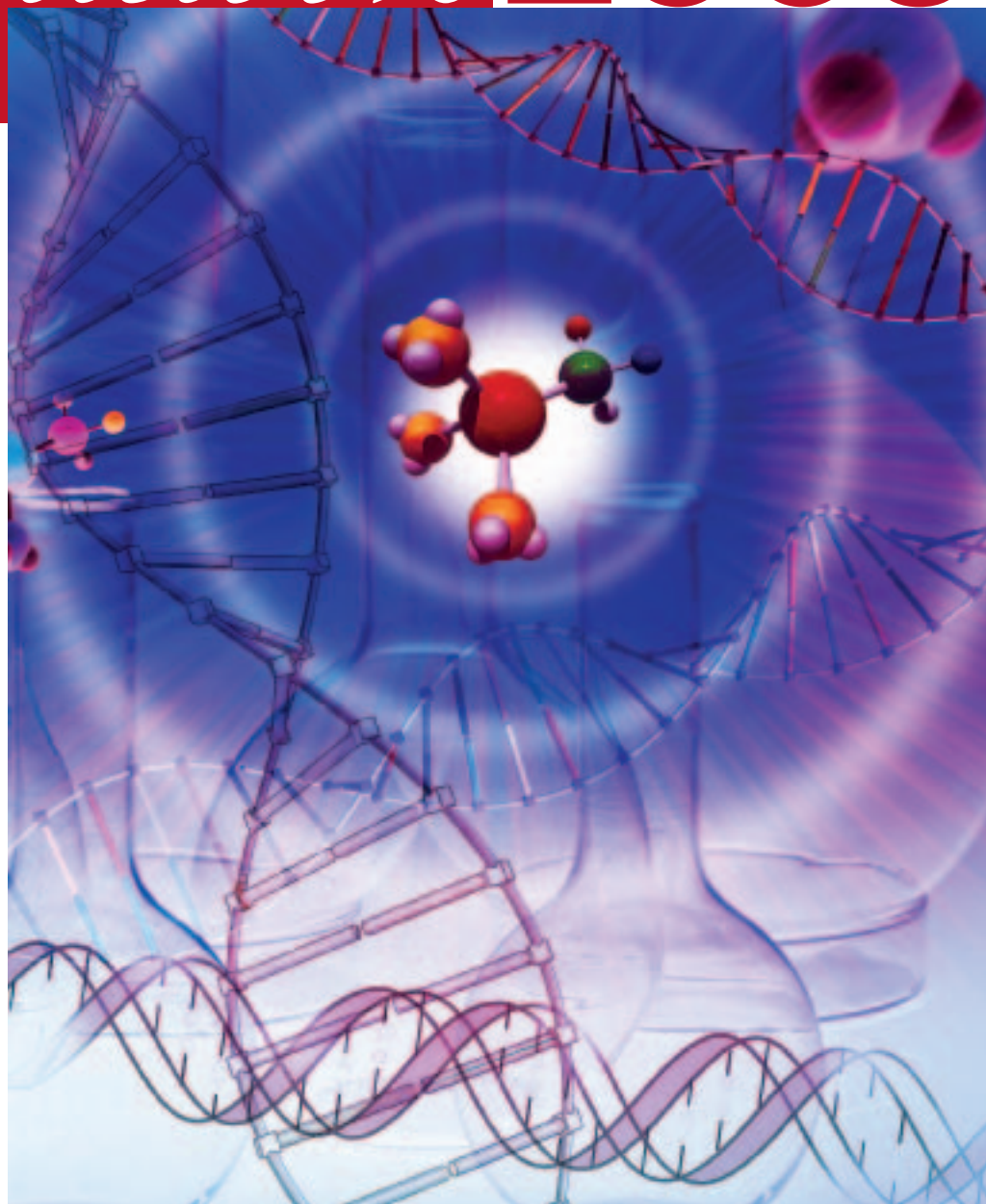




Tufts Center for the Study of Drug Development

Outlook 2005



R&D Efficiency

Regulatory Environment

Biotechnology Trends

Prescription Drug Policy



Glossary

Approval phase time — Time from date of submission of an NDA or BLA to date of U.S. Food and Drug Administration (FDA) approval.

