis on highly prevalent diseases and widely applicable treatments, and “orphan” diseases were neglected as targets for drug discovery. The sales threshold for blockbuster drugs increased from $500 million to more than $1 billion, setting the stage for major conflicts among the commercial goals of industry, the public health mission, and overarching needs to improve trial methodology.

As clinical research has drifted from its early public health orientation and toward RCTs as a business, trial methodologies, including statistical methods, quality-control standards, and data monitoring and analysis procedures, are now largely shaped by imperatives to develop new approved products (or increase sales of existing products) while meeting regulatory requirements. Industry now drives much of the design, conduct, and analysis of trials, while academics are often relegated to comparatively minor roles. Contract research organizations have arisen to provide efficient trials conduct according to current practices, rather than furthering innovation in trial design and conduct. In some cases, trials have been terminated by sponsors for commercial reasons, leaving public health questions unanswered. In such situations, academic investigators and participants have little recourse, and a counterpoise to commercial interests is essential.

With the advent of national health care reform, payers and advocacy groups have emerged as major players. Interest in comparative effectiveness research is rapidly coming to the fore as costs increase. Soon, in addition to demonstrating effectiveness and safety, new interventions most likely will have to demonstrate reasonable costs compared with alternatives to gain approval—a requirement not currently part of NIH or FDA mandates, but inevitable as payers are increasingly constrained.

Insurance providers, private or public, have not actively participated in clinical trials and thus have missed sharing in decades of experience and methodological development. Here, then, is an opportunity for the academic community and the physicians and researchers trained in academic health and science systems—who must live with the costs of interventions in daily practice—to assert pivotal roles in the design, conduct, analysis, and interpretation of comparative-effectiveness trials.

Even greater challenges are posed by the growing congressional interest in clinical trials, the need for independent, unbiased conduct of research and evaluation of results, and the potential influence of conflicts of interest. The academic community has failed to adequately educate the public and Congress about the strengths and limitations of clinical trials—what information can be obtained reliably; the dangers of insufficiently rigorous research designs. To realize the potential of a rejuvenated clinical trials enterprise will require development of approaches to conflict-of-interest management that convince both Congress and the public that academia is acting for the public’s benefit.

The NIH and the nation’s academic health and science systems (and their schools of medicine and public health) should work to reinvigorate the academic clinical trials enterprise. The newly formed National Center for Advancing Translational Sciences can, through the Clinical and Translational Science Awards, leverage support for academic homes for trialists at most academic institutions, where new methods can be developed, trials can be conducted, and new generations of researchers and statisticians can be trained. If academics do not assert leadership in clinical trials, they will remain minor players carrying out someone else’s research, chairing steering committees or putting their names on manuscripts in which they have had little input. Without significant, vigorous academic involvement, critical issues may go unaddressed, diseases may be neglected, and important trials may never be conducted. The results will be needless delays in public health improvements and increased morbidity among patients whose health needs may go unstudied and unaddressed within a profit-oriented system.

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NIH director wins bid for translational medicine centre

New nexus will bridge basic and clinical research to improve health.

Meredith Wadman

Sixteen months after taking charge of the US National Institutes of Health (NIH), the world's largest funder of biomedical research, director Francis Collins is now on course to lead the agency through its most significant evolution to date.

On 7 December, the NIH's Scientific Management Review Board (SMRB) voted 12-1 to establish a new centre devoted to speeding therapies from the lab to the clinic. With all the grant-making powers of any of NIH's 27 existing institutes, the new centre for translational medicine and therapeutics could receive funding as soon as next October, when the US government's 2012 fiscal year begins.

Collins, who has made translational research a top priority for his tenure, celebrated the vote as "a momentous occasion". He noted that, in the past, the creation of new institutes at the NIH was often motivated by congressional politics. By contrast, he said, the current recommendation is driven mainly by scientific arguments. "You could call this disruptive innovation on an institutional scale," Collins added.

Disruptive may prove to be an apt word for the new centre as it jostles for position within the NIH firmament. For example, it is expected to house an existing half-billion-dollar funding programme called the Clinical and Translational Science Awards (CTSAs), which are currently held by 55 centres nationwide. However, such a move might seal the fate of the programme's administrative home, NIH's National Center for Research Resources (NCRR) in Bethesda, Maryland, which provides translational researchers with the training and tools to transform basic discoveries into health gains. The CTSAs comprise nearly 40% of the NCRR's US$1.3-billion budget.

Asked if the NCRR would be dissolved under the new proposal, Collins told Nature: "That is a possibility, but it's not the only possibility."
Barbara Alving, the NCRR's director, said after the vote: "I feel much more discussion needs to be done, absolutely. This is a very confusing process for all of our stakeholders."

Alving questioned, among other things, whether adequate funding would exist to support the new centre in the future, because some of its elements are funded from the NIH director's discretionary 'Common Fund' and are not permanent fixtures of the NIH budget.

