Tufts Center for the Study of Drug Development

OUTLOOK 2008

R&D EFFICIENCY

REGULATORY ENVIRONMENT

BIOTECHNOLOGY TRENDS

PRESCRIPTION DRUG POLICY

DRUG DEVELOPMENT MANAGEMENT TRENDS

CONTACT THE TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

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Tufts CSDD Outlook, *published each January, highlights near-term pharmaceutical and biopharmaceutical drug development trends. Data and analyses contained in* Tufts CSDD Outlook 2008 *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 2008

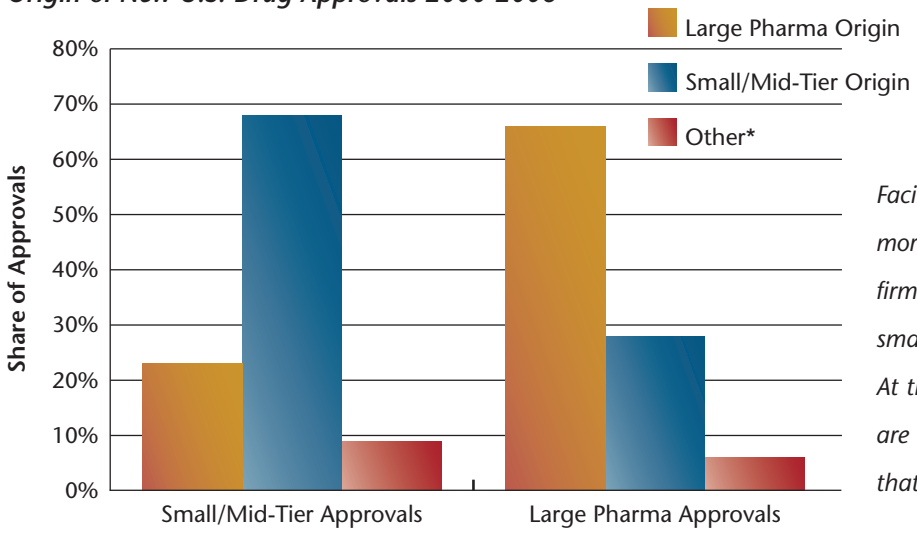
Managing contradictory forces of change is the order of the day for drug developers. For example, whereas globalization makes China an attractive place to conduct less expensive clinical studies, time-consuming negotiations with local agencies and industry can offset out-of-pocket savings. Controlling, and even reducing, the cost of development remains an important goal for the research-based industry, but finding treatment-naïve patients for clinical studies has become a major bottleneck in the drug development process. Greater regulatory emphasis on safety is a laudable objective that benefits everyone, including developers, but it often means that companies must divert resources from innovative development projects, impinging on opportunities for future growth.

Drug developers are responding to these challenges by establishing new collaborations with other companies, academic institutions, and government agencies, such as the National Institutes of Health. Their near- and medium-term ability to thrive will flow largely from their ability to evolve their management and information systems to improve access to new development platforms and tools, reducing development time and cost. In the longer term, the most successful developers will be those who radically change their entire approach to business—from R&D to project management, manufacturing, and marketing.

Some ask if this is doable. Given that the pharmaceutical industry essentially has not changed its R&D paradigm in more than four decades, while nearly every other global industry has undergone major change within the last decade, the better question might be: Do they have a choice?

Big and small/mid tier pharma rely on each other for growth

Origin of New U.S. Drug Approvals 2000-2006



** Includes government, academic centers, non-government organizations, non-profit groups, and hospitals*

Source: Tufts Center for the Study of Drug Development analysis

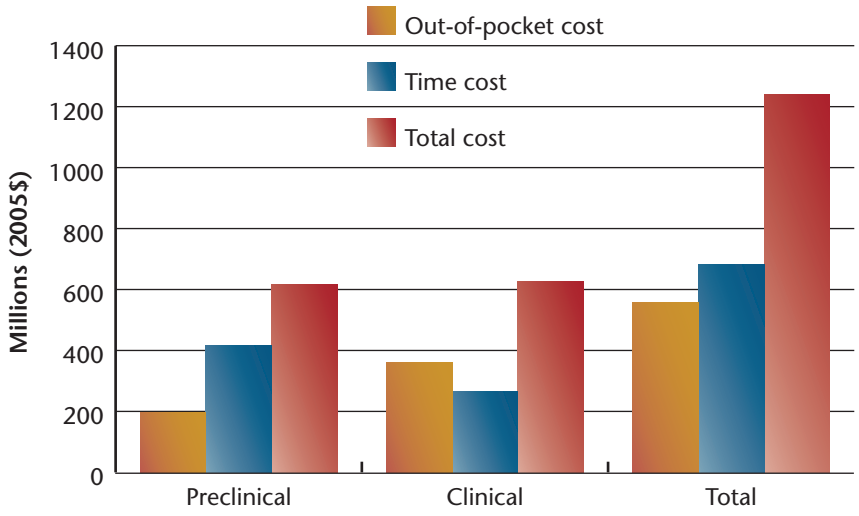
Facing growing pressure from investors to bring more new drugs to market, large pharmaceutical firms are looking to increase R&D partnerships with small/mid-sized pharma and biotech companies. At the same time, small/mid-tier drug developers are looking to large pharma for new molecules that they are well suited to develop.