Attrition and approval success rates — Attrition rate refers to the percentage of NCEs that drop out of testing during development. Approval success rate refers to the percentage of NCEs in clinical development that eventually obtain FDA marketing approval.

BLA — Biologics license application. An application to FDA to market a new biological product in the U.S.

Clinical phase time — Time from filing of an investigational new drug application (IND), which is necessary to begin testing of a new compound in human subjects, to the submission of an NDA or BLA.

Fast track program — FDA program begun in November 1997 to expedite development and approval of new prescription medicines that address unmet medical needs for serious or life-threatening conditions.

Formulary — A list of selected pharmaceuticals and dosages recommended by health insurers. Formularies are developed by Pharmacy and Therapeutics Committees, which consider drug safety, efficacy, quality, and cost-effectiveness in the decision whether or not to include a drug in a formulary.

NCE — New chemical entity. A new therapeutic compound that has never been used or tested in human subjects.

NDA — New drug application. An application to FDA to market a new drug in the U.S.

Orphan drug — Drugs developed for rare diseases and conditions, which, in the U.S., affect fewer than 200,000 people, or, in the European Union, affect 5 per 10,000 people or fewer. Because sales of orphan drugs are likely to be small relative to their development costs, pharmaceutical companies are awarded exclusive rights to market these medicines for a period of time as an incentive to develop them.

PDUFA — The *Prescription Drug User Fee Act of 1992*. Legislation passed by Congress authorizing the FDA to collect user fees for regulatory review of new drug applications. The FDA agreed to use the revenue generated from user fees to hire more reviewers to speed up the drug review process without compromising review quality. PDUFA was reauthorized in 1997 and again in 2002.

U.S. Pharmacopeia — USP is a non-governmental, standards-setting organization that advances public health by ensuring the quality and consistency of medicines, promoting the safe and proper use of medications, and verifying ingredients in dietary supplements.

Tufts CSDD Outlook reports, published each January, highlight near-term pharmaceutical and biopharmaceutical drug development trends. Data and analyses contained in Tufts CSDD Outlook 2005 are based on proprietary research conducted by the Tufts CSDD research staff. For more information, call 617-636-2170 or click on <http://csdd.tufts.edu>.

Outlook 2005

Productivity and quality improvements are indisputable R&D mandates for drug and biotech companies, whether located in the United States or abroad. To improve their product pipelines, drug developers must address big-picture issues such as creating more innovative R&D strategies, and small-picture issues such as cutting recruitment costs for patients in clinical studies.

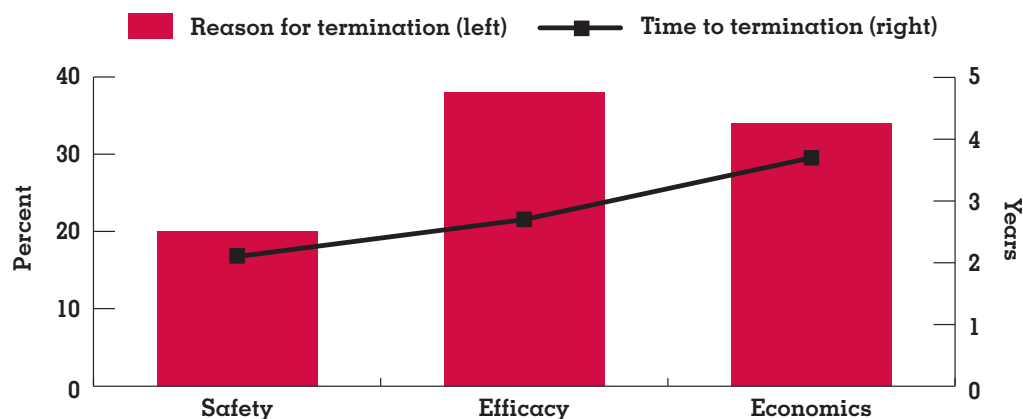
Early termination of unpromising R&D projects remains a key challenge for drug companies and an imperative if they want to remain competitive. Recent history makes the case. Despite rapidly rising increases in R&D spending, the number of new drugs and biologics being submitted to the FDA for review has been steadily decreasing in recent years.