Pros and cons

Others cautioned that the rush to launch a new centre may work against the NIH's purposes. The creation of a "new bureaucratic structure" could even end up delaying translational research, argued William Talman, a neuroscientist at the University of Iowa in Iowa City, who is also president of the Federation of American Societies for Experimental Biology. At the meeting, Talman urged the SMRB to delay its vote and make more information available about the role of existing translational research at other NIH centres under the new regime.

But the proposal also has fans. Garret FitzGerald, who directs the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania in Philadelphia, said it will raise the profile of a discipline that bridges basic and clinical research, and which is desperately lacking in personnel. "This can offer the beginning of a brand that can lure the best and the brightest into training. Because the absence of those people has come at an immense price," he says.

The only SMRB member who opposed the new institute was Jeremy Berg, director of the National Institute of General Medical Sciences in Bethesda. "It was done in such a hurried way that there hadn't been time for adequate discussion of the implications," Berg said after the vote. "I didn't really know what I was voting for." Earlier this week, Berg announced he will be leaving the NIH next summer.

Collins had pushed the SMRB to report to him by this month so that the new translational research centre could be funded in the government's 2012 fiscal year. A working group of the SMRB, headed by Arthur Rubenstein, the dean of the University of Pennsylvania School of Medicine in Philadelphia, has since May held half a dozen meetings to gather input. Its charge was to outline how to improve the NIH's existing translational research.

Pipeline push

In its effort to develop drugs, biologics, diagnostics and devices, the proposed centre would draw together several recent programmes that have arisen as part of an increasing push in Congress to speed therapies to the bedside, as new drug pipelines at pharmaceutical companies have languished.
In addition to the CTSAs, the new centre would administer The Cures Acceleration Network, a competitive grant programme for drug development authorized by Congress early this year in the new health reform law. The programme can be funded at up to $500 million annually; congressional spending committees have awarded it $50 million for 2011, although that budget has yet to be finalized. Another congressional favourite, the $24-million Therapeutics for Rare and Neglected Diseases (TRND) programme, would also be housed at the new centre, as would the $113-million Molecular Libraries Program, which allows NIH-funded researchers access to large-scale screening to identify small molecules that can be used as chemical probes to study the functions of genes, cells and biochemical pathways.

Although the Clinical Center, the NIH’s huge research hospital in Bethesda, would not be a part of the new centre, the two would work very closely together under the proposal.

Collins immediately charged NIH principal deputy director Lawrence Tabak and Alan Guttmacher, head of the National Institute of Child Health and Human Development, with the three-month task of appraising the mechanics of creating the centre and looking at what might happen to remaining NCRR programmes. Acknowledging the concerns voiced by the parade of public witnesses at the meeting, Collins said: "We need to deal with [the concerns] in a very careful way to make sure that there are not unintended consequences."

Collins will take the proposal for the new translational medicine centre to Kathleen Sebelius, Secretary of the Department of Health and Human Services, as soon as this week. Under the law that created the SMRB in 2007, Sebelius must sign off on the plan and then present it to Congress. The proposal will go ahead unless Congress acts against it in the next 180 days.

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NCRR has successfully enabled basic, translational, and clinical research for nearly 50 years. Why didn't the SMRB consider a model where other translational medicine programs would be placed within the existing NCRR organization?  

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Posted by: Chris Parkman  |  2010-12-09 03:40:00 PM

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From yesterday's stakeholder call, Director Collins gave the impression that there is no budget or organizational plan for the proposed new center. If NIH believes a reorganization will allow for a
Biomedical Research and Health Advances

Hamilton Moses III, M.D., and Joseph B. Martin, M.D., Ph.D.

In 1945, the President’s science advisor, Vannevar Bush, wrote in *Science, the Endless Frontier*¹ that basic scientific research was “the pacemaker of technological progress” and that “new products and new processes do not appear full-grown. They are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science.” He recommended the creation of what would become the National Institutes of Health (NIH), which was created in 1948, and the National Science Foundation, created in 1950.

The biomedical-research enterprise in the United States soon became the envy of other nations, as well as the primary source of the world’s new drugs and medical devices. Since 1945, biomedical research has been viewed as the essential contributor to improving the health of individuals and populations, in both the developed and developing world.

Financing of research was ensured by the successes in the early 1950s of polio vaccination, antibiotics, and antipsychotic agents. Equally dramatic advances in surgery and medical devices, such as cardiopulmonary bypass, dialysis, and organ transplantation, followed in the 1960s. In the 1990s, the conversion of the acquired immunodeficiency syndrome and some cancers from uniformly fatal diseases to chronic conditions created an expectation that similar advances would occur for other devastating diseases.

These accomplishments led to mutual trust among supporters in Congress, disease advocacy groups, universities, and companies. The clinical advances would not have come about without such trust. Moreover, progress was based on an underlying faith that new technology was valuable and that it would produce effective preventive measures and treatments as long as the translation of basic science to clinical application was sustained.

