The last five years have been among the most productive in history for new drug approvals and innovation. In 2014 alone, the Food and Drug Administration (FDA) approved 51 new medicines, the highest number since 1996. Among the 41 medicines approved by FDA’s Center for Drug Evaluation and Research (CDER), 40% were first-in-class treatments, which use a completely new approach to fighting disease, nearly 40% treat rare diseases, and about 20% were personalized medicines.

This remarkable progress, however, follows a decade of reduced productivity levels with an average of 31 approvals per year between 2000 and 2010, compared with an average of 37 per year in the 1990s. (See figure 1.) A variety of factors converged to slow progress and biopharmaceutical companies have worked to adapt to evolving trends and make innovative changes to the research and development (R&D) process. However, much work remains as the costs and complexity of drug development are growing rapidly.

Many interrelated factors have contributed to these trends:

**INCREASINGLY COMPLEX TRIALS:** The complexity of clinical trials has increased as trial designs and procedures have become much more intricate and trial sizes have increased, demanding more staff time and effort, and creating substantial patient enrollment and retention challenges.

**CHANGING SCIENCE:** Expanding understanding of the biology of disease on the molecular level has meant great promise for patients, but it has also been one factor in the major challenges impacting drug development. Applying new molecular and genetic approaches to developing new medicines is a challenging undertaking as the science is a moving target. These dynamics require continual retooling of the approaches to R&D.

**SHIFTING DISEASE TARGETS:** Scientific challenges have increased as the industry has followed new scientific opportunities and ramped up its focus on more complex diseases and conditions—such as Alzheimer’s disease, mental health disorders, and cancer. Industry is increasingly focusing on areas where the science is difficult and the failure rates are higher as a result.

**SUCCESS RATES:** Failure is inherent in the drug development process, but success rates have also decreased in recent years. In fact, less than 12% of molecules that enter clinical testing gain approval from the FDA.

**HIGHER REGULATORY HURDLES:** Regulatory requirements have expanded over time, increasing uncertainty associated with drug development and approval timelines as well as post-marketing commitments.

**IDENTIFYING CHALLENGES**

As a recent report from the Tufts Center for the Study of Drug Development (CSDD) found, the operating environment for biopharmaceutical innovation has been rife with challenges. R&D costs have steadily risen since the 1970s, reaching an average of $2.6 billion to develop one new medicine in the early 2010s, including the cost of failures, (see figure 2) and the length of the process remains about ten years on average.
Figure 1: New Medicine Approval Rates Have Rebounded

![Bar chart showing new medicine approval rates from 1990s to 2010s.](image)

- **1990s**: 37 new medicines approved by the FDA per year
- **2000s**: 31 new medicines approved by the FDA per year
- **2010s**: 38 new medicines approved by the FDA per year

Figure 2: Average Drug Development Costs Continue to Rise

![Bar chart showing average drug development costs from 1970s to 2010s.](image)

- **1970s**: $179M
- **1980s**: $410M
- **1990s-Early 2000s**: $1.0B
- **2000s-Early 2010s**: $2.6B

*Previous research by same author estimated average R&D costs in the early 2000s at $1.2 billion in constant 2000 dollars (see J.A. DiMasi and H.G. Grabowski. “The Cost of Biopharmaceutical R&D: Is Biotech Different?” Managerial and Decision Economics 2007; 28: 469–479). That estimate was based on the same underlying survey as the author’s estimates for the 1990s to early 2000s reported here ($800 million in constant 2000 dollars), but updated for changes in the cost of capital.

**When the costs of post-approval R&D are included the cost estimate increases to $2.8 billion.
Innovation in the Biopharmaceutical R&D Process

Biopharmaceutical companies have not idly accepted the growing challenges to the development of new drugs. Companies are using a wide variety of innovative approaches to adapt the R&D and manufacturing process to the changing scientific landscape. These innovative approaches to drug discovery, development, and manufacturing shed light on a resilient enterprise making progress in improving the quality, performance and efficiency of R&D and manufacturing.”

–TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

To address the increasing challenges, costs, and uncertainty associated with drug discovery and development, biopharmaceutical companies have been seeking to increase the efficiency and effectiveness of their R&D capabilities and processes. Although more progress is needed, these efforts are beginning to bear fruit in the form of an increase in the number of innovative new approvals in recent years. Tufts CSDD recently examined the various approaches used by biopharmaceutical companies to improve the efficiency and productivity of their research efforts. These approaches range from improving validation of drug targets, to increased integration of real world data into the R&D process, to exploring new approaches to the conduct of clinical trials including through adaptive clinical trial including design.5

New research from Boston Consulting Group (BCG) further suggests these efforts may already be working, contributing to the record number of new drug approvals in 2014.6 This improved productivity helps sustain the biopharmaceutical R&D ecosystem and fosters continued investment in future research.

“Significant investment in science, both in furthering our understanding of the basis of disease and in applying new platform technologies (fundamental technologies that can be leveraged across multiple drug candidates), is clearly bearing fruit...the ultimate beneficiary of the continued investment in innovation will be the patients. A healthy biopharma industry – with R&D productivity as its core – is the necessary enabler for the industry to deliver on its promise to tomorrow’s patients.”

–BOSTON CONSULTING GROUP
INNOVATING THE R&D PROCESS

Biopharmaceutical companies have taken an array of new approaches to adapt and improve the R&D process as the scientific, regulatory, and business challenges change and increase. These efforts range from the earliest stages of basic research up to clinical trials and regulatory review. Below are select examples.

BASIC SCIENCE

- **Target Validation**: Target validation is the process of clearly defining the role of proteins, genes and other molecules involved in disease pathogenesis. This basic research is crucial for increasing the chances that potential drugs act on targets that will affect the underlying causes of the disease and, therefore, work for patients. According to Tufts, "Improving the target validation process earlier in the R&D process would inform critical decisions about which compounds to take into clinical research and those to be terminated. As a result, more effective target validation holds promise in improving later-stage R&D success rates and in conserving valuable R&D resources." New models of collaboration and partnering between companies, academia, and government agencies are essential to build upon the promise of target validation. (See Partnerships section on the following page.)

CLINICAL DEVELOPMENT

- **Innovative Trial Designs and Methodologies**: Innovative clinical trial designs and methodologies, such as adaptive trial designs and the use of Bayesian statistical approaches, hold immense potential for improving success rates and creating greater efficiencies in conducting clinical trials. Adaptive trial designs enable researchers to modify one or more clinical trial design element(s) while a trial is underway based on the collection and review of interim data. Bayesian methods provide a robust platform for learning from evidence as it accumulates, bringing efficiency to the drug development process by providing a mechanism to formally incorporate all available information and evaluate how each piece of information influences the decision at hand.

According to Tufts, "adaptive trial designs enhance R&D efficiency because the need to repeat trials that closely miss their clinical end-point or fail to identify the correct dose is eliminated. Early clinical trial terminations due to safety or efficacy futility allow companies to re-allocate resources to more promising drug candidates." R&D productivity is improved in many cases because adaptive trials in early phases can help identify the right dose and the right patients for Phase III trials by providing early quantitative data on treatment efficacy.
• **New Drug Development Tools:** Drug development tools, such as patient-reported outcomes or biomarkers, have the potential to improve efficiency at many points in the drug development process. Patient-reported outcomes (PROs) are endpoints that are collected directly from patients often as self-administered questionnaires. They can include questions about how they feel or what they are able to do, providing valuable information from the patient’s perspective. Biomarkers are biological molecules within the body that are measures for biological processes, including the potential for or progression of a disease.

By providing innovative ways to measure disease potential, progression, and impact, these tools can help researchers in early development understand the effect of a drug on a specific target and develop models and measurements to capture meaningful information at earlier time points in the R&D process. They can also drive the enrichment of clinical trial populations, which means that researchers are better able to select patients in whom it will be most clear whether the drug candidate is safe and effective. In addition, PROs and biomarkers can serve as endpoints in clinical trials meaning that they can provide measurable outcomes that contribute to the understanding of the safety and efficacy of the drug candidate. The increased use and regulatory acceptance of drug development tools has the potential to significantly improve efficiency of the R&D process and ensure new medicines are meeting patient needs.

• **Improvements in IT Structure to Enhance Data Utilization:** Data on patient outcomes from clinical trials and in real world clinical settings can provide invaluable information on the benefits and risks of a medicine. This can help speed drug development and make it more efficient by informing and providing the types of data needed to facilitate uptake of new medicines.