Fortunately, there are actions available to drug and biotech companies. Key among them:

- Investing in state-of-the-art information technologies to better understand and utilize the data generated in discovery and development of potential products.
- Developing strategic alliances between biotechs and small pharma on the one side and big pharma on the other. This allows both parties to leverage their core strengths and capabilities and optimize R&D efficiency.
- Maximizing interactions with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to shape clinical studies and efficiently develop the data needed for review.

ECONOMICS IS AN IMPORTANT FACTOR IN DECISIONS TO TERMINATE R&D PROJECTS

Reasons for Terminating Unpromising New Drugs and Time to Terminate



Source: Tufts Center for the Study of Drug Development

Rapidly rising R&D costs has led economics to gain ascendancy as a major reason for killing unpromising products in the R&D pipeline. New development tools — such as bioassays, computer modeling techniques, biomarkers, and validated surrogate endpoints — will help drug developers lower research costs and improve the predictability of development cycles by terminating unpromising compounds earlier in development.

R&D Efficiency

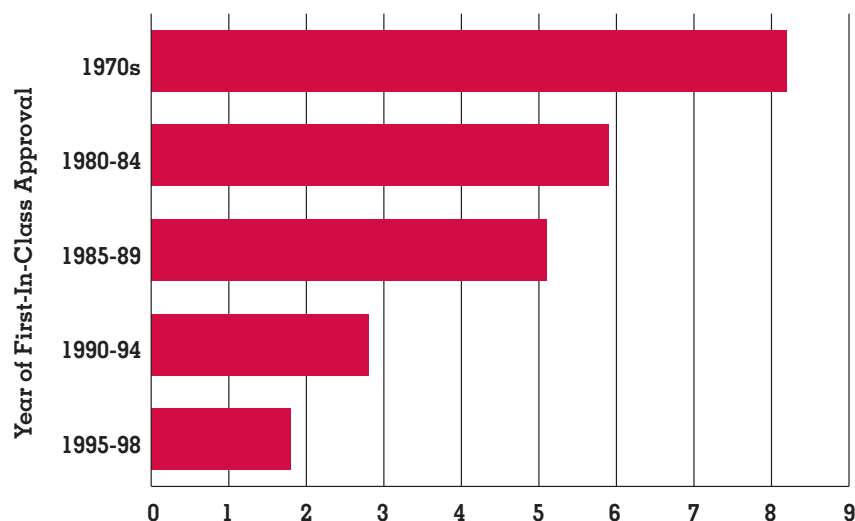
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irms will face growing pressure to improve R&D productivity to get new drugs to market sooner, and to develop medicines with demonstrable advantages over current therapies.

- As marketing exclusivity periods for first-in-class drugs decline, drug developers will face increasing pressure to improve productivity in their drug development activities to help bolster return on investment.
- R&D strategies that strive to attain a best-in-class status for new drugs or, at the least, clear advantages over existing therapies with patient subgroups or particular indications will dominate.
- Growing pressures to contain costs from managed care organizations in the United States and pricing and reimbursement authorities abroad will increase pressure on firms to get new drugs to market sooner, preferably with clear advantages in safety, efficacy, or economic value.
- Implementation of the *Medicare Prescription Drug, Improvement, and Modernization Act of 2003* will spur efforts to learn more about costs and benefits of drugs in the marketplace. Health care plans and pharmacy benefit managers will seek such information to help make formulary decisions and negotiate rebates.