Today, the primacy of biomedical research and technology development is being challenged. Patients, physicians, insurers, and policymakers are all questioning the slow pace of advance, escalating cost, dubious clinical value, inappropriate commercial exploitation, and lure of false hope for patients with serious diseases.² The backdrop is growing skepticism of the value of science itself as a solution to global problems.³ Moreover, the mutual trust among patients, clinicians, and researchers, which was so apparent after the 1950s, is in danger of forfeiture.⁴ This is due to suspicion that economic self-interest is disrupting medicine’s compact with patients, as exemplified by a number of high-profile ethical lapses in the protection of human research subjects and the involvement of physicians in the marketing activities of companies.

Illustrative is recent commentary in both the general⁵ and scientific⁶ press about slow progress in the decade after elucidation of the first human genome sequences. Despite the justified scientific excitement about using knowledge of the genome as a fundamental exploratory tool, unrealistic expectations for a quick route to clinical application have produced disappointment, especially among disease advocacy groups and companies. It is a reminder that with few exceptions, new scientific discoveries require 15 to 25 years for their application. This interval has not shortened in more than a century.⁷

Given that different perceptions and priorities color the debate over the value and role of biomedical research, we believe that the biomedical community must take stock and recommit its efforts to diseases that have a major effect on the population. This requires a reexamination of funding priorities, open interactions among researchers, and more effective relations among companies, government, foundations, and universities. Old assumptions and old models must be replaced.

Biomedical research in the United States is a $100 billion enterprise, with approximately 65%...
supported by industry, 30% by government (predominately the NIH), and 5% by charities, foundations, or individual donors. Although total sponsorship tripled between the mid-1990s and mid-2000s, the rate of increase has fallen since 2003 and declined in real (inflation-adjusted) terms since 2007. The number of new drugs entering human trials has also fallen during the past two decades, especially for new molecular entities and entirely new classes of drugs. In contrast, the number of approvals of medical devices by the Food and Drug Administration (FDA) has increased steadily each year. Driven by demand, total medical spending on devices has increased at a rate that is several times that for health services and twice that for drugs.

Since the mid-1990s, the United States has invested approximately 4.5% of its total health expenditures on biomedical research. In contrast, only 0.1% supports research in health services, comparative effectiveness, new care models, best practices, and quality, outcome, or service innovations. This funding will increase to approximately 0.3% from appropriations in 2010 health legislation.

Misconceptions regarding the scientific process are common. Research is costly, capital-intensive, and collaborative. Researchers in both academic and industrial settings require access to much the same information, samples and tissue, instrumentation, and specialized technical skills. They also depend on one another as a source of new ideas. It is a paradox, during this decade of growing scrutiny of ties between academic institutions and companies, that academic investigators value their nonfinancial company ties (with access to technology or research materials) more than personal compensation or support of their laboratory. Moreover, the notion that “pure” (basic) and “applied” (clinical) research exist as distinct activities is belied by their source of sponsorship and the self-reports of how researchers actually spend their time. Such multimode researchers are more productive, as judged by the number of publications, impact factor, success at winning peer-reviewed NIH funding, and number of patents. This reality was cited by a recent U.S. Federal Court opinion overturning the patentability of several genes that predispose women to breast cancer. The court called for patenting practices that favor openness whenever basic discovery is inhibited.

Sponsors have sought to improve their research productivity through the NIH Roadmap initiative (especially Clinical and Translational Science Awards) by encouraging alliances between companies and universities, alternative organizational models, and joint investment in costly facilities, such as imaging or gene sequencing. We reviewed the lessons from 70 such alliances from the mid-1960s through 2000. Although it is too soon to judge the success of the most recent models, in the main, earlier ones have not accelerated the pace of either discovery or clinical application. The sources of difficulty are idiosyncratic, but recurrent problems are a failure at inception to agree on intellectual-property provisions, excessive secrecy, and disagreements over research aims. In our view, the most salient reason for failure is the centralization of authority within large, inherently cautious bureaucracies in government, universities, foundations, and companies. Collectively, such factors inhibit scientists’ creativity by disregarding the pluralism of ideas and the diversity of approaches that are necessary for innovation. Conversely, the most successful collaborations have found a balance between external direction and scientists’ curiosity. Many of the most experienced observers from government, industry, and academia concur with this viewpoint.

Economic forces are also relevant. In the United States, the gain in life expectancy between 1970 and 1990 added $2.4 trillion per year to the gross domestic product by 2000. Moreover, biomedical research bolsters employment, economic development, balance of trade, and exports. Studies from many countries show that investment in new technology of all types is the primary source of economic growth, especially when such investment is made by the private sector. In contrast, in areas in which public spending on technology is dominant, the rates of productivity and growth are lower. The differences are most marked in medical research. Despite these observations, some federal policymakers express doubt that scientific advance is a prerequisite for improved health. They favor predictable, low-cost public health measures and expanded access to basic care during the current decade of austerity. Other policymakers question whether spending on new devices and high-cost bioengineered drugs produces commensurate clinical value. Such criticism is driven...
by estimates that new technology of marginal benefit (as measured by reduced disease burden or improved longevity) accounts for one half to two thirds of health care inflation in Western countries. Even the commercial value of biomedical research is questioned by some companies, as is reflected by their reduced rates of research and development because of unfavorable returns as compared with marketing or mergers and acquisitions.

