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Abstract
The rate of new drug approvals in the US has remained essentially constant since 1950, while the costs of drug development have soared. Many commentators question the sustainability of the current model of drug development, in which large pharmaceutical companies incur markedly escalating costs to deliver the same number of products to market. This Issue Brief summarizes the problem, describes ongoing governmental efforts to influence the process, and suggests changes in regulatory science and translational medicine that may promote more successful development of safe and effective therapeutics.

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Re-engineering Drug Discovery and Development

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Editor's note: The rate of new drug approvals in the US has remained essentially constant since 1950, while the costs of drug development have soared. Many commentators question the sustainability of the current model of drug development, in which large pharmaceutical companies incur markedly escalating costs to deliver the same number of products to market. This Issue Brief summarizes the problem, describes ongoing governmental efforts to influence the process, and suggests changes in regulatory science and translational medicine that may promote more successful development of safe and effective therapeutics.

Current model of drug development is unsustainable

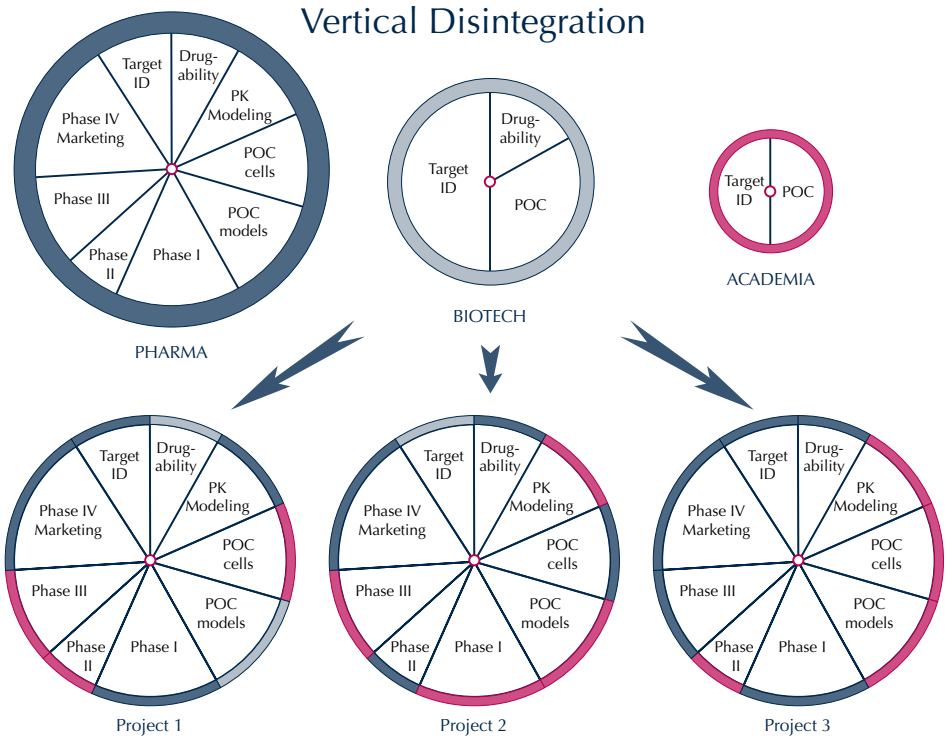
Despite enormous investments in drug discovery and development, the number of new molecular entities (NMEs) annually approved by the Food and Drug Administration (FDA) has hovered around 20-25 for the past 60 years. The rate-limiting step occurs at drug development, not drug target discovery. New molecular and genomic technologies have produced far more potential drug targets than can be pursued through the current development process. Targets, and the chemistry needed to probe them, can be selected more rationally than ever—yet more and more candidate drugs are proving expensive failures.

- In the present system, large, vertically integrated pharmaceutical companies retain in-house expertise at each phase of drug discovery and development. They protect their property interests through patents on molecules, most of which never become approved drugs.
- According to pharmaceutical industry data, a new drug can take 10-15 years to develop and bring to market. For every 5,000-10,000 compounds that enter the research and development (R&D) pipeline, only one receives approval. Although substantial variation exists in estimating drug development costs, industry analysts estimate that companies spend $1 billion to $4 billion in R&D for every new drug brought to market.
- Increasing public and political pressure to lower prescription drug prices may signal lower returns on a company's R&D investment. In response, pharmaceutical companies have shifted their focus to opportunities that promise only the broadest markets or the most favorable pricing, such as those for cancer treatment. Companies have also pursued a strategy of mergers, but there is no evidence to suggest that these mergers have fostered innovation or accelerated the delivery of new drugs.

Toward a more modular, disaggregated model of drug development

Drug development passes through several stages, including: [1] the identification of drug targets—typically through an understanding of the biological pathways of health and disease; [2] medicinal chemistry, in which molecules are structured to attack such targets; [3] "drugability" in which those molecules are modified so that their absorption, distribution, metabolism, and elimination are consistent with their use in humans; [4] proof of concept (POC) studies in cells, animal, or human models; and [5] clinical development, including Phase I-IV trials required by the FDA.

- In the traditional model of drug development, the pharmaceutical company has expertise in all of these phases, with much more limited roles for academia and biotechnology companies. As illustrated below, the traditional approach is slowly shifting to a modular, collaborative one that capitalizes on the strengths of government, academia, industry, and non-profit organizations. Depending on the project, expertise can be drawn from any sector, with risk distributed among the various stakeholders.