THE FIRST-IN-CLASS DRUG IS NOT NECESSARILY THE WINNER

Mean Time from First-in-Class to First Follow-on Approval



Source: DiMasi, Paquette, *Pharmacoeconomics* 2004;22(Suppl 2):1-14

First-in-class drugs may not be the best in the class and may not be the only drug in the class for long. Effective market exclusivity for first-in-class drugs declined five-fold since the 1970s — from an average of 8.2 years in the 1970s to 1.8 years in 1995-98. (Median values declined 88% during the same time period—from 10.2 years to 1.2 years.) Follow-on drugs often provide a therapeutic advance over first-in-class drugs.

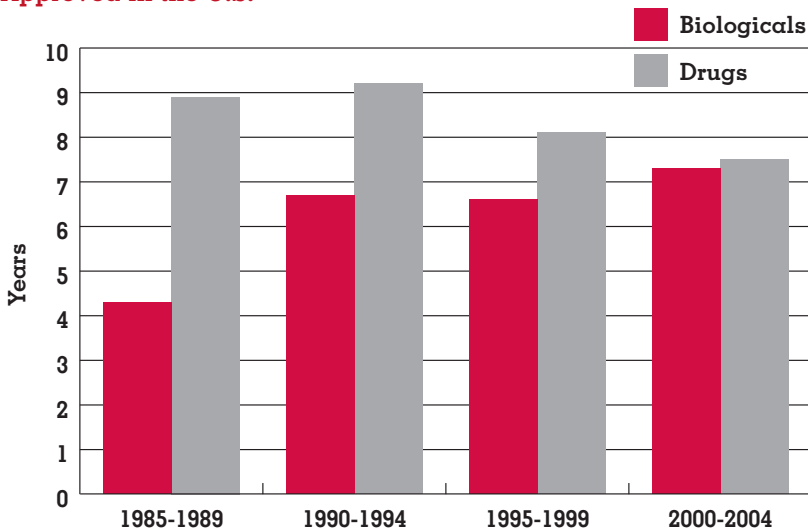
Regulatory Environment

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crowded agenda, growing public and private scrutiny, and fewer resources will steer the FDA to promote R&D productivity improvements and encourage development of prevention-oriented medicines.

GOOD NEWS, BAD NEWS: DEVELOPMENT TIME DOWN FOR DRUGS, UP FOR BIOPHARMACEUTICALS

Total Development Times for Drug and Biological Products Approved in the U.S.



Source: Tufts Center for the Study of Drug Development

Total development times for drug and biological products have been converging since the mid-1980s. Important factors include increasing biotech and big pharma alliances, in-licensing, mergers and acquisitions, increasing harmonization of international regulatory requirements, and globalization of clinical trials. Despite this trend, the number of new drugs and biologics being submitted to the FDA for review has been decreasing.

- The “critical path” initiative to improve industry productivity and the process analytical technology (PAT) initiative to encourage industry to apply innovation to its manufacturing processes will aid development of new prevention-oriented drugs and biologicals.
- FDA will continue to be resource-constrained as it struggles with demands to address counter-bioterrorism, Medicare Modernization Act rollout, the critical path initiative, and implementation of PDUFA III.
- The well-publicized withdrawal for safety reasons of a popular analgesic in the COX-2 class during the fourth quarter of 2004 will strengthen FDA’s commitment to raising the safety bar pre-market, as well as enhancing post-market risk management and surveillance programs.
- Pressure on FDA from congressional critics and watchdog groups may also influence staff turnover rates and the choice of top FDA leadership positions. Ongoing reorganizations could spark another wave of departures.