Other observers assert that social, educational, and macroeconomic factors are more important than medicine or public health practice in promoting a population’s health. They see technology as a distraction from enlightened social, tax, and regulatory policies. Debate over the goals has already begun.

As a consequence, we believe that steps must be taken to reestablish public confidence in researchers and clinicians, along with their institutions. Measures are needed that go beyond those recommended by the Institute of Medicine, the Council of Medical Specialty Societies, and the NIH. These reports emphasize remedies that focus primarily on competing interests without dealing with the opportunities. We are concerned that the recommendations overlook the potential for new models to foster productivity.

## Seven Remedies for Consideration

The discontent arising from the current circumstances demands the consideration of sweeping changes in the way we conduct biomedical research. We believe that seven measures should be considered to reconcile competing goals. They require recognition of the multilayered sources of conflict, especially those based on different scientific aims and social values.

### Improve Data on Clinical Value

We must develop and apply better objective information about clinical value. This goal implies a higher standard for adopting new devices (including clinical trials similar to those for drugs) and better information on the effectiveness of existing drugs and devices, especially data that are available only from proprietary insurance databases. It is unlikely that provisions for comparative-effectiveness research in the 2010 health care legislation or the changes proposed by the NIH for device approval will be sufficient. New incentives are needed for private and government insurers to disclose clinical data to researchers, along with expanded access to device registries, easier access to data from Medicare and Medicaid, and development of more robust analytical techniques for ascertaining clinical value. Moreover, physicians and surgeons must commit to a new level of objectivity in judging clinical value, while resisting the influence of commercial potential or personal financial interests.

### Change the Role of Teaching Hospitals

The roles of academic health centers and teaching hospitals must be modified to improve their ability to conduct early-stage (proof-of-concept) clinical trials. Here, entirely new models for interaction are required, probably involving freestanding independent institutes or autonomous units within academic centers, where patients come specifically for access to such early-stage studies and where the mutual expectations for investigators, companies, and patients are clear and unambiguous. This change will hasten the divergence between institutions that offer routine care (and that are managed to provide low-cost, reproducible high quality) and those with capability for scientific innovation (where early-stage investigations occur). Making these interactions effective and avoiding the shortcomings of past attempts will require new models of intellectual property, patents, and licensing by moving these aspects farther down the chain of discovery.

Two very different approaches should be tried: creating patent pools involving multiple companies and universities and a renunciation of patenting in return for more latitude to conduct high-risk laboratory experimentation and initial clinical trials. It is likely that only some of the 130 academic health centers will choose to undertake such changes.

### Develop New Models for Collaboration and Finacing

In asserting the need for an increase of total spending on biomedical research and the need to foster the diversity of scientific approaches, consideration should be given to new models of collaboration and cooperation. Such measures would allow the NIH to concentrate on basic biomedical science and large, multi-institutional projects, where its scale can be most valuable, while providing offset to industry’s declining...
investment in research. These models might include the following:

Establish Biomedical Innovation Trusts
The formation of new nonprofit, public–private partnerships — biomedical innovation trusts — could enable individuals and corporations to receive immediate federal tax credits (not deductions) for contributions to support research in high-priority diseases. Such trusts might be administered by decentralized new foundations or new regional public entities and be directed at particular diseases, universities, freestanding laboratories, or small companies. Similar tax incentives have been used historically to preserve land, create parks, and build factories.

Create a New Class of Bonds
States and the federal government might issue bonds to support innovation in biomedical science and health services, with preference given to high-risk research and diseases important to public health. Such bonds have long been used to support athletic facilities, airports, and roads. They provide a mechanism for private investment to meet public needs.

Use Incentives to Promote Pluralism
To enhance the diversity of scientific approaches and innovation in its application, preference in funding might be given to new research institutes or entities, rather than existing universities or companies.

Defer Patents to Later in the Discovery Chain
In return for new sources of funding and greater latitude to conduct high-risk research, the new entities would forgo claims to patents or other intellectual property and place positive and negative findings immediately in the public domain.

Emphasizing new incentives, creating new entities, and mobilizing additional funding sources avoid the risk of disrupting productive research relationships currently found in universities, established research institutes, and the NIH. The measures also allow new laboratories to attract the best talent, while providing a route to enhance the productivity of research and its early clinical application.

RENEW PROFESSIONAL COMMITMENTS
All physicians must renew their commitment to professionalism and their duty to their patients. This will not be easy in an age when commercial values are paramount and the competition of the marketplace drives personal and institutional financial decisions. Yet, without such a recommitment, no safeguards will prevent an inexcusable loss of trust in our institutions and us. Professionalism, as interpreted today, means not a return to paternalism, but objectivity in judgment on behalf of the patient, with open communication and an absence of bias. It must be translated into action by a blanket proscription of product promotion in any guise.