R&D EFFICIENCY

Ever increasing R&D costs coupled with the looming loss of patent protection on blockbuster products and growing demand for more safety and comparative efficacy information will lead pharmaceutical and biotechnology companies to re-align their business model.

Cost to develop a new biopharmaceutical surpasses $1 billion

Pre-approval R&D Costs per Approved New Biopharmaceutical



Source: DiMasi and Grabowski, Managerial and Dec Econ 2007;28(4-5):469-479

Total biopharmaceutical R&D costs include the cost of molecules that fail in testing and the time cost of investing in development years before any potential returns can be earned. Time costs account for more than half of the total cost per approved new biopharmaceutical of $1.2 billion for recombinant proteins and monoclonal antibodies that entered the clinical testing pipeline from 1990 to 2003.

- Companies will continue to increase their investments in the development of personalized drugs and biologics. This will lead to an increased focus on diagnostic companies as potential partners and take-over targets.
- To speed development of new therapies and decrease development costs, drug developers will seek closer alliances with academic and NIH scientists to validate new biomarkers and leverage new technologies for identifying and testing new drug candidates.
- To improve the efficiency of the drug development process, developers will increase their use of information technology in clinical trials as well as in patient recruitment and retention.
- To optimize their development portfolios and fill pipeline shortfalls, drug companies will continue to rely on a combination of internal discovery and development, acquisition of external technologies and drugs, and co-development alliances. In-licensing, acquisitions of smaller companies by larger ones, and strategic alliances between companies will likely increase.

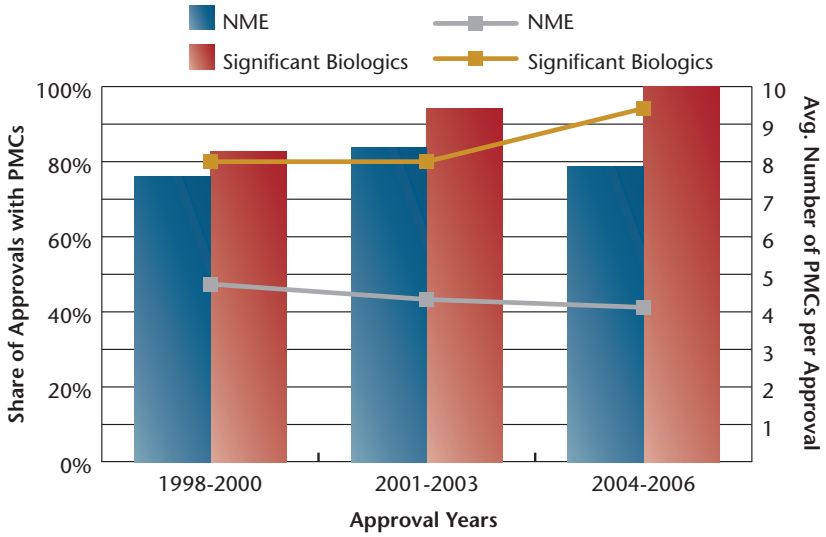
REGULATORY ENVIRONMENT

Closer ties between European and U.S. regulators are expected to improve the development environment in general, while region-specific initiatives should help developers bring new medicines to market faster.