Biotechnology Trends

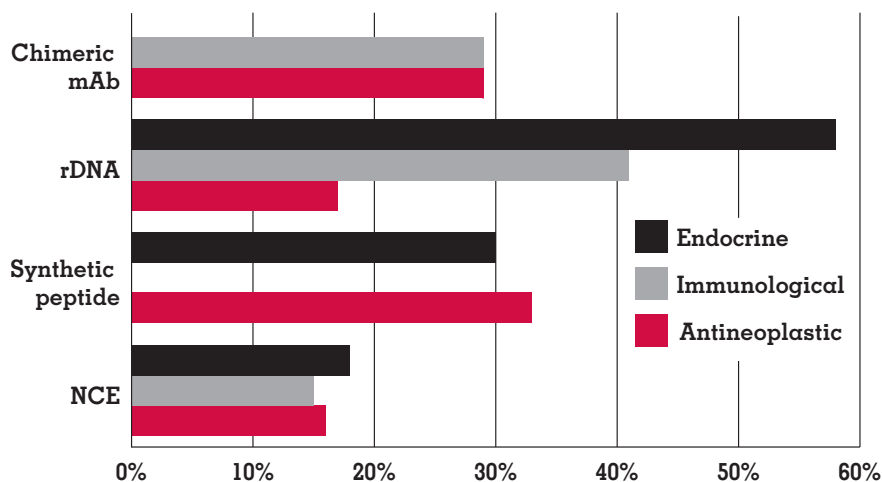


Biotechnology firms are poised to prosper in the near to medium term due to their ability to engage in more innovative R&D strategies and field products with higher approval success rates.

- Based on historical success rates and the current pipeline, 33 of the recombinant therapeutics currently in development will be approved by the FDA in the near term. Three products are now undergoing regulatory review.
- Biotech development of innovative and orphan therapeutics will become more efficient if firms capitalize on scientific advice available from the FDA and EMEA in 2005.
- Oncology monoclonal antibodies (mAbs) will enter clinical studies in increasing numbers due to recent successful launches. Oncology mAbs accounted for eight of 15 of the mAbs approved since 1997.
- Vaccine production methods and other issues affecting the vaccine industry will come under intense scrutiny due to the 2004-05 flu vaccine shortage in the U.S.

BIOTECH PRODUCTS ARE WINNING THE RACE FOR REGULATORY APPROVAL

Comparative Approval Success Rates of U.S. Biopharmaceutical Products and Drugs



Source: Tufts Center for the Study of Drug Development

Biotech products have equivalent or better U.S. approval success rates compared to new chemical entities (NCE). Productivity declines and rapidly rising R&D costs are putting more pressure on drug and biotech companies to terminate unpromising projects as early as possible. Doing so helps cut costs, improves success rates, and gets new products to market more quickly.

Prescription Drug Policy

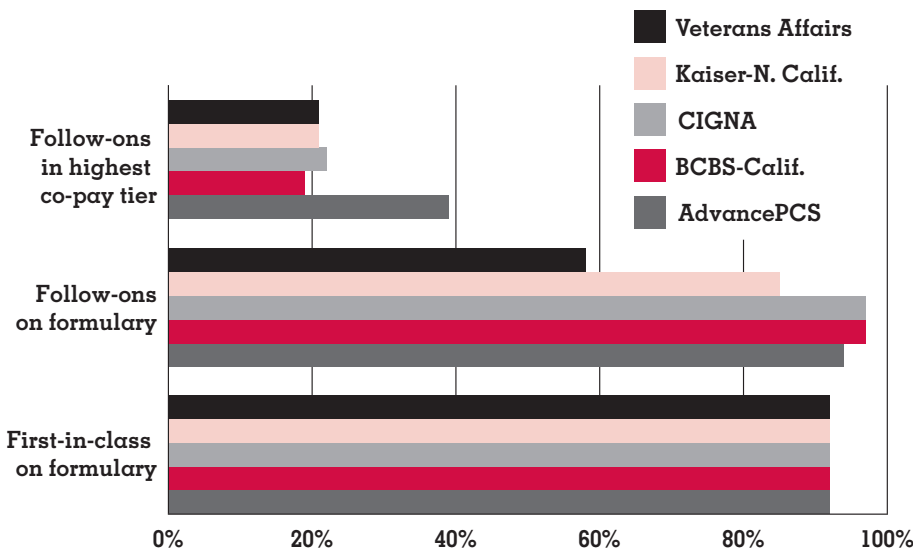


apidly rising prescription drug spending will increase pressure on drug developers to prove the cost-effectiveness of their products to ensure reimbursement in private and public markets.