FOCUS ON COST-EFFECTIVE TARGETS
We must recognize that new technology creates value to the general economy and has many clinical benefits but that it also usually spurs new clinical costs. Observers who are the most critical of medicine believe we have failed to recognize that historical compromise. In an era in which many favor public-policy goals to ensure a basic level of care for all citizens and a reduction in the rate of increase of aggregate health care spending, the technological imperative will surely be challenged with greater stridency. This requires incentives for researchers to focus on diseases that are common, cannot currently be prevented or effectively treated, are expensive, and have a major effect on the patients’ health. Such choices among diseases are onerous but inescapable.

ADOPT REALISTIC RESEARCH GOALS
We must embrace a new realism about the difficulty of the scientific process and what can (and cannot) be expected from it. We must not overpromise. Such realism will not be popular with patient advocacy groups, the press, politicians, benefactors, or company investors. Each of these groups has a vested interest in overstating their case. Yet to do otherwise runs the risk of eroding the trust on which so much depends. Paradoxically, a commitment to realism may itself have a positive effect on the scientific process by reducing the pressure to promote findings prematurely and by fostering openness.

REDEFINE THE TERMS OF CONFLICT
Finally, we in medicine must recognize that those who have a public health perspective or who see social and economic factors as paramount will not be sympathetic to increasing the technology-driven momentum of the past 60 years. Inevitably, we face growing conflict over individual
choice, access to the latest drug or device, the true cost of technology over a lifetime, perceptions of value, and preferences for competition versus regulation. Such tensions have long been implicit. They are now explicit. Not everyone believes biomedical research is essential.

CONCLUSIONS

These considerations will require decades of re-orientation of our biomedical research efforts, not unlike those that led Vannevar Bush to propose new structures and entities in 1945. Failure to resolve conflicts, be they political, policy-related, or personal, with a deaf ear to the claims of legitimately competing priorities will limit progress and encourage new regulatory constraints. Our institutions must be willing to recognize and confront these legitimate conflicts, not look to others to do it for them. The choice is stark, but the stakes are high.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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The Role of Public-Sector Research in the Discovery of Drugs and Vaccines


ABSTRACT

BACKGROUND
Historically, public-sector researchers have performed the upstream, basic research that elucidated the underlying mechanisms of disease and identified promising points of intervention, whereas corporate researchers have performed the downstream, applied research resulting in the discovery of drugs for the treatment of diseases and have carried out development activities to bring them to market. However, the boundaries between the roles of the public and private sectors have shifted substantially since the dawn of the biotechnology era, and the public sector now has a much more direct role in the applied-research phase of drug discovery.

METHODS
We identified new drugs and vaccines approved by the Food and Drug Administration (FDA) that were discovered by public-sector research institutions (PSRIs) and classified them according to their therapeutic category and potential therapeutic effect.

RESULTS
We found that during the past 40 years, 153 new FDA-approved drugs, vaccines, or new indications for existing drugs were discovered through research carried out in PSRIs. These drugs included 93 small-molecule drugs, 36 biologic agents, 15 vaccines, 8 in vivo diagnostic materials, and 1 over-the-counter drug. More than half of these drugs have been used in the treatment or prevention of cancer or infectious diseases. PSRI-discovered drugs are expected to have a disproportionately large therapeutic effect.

CONCLUSIONS
Public-sector research has had a more immediate effect on improving public health than was previously realized.
Historically, there has been a clear distinction between the roles of public-sector research and corporate research in the discovery of new drugs and vaccines to solve unmet medical needs. Public-sector research institutions (PSRIs) have performed the upstream, basic research to elucidate the underlying mechanisms and pathways of disease and identify promising points of intervention, whereas corporate researchers have performed the downstream, applied research to discover drugs that can be used to treat diseases and have then carried out the development activities to bring the drugs to market. The intellectual property that protects the investment in developing these drugs is created in the applied-research phase.

An excellent example of this traditional approach was Julius Axelrod’s research at the National Institutes of Health (NIH) regarding the basic mechanisms of neurotransmitters, for which he received the Nobel Prize in 1970. This research provided the foundation for the pharmaceutical industry’s discovery of an entirely new class of drugs, the selective serotonin-reuptake inhibitors (SSRIs), which have been important in the treatment of depression. All the major SSRIs were discovered by pharmaceutical companies with the use of Axelrod’s basic discoveries and are therefore not included in our study (e.g., Eli Lilly’s discovery of fluoxetine [Prozac], which received approval from the Food and Drug Administration [FDA] in 1987). However, Richard and Judith Wurtman at MIT discovered the role of these drugs in the treatment of premenstrual dysphoric disorder and obtained a method-of-treatment patent for this new use. MIT licensed their work to Interneuron Pharmaceuticals, which later licensed it to Eli Lilly. Eli Lilly then received FDA approval for a new use of fluoxetine and created a separate product, Sarafem, for this new use. Thus, we have included Sarafem in our study.