- The European Medicines Agency (EMEA) and FDA will continue efforts to harmonize regulatory approaches in areas of common interest, such as pandemic vaccines, medicines for children, rare diseases, and cancer, but they also will have to ascertain why the pilot program for joint scientific advice failed to attract industry participation.
- Pharmacogenomics (PGx) will become an even more active focus of interest and cooperation for the FDA and EMEA because of recent scientific revelations that the medical utility of genetic information may be more complicated than previously thought.
- The European Commission will devote attention to bringing consistency and continuity among its member states on several problematic regulatory initiatives — implementation of the EU clinical trials directive, reviews of proposed pediatric studies by ethics committees, and electronic data management.
- The FDA will be challenged to implement the *FDA Amendments Act of 2007* in the wake of large staff turnovers, a new administration, and a vigilant and concerned public and Congress.
- Despite resource constraints, the FDA during the coming year will continue to address a number of issues demanding further regulatory action, such as counterfeit drugs, personalized medicines, adaptive clinical trials, and nanotechnology.

Postmarketing studies are expected to streamline the approval process

Approvals with Commitments to Conduct Postmarketing Studies (PMCs)



Source: Tufts Center for the Study of Drug Development

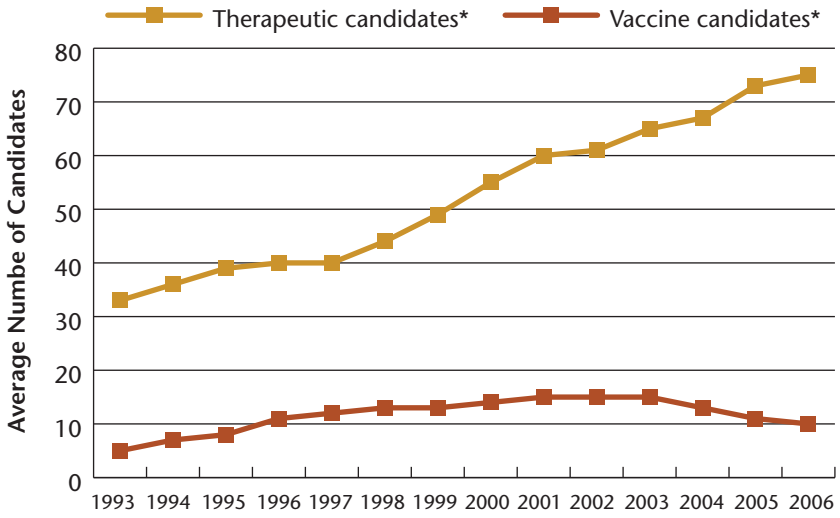
Under the FDA Amendments Act of 2007, *which granted the FDA authority to require postmarketing studies, those studies will now have to be conducted throughout the life cycle of many products. Intended to create a more efficient and effective evaluation process, the new regulations alleviate the burden on drug developers and FDA to determine everything that might need to be known about a drug before it even enters the marketplace.*

Biotech companies will continue to occupy a central role in the development of cancer therapeutics, and their success will be tied to their ability to obtain approval for new therapies.

- Cancer therapeutics will increasingly become important drivers for success by biotechnology companies. A key driving force for the overall rise in the number of candidates has been the entry of new biotech firms into the cancer drug development arena.
- Approval success of biotech cancer drug candidates will help determine the future independence of the firms.
- Interest in commercial cancer vaccine development will wane in the short term as targeted cancer therapeutics, such as protein kinase inhibitors and monoclonal antibodies, reach the market in larger numbers.
- The long-term outlook will brighten if predictive biomarkers and preclinical models are developed, and the FDA and industry work together to establish a defined path to regulatory approval.
- The number of therapeutic monoclonal antibody (mAb) and antibody fragments entering clinical study will rise as additional resources of the pharmaceutical industry are dedicated to their development.

More cancer therapies and vaccines in R&D, but the jury is out on approvals

New Cancer Therapeutics and Vaccines Entering Clinical Study, 1993-2006



** 4-year moving average*

Source: Tufts Center for the Study of Drug Development

While the average number of cancer therapeutics entering clinical study more than doubled during 1993-06, overall U.S. clinical success rate was only 8% for all candidates, 10% for small molecule drugs, 9% for monoclonal antibodies (mAbs) of all types, and 14% for humanized mAbs.