- Although Medicare's prescription drug benefit does not launch until January 2006, the pharmaceutical industry will be jockeying for position in 2005 to get drugs, particularly follow-on drugs, on insurers' formularies. Expect insurers that currently exceed the Medicare law's minimum formulary requirements to gravitate toward standards set by the U.S. Pharmacopeia.
- As prescription drug cost pressures continue to build, doctors will be under growing pressure to follow clinical practice guidelines advocating the use of cheaper, generic products.
- While pharmaceutical firms see voluntary switches as a lucrative way to extend brand name viability, third party payers view switches as a way to cut costs. Watch for Britain, which became the first country in the world to sell statins over-the-counter, to become a test market for potential switches of statins in the U.S. in 2005.

FOLLOW-ON MEDICATIONS FACE A CHALLENGE GETTING FORMULARY APPROVAL

U.S. Formulary Coverage of First-in-Class and Follow-On Drugs: 2003



Source: Tufts Center for the Study of Drug Development

Gaining and maintaining market access for follow-on medications remains difficult, as formularies tend to favor first-in-class drugs and assign higher co-pays to follow-ons. A new Tufts CSDD study that examined 45 top-selling pharmaceuticals in 12 therapeutic classes, which accounted for approximately 25% of total pharmaceutical costs in the U.S. in 2003, shows wide variation in coverage of follow-ons across insurers.

Agenda2005

TUFTS CENTER RESEARCH PROJECTS DUE FOR COMPLETION

PDUFA III Initiatives	Evaluation of FDA programs under PDUFA III and assessment of FDA's Strategic Plan.
Approval Success and Attrition Rates	Updated analyses of approval success rates and phase at time of termination for new chemical entities entering clinical development.
FDA Special Programs	Update and analysis of special regulatory programs at FDA and impact on industry R&D, including Fast Track, pediatric studies, and counter-terror.
Post-Marketing Commitments	Retrospective study of post-marketing commitments, evaluating trends in the scope, frequency, and rationales for the studies requested, as well as the outcomes, resource requirements, and utility of studies completed.
Role of Outsourcing in Pharmaceutical Development	Analysis of outsourcing within the research-based industry to examine trends and assess cost impact.
Success Rates for Therapeutic Peptides and Oligonucleotides	Analysis of clinical success rates for synthetic peptides and oligonucleotides.
Orphan Product Grants	Assessment of the role of orphan product grants in R&D of medicines for rare diseases and conditions.
Vaccine Development Trends	Evaluation of the pharmaceutical industry's vaccine development programs.
Pharmacy Benefit Managers (PBMs) and Prescription Drug Coverage	Analysis of PBM's role as a pharmacy claims processor and formulary manager in a Medicare prescription drug benefit.
Disease Management Organizations (DMOs) and Medical Care	Examination of the DMO industry, with qualitative and quantitative assessments of its impact on Medicare beneficiaries' pharmaceutical care.

Agenda 2005

EDUCATIONAL PROGRAMS, CONFERENCES, AND PUBLIC FORUMS

February 7 - 11
Boston

Postgraduate Course in Clinical Pharmacology, Drug Development, and Regulation

Now in its 32nd year, this highly popular program is aimed at professionals in the pharmaceutical and biotechnology industries, as well as physicians, regulators, academics, service providers, consultants, lawyers, and investors. Concentrated instruction and interactive workshops focus on clinical trials, experimental design, drug development, clinical pharmacology, pharmacogenomics, and biostatistics.