There is little dispute about the importance to drug discovery of basic research at PSRIs under the traditional approach. Studies by Cockburn and Henderson1 showed the complex relationships between public and private research in the pharmaceutical industry. Zycher et al.2 found that at least 80% of 35 major drugs that they studied were based on scientific discoveries made by PSRIs, whereas Toole3 found a quantifiable correlation between investment in publicly funded basic research and corporately funded applied research: an increase of 1% in the funding of public basic research led to an increase of 1.8% in the number of successful applications for new molecular entities (compounds that have not been approved for marketing in the United States)4 after a lag of about 17 years. He found that a $1 investment in public-sector basic research yielded $0.43 in annual benefits in the development of new molecular entities in perpetuity.

Historically, PSRIs did not play a major role in the downstream, applied phase of drug discovery, in which the actual products are discovered and patented. However, in the mid-1970s, the newly emerging tools of biotechnology — recombinant DNA and monoclonal antibodies — allowed PSRIs to create and patent biologic drug candidates and discover and patent small-molecule drugs. At that time, all products created in academic institutions were owned by the government, which granted only nonexclusive licenses. This system resulted in the ineffective transfer of academic technologies.5,6 For instance, by 1978, the government had licensed less than 5% of the 25,000 to 30,000 patents it owned.7,8

In 1980, Congress passed two pieces of legislation that transformed the ownership, management, and transfer of intellectual property that is created by PSRIs. First, the Bayh–Dole Act (Public Law 96-517) allowed universities, nonprofit research institutes, and teaching hospitals to own the intellectual property resulting from federally funded research and to license it according to terms of their choosing. Second, the Stevenson–Wydler Technology Innovation Act (Public Law 96-480), as amended by the Federal Technology Transfer Act of 1986 (Public Law 99-502), provided a corresponding authority to federal laboratories.

Under this new approach, inventions that arose from PSRIs, in addition to being freely published in the scientific literature, could also be converted into intellectual property and transferred through license agreements to the private sector for commercialization and public use. The new approach is thought to be considerably more effective than government ownership of academic inventions9,10 and was introduced just as the fruits of the biotechnology revolution started to emerge.

Our objective in this study was to quantitate the contribution of public-sector research to the applied-research phase of drug discovery. Other investigators have addressed this issue previously,
using a variety of approaches and definitions. Zycher et al.\textsuperscript{2} found that of the 35 drugs they studied, only 1 (3\%) originated from PSRIs. DiMasi et al.\textsuperscript{11} found that of the 284 new drugs approved in the United States from 1990 through 1999, only 6.7\% originated from sources other than private industry, whereas Kaitin et al.\textsuperscript{12} found that only 7.6\% of new drugs approved from 1981 through 1990 originated from non-industry sources. Sampat\textsuperscript{13} examined listings of patents that protected approved drugs in the Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book,\textsuperscript{14} published by the FDA, and identified 60 new molecular entities that originated from public-sector research, resulting in the filing of 72 new-drug applications; however, the author did not relate this number to total approvals during the period of his study. Kneller\textsuperscript{15} examined new molecular entities and new biologic molecules receiving FDA approval between 1998 and 2007 and found that 24.1\% originated from PSRIs.

**METHODS**

**DEFINITIONS**

In this study, we have used the term PSRI in a broad sense to include all universities, research hospitals, nonprofit research institutes, and federal laboratories in the United States. We have used the term “drug” to refer to any product that received U.S. marketing approval after 1962 from either the Center for Drug Evaluation and Research (CDER) or the Center for Biologies Evaluation and Research (CBER) of the FDA. We have therefore included small-molecule drugs, protein-based biologic drugs, vaccines, and in vivo diagnostic materials.

We considered a PSRI to have participated in the applied phase of research that led to discovery of a drug if it, solely or jointly, created intellectual property specific to the drug that was subsequently transferred to a company through a commercial license. In most cases, the intellectual property was a patent or patent application. However, a few products have used proprietary biologic materials developed and licensed by the PSRI.

We classified patents into six categories according to the following definitions: screening, a way of detecting the existence of a condition either in vitro or in vivo and of identifying a molecule that is pharmacologically active against the condition; the method of synthesis, a specific way of making a compound or class of compounds but does not cover the composition of matter of the pharmacologically active constituent of the marketed drug; the composition of matter, a pharmacologically active molecule, or family of molecules, contained in the marketed drug, including peptides, proteins, and the specific DNA sequences used to produce them; the method of treatment, a way of treating a specific condition with the use of a pharmacologically active molecule; the formulation, a way of delivering a compound or of preparing a pharmacologically effective combination of compounds but not the composition of matter of the pharmacologically active compounds that make up the combination; and a medical device, an instrument or apparatus that does not depend on a chemical action or metabolism for the achievement of its primary intended purposes.