- Examples of this approach exist in the not-for-profit sector, including Medicines for Malaria Venture (MMV), TB Alliance, and Institute for OneWorld Health. These product development partnerships (PDPs) have taken on R&D for neglected diseases where there is little commercial incentive to develop drugs. Although the details vary, they usually operate as virtual R&D organizations, drawing on the expertise of a group to identify targets and partnering with a network of research institutions and companies to outsource activities, using philanthropic resources and in-kind contributions from partners. One analysis found that PDPs introduced nine new products for TB, malaria, meningitis, and leishmaniasis in 10 years, compared to 14 new drugs developed for neglected diseases in the previous 25 years.

Re-engineering the process calls for changes in educational, regulatory, and informatics infrastructure

The transition to a more modular approach will require linked initiatives among academia, the pharmaceutical industry, the National Institutes of Health (NIH), and the FDA.

- It will have to address the serious deficit in scientists with expertise in translation medicine and therapeutics (TMAT) and regulatory science. A working group recently recommended that the NIH develop clear career tracks for translational medicine, with programs that include training in clinical pharmacology, systems biology, biomarker development, and cross-sector training with the FDA and the pharmaceutical industry. The Wellcome Trust has funded four centers of excellence in Great Britain; each center has an industrial partner that contributes expertise to the teaching program and an environment where trainees can be exposed to drug development in the setting of a for-profit company.
- Increasingly, policymakers are recognizing that encouraging and rewarding innovation requires changes in regulations, and that improving regulations requires science of its own—regulatory science. Regulatory reforms could protect and expand the precompetitive space, fostering an earlier, more thorough understanding of drug action. The FDA might create a "safe haven" for systems physiology and pharmacology, akin to its approach to pharmacogenomics. The FDA could also consider incentives for earlier detection of adverse events and unintended therapeutic effects by using a more graded or gradual approach to introduction to and withdrawal from the marketplace.
- The new approach requires an informatics infrastructure that permits global, secure, and compliant sharing of data across academic, industry, and regulatory sectors. Some of this activity has begun. For example, the NIH Chemical Genomics Center (NCGC) recently created the NCGC Pharmaceutical Collection, a complete list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules available for further screening for new uses in rare and neglected diseases.
- Recognizing the need to re-engineer the translational process, the NIH has proposed a new National Center for Advancing Translational Science, which would aggregate existing resources pertinent to translational medicine. The proposed center would house the 60 existing Clinical and Translational Science Awards (CTSAs) and their educational infrastructure, as well as a collaboration between the NIH and FDA, and foster academia-industry interactions.

POLICY IMPLICATIONS

The current drug development process is inefficient and unsustainable. Development, approval, and monitoring of drugs will rely increasingly on coordination and collaboration among industry, academia, and regulatory bodies, as well as on the sharing of information in an open and timely manner. Several initiatives at the NIH and FDA are underway to facilitate the shift to a more modular, collaborative model.

- In August 2011, the FDA released a strategic plan for advancing regulatory science. The plan calls for the FDA to develop new tools, standards, disease models and science-based pathways to improve the speed, efficiency, predictability, capacity and quality of the entire process, from drug development to evaluation to manufacturing. However, budget restrictions have eliminated the FDA's plans to devote an additional $25 million to regulatory science. The initiative is now being supported through existing funds, which will likely limit its scope.
- The proposed National Center for Advancing Translational Science (NCATS) has run into political and budgetary obstacles. As of this writing, it remains unfunded. The original proposal called for NCATS to be supported through transfer of funds from existing institutes (primarily the National Center for Research Resources, which would be eliminated) and the $100 million authorized (though not appropriated) for the

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POLICY IMPLICATIONS
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Cures Acceleration Network, a drug development grant program included in last year's health reform legislation. More efforts are needed to communicate how, in this new drug development model, NCATS will complement, rather than compete with, public and private sector translational activities.

- The FDA Science Board recently recommended funding FDA Centers of Excellence within academia. Such centers would provide FDA experts in regulatory science with a critical mass of complementary expertise and a neutral testing ground on which to explore drug action independent of the sponsor while remaining mindful of proprietary interests—a kind of Jet Propulsion Laboratory for the FDA. A call for one such center—limited to within 50 miles of the FDA campus—has recently been made.
- A key issue in applying the non-profit modular model to the for-profit world of drug development is the role of intellectual property and patents. A new framework of intellectual property should be considered—one that rewards successful R&D investment while encouraging early collaboration and data sharing. Perhaps the financial rewards of a patent should be postponed until a drug is a profitable success—and a formal mechanism found to distribute rewards among all those who helped make it happen.

This Issue Brief is based on the following articles: G.A. FitzGerald. NCATS purrs; emerging signs of form and function. Science Translational Medicine, May 18, 2011, vol. 3, 83ed2; G.A. FitzGerald. Regulatory science: what it is and why we need it. Clinical Pharmacology & Therapeutics, February 2011, vol 89, pp. 291-293; G.A. FitzGerald. Perestroika in Pharma: evolution or revolution in drug development? Mt. Sinai Journal of Medicine, July-August 2010, vol. 77, pp. 327-332; C. Skarke, G.A. FitzGerald. Training translators for smart drug discovery. Science Translational Medicine, April 7, 2010, vol. 2, 26cm12.

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