April 4 - 6
San Francisco

Leadership for Drug Development Teams

This highly interactive course presents current best practices in leading drug development teams. Conducted by nationally recognized experts in team-based product development, the program helps R&D, strategic planning, regulatory affairs, marketing, and public policy leaders develop solutions to critical issues.

October 17 - 19
Boston

Leadership for Drug Development Teams

See listing above.

November 3
Boston

Senior Executive R&D Roundtable

Highly acclaimed by past participants, this one-day program, now in its ninth year, brings together senior pharmaceutical and biotech executives for a candid discussion of strategies for improving the efficiency of pharmaceutical R&D. Attendance is limited to facilitate discussion.

New in 2006!

Decision Making Skills

This new course will focus on the decision making process within research based drug companies. The interactive three-day program will help decision makers plan and conduct more effective meetings on complex, early-development issues, and create presentations on specialized scientific areas that will enable non-specialists to incorporate best scientific knowledge into their decisions.

For more information about these programs, contact the Tufts Center for the Study of Drug Development by calling 617-636-2170, emailing to csdd@tufts.edu, or clicking on <http://csdd.tufts.edu>.



Tufts CSDD Research Milestones

DRUG POLICY AND STRATEGY ANALYSES TO INFORM R&D AND STRATEGIC PLANNING DECISIONS

1976	Conducts first comprehensive analysis of innovation in the U.S. pharmaceutical industry.
1976	Identifies “drug lag” between the U.S. and the U.K.
1979	Conducts first comprehensive study of the cost to develop a new drug: \$54 million.
1981	Demonstrates dramatic decline in effective patent life for new therapeutic compounds.
1982	Provides first comprehensive evaluation of R&D effort of the U.S. pharmaceutical industry.
1982	Completes first analysis of availability of drugs for limited populations, paving the way for the <i>Orphan Drug Act of 1983</i> .
1984	Develops first comparison of the rate of drug safety withdrawals in the U.S. and other nations.
1987	Publishes first comprehensive analysis of FDA’s practice of requiring post-approval research as a condition of approval.
1991	Updates its seminal drug cost study: bringing new drugs to market now costs \$231 million.
1993	Develops first international comparison of biotechnology product discovery, development, and marketing rates in the U.S., Europe, and Japan.
1995	Publishes first comprehensive analysis of biotechnology success rates.
1996-98	Provides critical data and public testimony at Congressional hearings that led to passage of the <i>FDA Modernization Act of 1997</i> (FDAMA).
1997	Completes comprehensive analysis of FDA/sponsor meetings, showing that meetings reduce the time of new drug development.
1999	Publishes analysis showing impacts of the <i>Prescription Drug User Fee Act of 1992</i> (PDUFA) on drug development times.
1999	Provides first comprehensive analysis and review of FDAMA’s pediatric research incentive program.
2000	Publishes first comparative analysis of new drug and biopharmaceutical approval times under the Centralized Procedure of the European Medicines Evaluation Agency (EMA) and the U.S. FDA.
2001	Updates its ongoing study of the average R&D cost of developing and bringing a new drug to market. It now costs \$802 million.
2002	Quantifies potential cost savings that could be achieved by improving product success rates and shortening development cycles.
2003	Provides first comprehensive assessment of the impact of FDA’s new fast track program on total development times.
2004	Demonstrates that follow-on drugs are typically developed contemporaneously with the first product in the class and offer therapeutic value.