We excluded the role of PSRIs in the development of platform technologies that have contributed to the development of whole new classes of drugs, such as recombinant DNA technology (Cohen–Boyer patents), bacterial production methods for recombinant DNA (Riggs–Itakura patents), production and chimerization methods for antibodies (Cabilly patents), methods to produce glycosylated recombinant proteins in mammalian cells (Axel patents), and methods of gene silencing with the use of small interfering RNAs (Mello–Fire patents). Although these platform technologies enabled the development of a large number of products (e.g., the Cabilly patents are used in the production of all antibody drugs), we excluded them because the PSRI scientists who developed the platforms generally did not use them to develop specific drug candidates, and therefore, the platform technologies were generally licensed nonexclusively (i.e., in a way that did not confer any protection of the investment in the development of the marketed drug) at relatively low royalty rates.

Our study encompasses a broad range of relationships. In some cases, the PSRI made the initial discovery independently and subsequently licensed it to the company that developed the drug. In other cases, the relationship started with a public–private collaboration, and the initial patents are jointly owned by the PSRI and its corporate partner, which generally obtained a license to the PSRI’s undivided interest in the patent. Sometimes, simultaneous inventions in the pub-
lic and private sectors resulted in interference proceedings, which were resolved through negotiation rather than through the patent office. In a few cases, the company that developed the drug did not respect the PSRI’s intellectual property and litigation ensued, ending in the judicial imposition of a license.

DATA SOURCES

There has been no systematic collection of the details of individual transfers of technologies invented by PSRIs. Since 1991, the Association of University Technology Managers has conducted an annual licensing survey that provides aggregate statistics on the outcomes of technology-transfer activities of academic institutions, but the specific technologies, the licensees, and the success or failure of the licensee’s development efforts are not identified. We therefore created a database of successful drug-discovery and drug-development projects that owe their origin, at least in part, to PSRI inventions. The most difficult task was to identify which drugs originated in PSRIs.

Our primary source was the FDA’s Orange Book, which contains details of the patent protection underlying drugs that have received approval under new-drug applications but not under biologics license applications. If any patent that is listed in the Orange Book is assigned to a PSRI, it is highly likely that the drug originated at that PSRI.

We augmented the Orange Book with a number of sources: collections of stories of specific technology-development projects, including accounts of drug development published by the Association of University Technology Managers; the Web site of the University of Virginia Patent Foundation, which contains a substantial number of success stories of academic licensing; announcements by specialized financial firms that purchase the right to receive royalty streams from academic institutions or their inventors; lawsuits; and newspaper articles. As a final check, we sent the list of products we had identified to the directors of offices of academic technology licensing. They identified nine additional drugs that their institutions had discovered and licensed.

The second step in our research was to search the databases for drug and biologic approvals. For each product (whenever possible), we identified principal investigators or lead inventors and their institutions; the funding source and dates of any federal grant; the date of the first patent application cited in the issued patents; the date, identity, and terms of the initial licensee; the date, nature, and value of any transactions by the initial licensee and subsequent sublicensees or assigns during the course of bringing the product to market, both before and after FDA approval; the dates of FDA approval of all new-drug and biologics licensing applications incorporating that active ingredient; and for small-molecule drugs, the FDA chemical classification, whether the product received standard or priority review, and whether it received orphan-drug designation.

RESULTS

NUMBER OF PRODUCTS

Our research has so far identified 153 FDA-approved drugs that were discovered at least in part by PSRIs during the past 40 years (Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We excluded drugs such as thyroxine, warfarin, nystatin, streptomycin, neomycin, and 5-fluorouracil because these drugs were discovered and introduced before the Kefauver–Harris Amendment (Drug Efficacy Amendment) of 1962, which ushered in the modern era of FDA regulation of drug approvals. Because our sources were not limited to products for which a public-sector patent was listed in the Orange Book, we identified 102 new molecular entities (including 8 in vivo diagnostic materials and 1 over-the-counter product) for which a total of 161 new-drug applications were approved. We also identified 36 biologic drugs and 15 vaccines that received approval under biologics license applications, for a total of 153 drugs that received 206 new-drug or biologics license applications.

TYPES OF PRODUCTS

We identified the distribution of the 153 products among four broad categories of therapeutic prod-
particularly noteworthy was the large number of vaccines. Virtually all the important, innovative vaccines that have been introduced during the past 25 years have been created by PSRIs.

**Therapeutic Categories**

The therapeutic categories into which the 153 products fall are shown in Table 1. Oncology and infectious diseases account for half the total. The order of these disease categories is very different from the priorities of the pharmaceutical industry. The disease priorities of the NIH institutes with the largest budgets— in order, the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases — broadly correlate with the top four categories of PSRI-discovered drugs (Table 2). One possible interpretation of this observation is simply that there was more funding available for research involving these disease categories, which resulted in more useful intellectual property.

**Discovering Institution and Rate of Discovery**

A total of 75 PSRIs discovered or codiscovered at least one product (Table 1 in the Supplementary Appendix). Of these institutions, the most prolific is the NIH (with 22 products), followed by the University of California system (with 11), Memorial Sloan-Kettering Cancer Center (with 8), Emory University (with 7), and Yale University (with 6).