Data sources are multiplying both within and outside biopharmaceutical companies. Information originates from the R&D process itself, pharmacies, payers, patients, practitioners, and caregivers. Real-time and predictive analytics built around these data are contributing to the compilation of large amounts of information in usable formats to facilitate more efficient drug development.

The ultimate beneficiary of these efforts to better utilize various data sources will be patients. As Tufts notes, “Biopharmaceutical companies are increasingly using real world evidence with the objective of achieving greater understanding of patient populations to advance current and future treatment options for patients. Companies are utilizing novel approaches and technologies to integrate, store, interrogate and analyze large datasets from multiple sources. Real world data will ultimately be used to develop more targeted therapies and personalized medicines.”

More than 300 global consortia have formed between 2005 and 2014 to share data, expertise and resources to support more collaborative global drug development activity. The number of consortia formed is nine times that formed during the prior five year period.”

–TUFTS CSDD
PARTNERSHIPS

In recent years, partnerships and other forms of innovative collaborations among biopharmaceutical companies, government, academia, patient groups, and others have become an increasingly common approach to spur efficiencies in basic science and biopharmaceutical R&D. Partnerships allow the public and private sectors to share certain risks and exchange intellectual, financial, and in-kind and/or human resources as mutually agreed upon.

The close and synergistic relationship between these sectors is critical to ensuring a robust national biomedical research capacity in the U.S. to discover the next generation of medicines to address our most costly and challenging diseases. According to a prior Tufts report examining the role of industry-academic partnerships, "As the scope of some of the scientific challenges is so large, collaboration is viewed as increasingly important to making significant progress." That same report found that these public-private partnerships are occurring across the entire R&D process; "the industry is funding and working collaboratively with the academic component of the public sector on basic research that contributes broadly across the entire spectrum of biomedical R&D, not just for products in its portfolio."

EXAMPLES OF INNOVATIVE PARTNERSHIPS HELPING DRIVE THE DRUG DISCOVERY PROCESS INCLUDE:

**AMP (Accelerating Medicines Partnership)**
The Partners: biopharmaceutical companies, NIH, patient and disease organizations

Announced in 2014, the Accelerating Medicines Partnership (AMP) is a groundbreaking collaboration among the National Institutes of Health (NIH), several nonprofit disease foundations, 10 biopharmaceutical companies and PhRMA. This partnership aims to transform the current model for developing new diagnostics and treatments by bringing together expertise from the private and public sectors to identify and validate promising biological targets of disease. AMP represents a new, integrated approach to increasing the number of new diagnostics and therapies for patients while reducing the time and cost associated with their development. The partnership has initiated pilot projects focused on three disease areas: Alzheimer’s; type 2 diabetes; and autoimmune disorders, including rheumatoid arthritis and lupus.

**Biomarkers Consortium**
The Partners: biopharmaceutical companies, NIH, CMS, FDA, patient and disease organizations

The Biomarkers Consortium is a combined effort by the Foundation for the NIH, FDA, CMS, NIH, 15 biopharmaceutical companies, and 13 non-profit organizations, including PhRMA, to pool expertise and resources to identify, develop, and qualify biomarkers, which are biological molecules that can be measured to predict, diagnose, and track disease. Biomarkers help researchers personalize therapies and improve their ability to evaluate the effectiveness of potential new medicines, thus increasing efficiency in the process. The Consortium aims to gain regulatory acceptance of new biomarkers so they can be used in drug development. Projects in areas such as Alzheimer’s disease, cardiovascular disease, breast cancer and others are underway by the Consortium.

**Lung-MAP (Lung Cancer Master Protocol)**
The Partners: biopharmaceutical companies, NIH, FDA, patient and disease organizations

Lung-Map is a first-of-its kind clinical trial that combines multiple clinical trials into one infrastructure. The study uses comprehensive genetic screening to examine more than 200 cancer-related genetic alterations in lung cancer patients. This information is used to direct patients to one of five specific sub-studies which each test a different treatment. This approach makes it more likely that each patient will enter the trial that fits their genomic profile best. By using a shared adaptive platform drug development has the potential to become much more flexible and efficient.
ENDNOTES