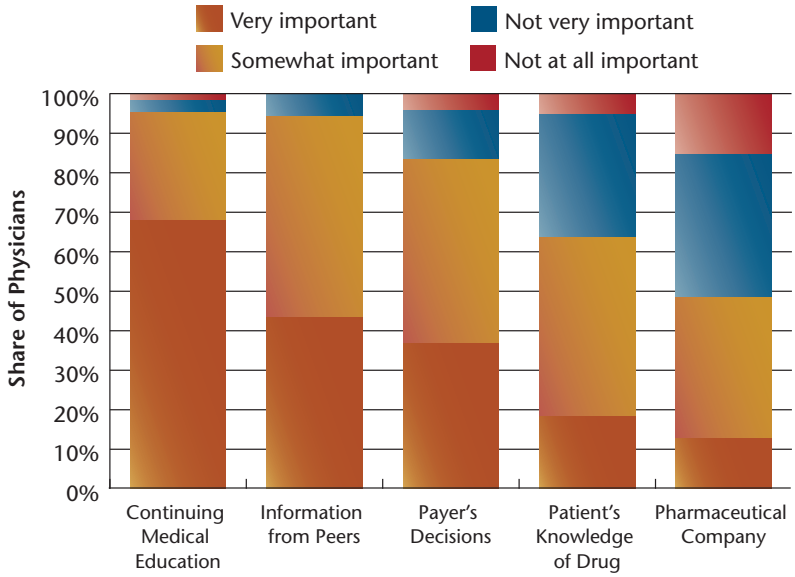
PRESCRIPTION DRUG POLICY

In continued efforts to restrain prescription drug spending without resorting to price controls, private and public sector payers will increasingly rely on comparative effectiveness research to determine prescription drug reimbursement.

- U.S. policy makers will increasingly look to postmarketing studies that assess comparative clinical- and cost-effectiveness to make decisions on prescribing guidelines and drug reimbursement.
- Comparative effectiveness research, an offshoot of evidence-based medicine, will help evaluate different drugs, usually from the same therapeutic class, in terms of comparative risks, benefits, and costs.
- Drugs with better risk/benefit or cost/benefit profiles will garner market share and more favorable reimbursement at the expense of medications with inferior profiles.
- Federal and state governments will likely set the comparative effectiveness research agenda, as it constitutes the most politically palatable way to contain prescription drug spending. For example, the *Medicare Prescription Drug, Improvement and Modernization Act* has earmarked tens of millions of dollars for comparative effectiveness research.
- One hypothetical outcome of the push for comparative effectiveness evaluations would be to change standards for new drug approvals to require comparative trials, although this is unlikely to happen in the near term.

Payer's influence gains as those of patients and drug companies wanes

Factors Influencing Prescribing Decisions in the U.S. in 2007



Source: Tufts Center for the Study of Drug Development

Payers are increasingly influencing physicians' prescribing decisions regarding newly approved drugs, while the role of patients and pharmaceutical firms is waning. Payers are influencing prescribing decisions directly through the use of formularies, and indirectly by funding more than 60% of continuing medical education activities based on evidence-based medicine.

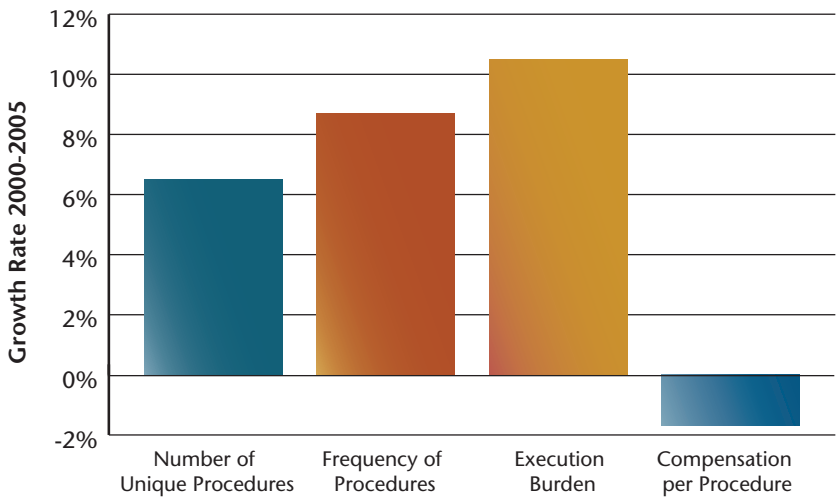
DRUG DEVELOPMENT MANAGEMENT TRENDS

Under growing pressure to reduce R&D costs while accelerating development timelines, sponsor companies will seek new ways to improve their collaborations with CROs and investigative sites.