**Clinical Effect of PSRI Drugs**

The FDA-approval process provides two indications of the clinical significance of a new drug. The FDA classifies new-drug applications into one of eight chemical types: type 1, a new molecular entity; type 2, a new ester, salt, or other noncovalent derivative; type 3, a new formulation; type 4, a new combination; type 5, a new manufacturer; type 6, a new indication; and type 7, a drug that is already marketed but does not have an approved new-drug application.

The FDA assigns the application one of two types of review on the basis of its therapeutic potential: priority review if the drug shows substantial improvement, as compared with currently marketed products for the treatment, diagnosis, or prevention of a disease, or standard review if the drug appears to have therapeutic qualities similar to those of one or more drugs that are already on the market. A drug that has been designated as a new molecular entity and that has received a priority review would therefore be considered by the FDA to have the highest potential therapeutic effect.

We obtained the total number of approvals of new-drug applications, according to chemical type and type of review, for the 18-year period from 1990 through 2007 from the FDA's Web site and by a request under the Freedom of Information Act. During this period, the FDA approved 1541 new-drug applications but granted priority review to just 348 applications (22.6%) (Table 2). Of the 1541 total approvals, 143 (9.3%) resulted from PSRIs. However, of the 348 priority reviews, 66 (19.0%) resulted from PSRIs, or twice the overall rate for priority reviews. Viewed from another perspective, 46.2% of new-drug applications from PSRIs received priority reviews, as compared with 20.0% of applications that were based purely on private-sector research, an increase by a factor of 2.3.

The total approvals of new-drug applications, 483 (31.3%) were for new molecular entities, of which 64 (13.6%) originated at PSRIs.

**Table 1. Number of Drug Products Approved by the Food and Drug Administration and Originating from Public-Sector Research, According to Therapeutic Area, 1970–2009.**

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>153</td>
</tr>
<tr>
<td>Hematology or oncology</td>
<td>40</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>36</td>
</tr>
<tr>
<td>Cardiology</td>
<td>12</td>
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<tr>
<td>Metabolic disease</td>
<td>12</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>12</td>
</tr>
<tr>
<td>Dermatology</td>
<td>7</td>
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<tr>
<td>Renal disease</td>
<td>7</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>6</td>
</tr>
<tr>
<td>Immunology</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>4</td>
</tr>
<tr>
<td>Women’s health</td>
<td>3</td>
</tr>
<tr>
<td>Allergy</td>
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</tr>
<tr>
<td>Pulmonary disease</td>
<td>2</td>
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<tr>
<td>Urology</td>
<td>2</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>1</td>
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<tr>
<td>Dental disorders</td>
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these new molecular entities, 209 (43.3%) received priority review during this period; of these, 44 (21.1%) came from PSRIs.

The largest category of new-drug applications was for new formulations, with 730 of total approvals (47.4%); of these, 53 (7.3%) originated in PSRIs. Of the new formulations, 99 (13.6%) were considered to have sufficient therapeutic importance to receive priority review; of these, 17 (17.2%) originated in PSRIs.

A total of 116 approvals of new-drug applications (7.5%) were for new drug combinations; of these, 9 (7.8%) originated in PSRIs. Of the new drug combinations, 20 (17.2%) were considered to have sufficient therapeutic importance to receive a priority review; of these, 3 (15.0%) originated in PSRIs.

Drug manufacturers file most applications for new indications of approved drugs as an efficacy supplement to the existing new-drug application rather than as a separate application. A large number of such supplements are filed every year. Only 10 approvals of new-drug applications (0.6% of the total) were for new indications, but 9 (90%) originated in PSRIs.

Thirty-nine of the products received an orphan-drug designation, indicating that the drugs addressed conditions that affected fewer than 200,000 patients.

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**DISCUSSION**

We believe that our data set is more comprehensive than those developed by previous investigators in part because we sought the input of the officers responsible for managing intellectual property for PSRIs. In addition, we did not limit ourselves to intellectual property listed in the Orange Book. However, we cannot be sure that our data are truly comprehensive.

We also did not set out to comprehensively identify the intellectual property generated by the companies that developed the drugs that augmented the intellectual property licensed from the PSRIs. Thus, our data identify drugs that were discovered in whole or in part at PSRIs.

We believe that our study supports the concept that the emergence of biotechnology in the mid-1970s, combined with policy changes implemented in the early 1980s regarding the ownership and management of the intellectual property of PSRIs, allowed these institutions to play an important role in the downstream, applied phase of drug discovery. Our data show that PSRIs have contributed to the discovery of 9.3 to 21.2% of all drugs involved in new-drug applications approved during the period from 1990 through 2007. These proportions are higher than those identified by some earlier researchers. Our
data also suggest that PSRIs tend to discover drugs that are expected to have a disproportionately important clinical effect.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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