About

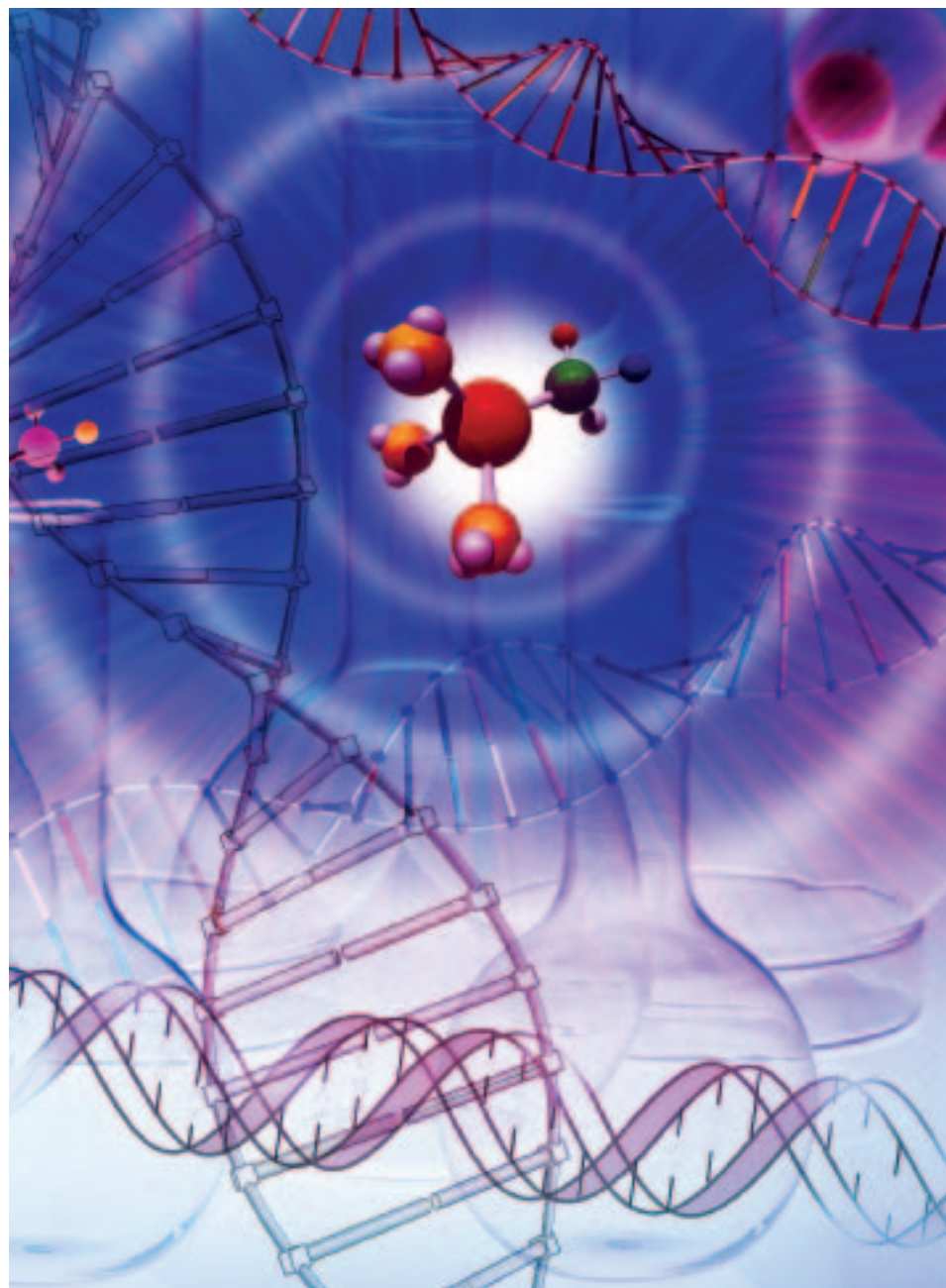
TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

Established in 1976, the Tufts Center for the Study of Drug Development at Tufts University provides strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. The Tufts Center conducts a wide range of in-depth analyses on pharmaceutical issues and hosts symposia, workshops, and public forums on related topics, and publishes the *Tufts CSDD Impact Report*, a bi-monthly newsletter providing analysis and insight into critical drug development issues.

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