- Drug sponsors will employ new site selection and management practices and electronic clinical trial technology solutions to improve study conduct inefficiencies. The mandate is clear: while global clinical grant spending exceeded $8 billion in 2007, half of all investigative sites under-perform or fail to enroll patients into clinical trials.
- Within three years, up to 65% of FDA-regulated clinical trials for the top pharmaceutical companies will be conducted outside the U.S., up from 43% today, due to economic advantages and ready access to large numbers of treatment-naïve patients.
- Sponsors will focus more attention on simplifying and streamlining study protocols to reduce study conduct delays and improve investigative site adherence and performance.
- Demand for contract research organization (CRO) services will likely grow by 16% annually over the next three years as sponsors seek assistance in managing large, complex global projects without increasing their internal headcount.

More difficult protocols and lower compensation could inhibit study efficiency

Investigative Site Protocol Design Changes



Source: Tufts Center for the Study of Drug Development

The burden on investigative site personnel to execute study protocols increased 10.5% annually between 2000 and 2005 as the number and frequency of procedures per protocol increased. During this same period, site compensation per procedure declined by nearly 2% in nominal dollars.

AGENDA 2008

TUFTS CSDD EDUCATIONAL PROGRAMS

FEBRUARY 4-8
Boston

Postgraduate Course in Clinical Pharmacology, Drug Development, and Regulation
Tufts CSDD's highly acclaimed, CME-accredited, five-day program—now in its 35th year—provides advanced instruction in practical and technical problem solving in the areas of *clinical pharmacology, drug development & clinical trial strategies, biopharmaceutical development, drug safety, and new drug regulation.* The 2007 program includes several new presentations that will focus on pharmacokinetics & phase I strategies, biostatistics, and the incorporation of marketing concerns in drug development design. The course also offers two unique and highly interactive breakout groups to assist participants in fully understanding the drug development process and how to manage specific marketing challenges. Breakout group discussions focus on clinical trial design and managing postmarketing surprises.

FEBRUARY 28
Boston

R&D Senior Management Roundtable I: Strategic Outsourcing & Global Drug Development
New in 2008, this program brings together senior R&D pharmaceutical industry executives to discuss common R&D issues, and new approaches that will guide the research-based industry to future success. *Read more on Inside Back Cover.*

MAY 1
Boston

R&D Senior Management Roundtable II: Change & Opportunity in the Phase I Landscape
See Inside Back Cover for details.

SEPTEMBER 11
Boston

R&D Senior Management Roundtable III: Optimizing Protocol Design — Strategies to Improve Clinical Research Performance
See Inside Back Cover for details.

OCTOBER 13-15
Boston

Leadership for Drug Development Teams: Improving Cross-Functional R&D Performance
This hands-on learning program is designed in collaboration with R&D leaders from every segment of the industry. The curriculum is based on specific challenges that hundreds of team leaders, program managers, and functional directors have described in real-life cases. The program focuses on critical skills participants need to meet their goals. Two-thirds of the course is devoted to hands-on casework, and one-third to interactive discussions with the faculty. Attendance is limited to thirty-five.

NOVEMBER 6
Boston

R&D Senior Management Roundtable IV: Leveraging Metrics & Market Factors for Portfolio Decision Making
See Inside Back Cover for details.

LOOKING AHEAD...
FEB. 2-6, 2009
Boston

36th Annual Postgraduate Course in Clinical Pharmacology, Drug Development, and Regulation
See description above.

For more information about these programs, call the Tufts Center for the Study of Drug Development at 617-636-2170, email us at ***csdd@tufts.edu****, or click on the Tufts CSDD Institute for Professional Development link at* ***http://csdd.tufts.edu****.*

AGENDA 2008

TUFTS CSDD RESEARCH PROJECTS DUE FOR COMPLETION

Trends in New Drug Clinical Approval Success Rates	Analysis of regulatory approval success rates and phase attrition rates for mid to large company investigational drugs.
R&D Performance and Best Practices of Fastest Drug Developers	Updated assessment of companies with fastest drug development times and analysis of factors that drive development speed.
Immunological Monoclonal Antibodies in Development	Analysis of clinical success rates and development times for immunological monoclonal antibody candidates in the pharmaceutical and biotechnology industry's pipeline.
Clinical Outsourcing and R&D Efficiency	Analysis of contract clinical service usage practices and their impact on development capacity and performance.
Operating Models and Pharmaceutical R&D	Assessment of how large and small/mid-tier company operating models drive commercial and R&D growth and innovation.
Output of Small/ Mid-Tier Pharma and Large Pharma	Critical analysis of recent product approvals by small/mid-tier pharma and comparison with products from large pharma.
Post-Approval Research in Europe, Japan, and the US	Comparative analysis of post-approval study requirements for EMEA, MHLW, and FDA, and their impact on product sponsors.
EMEA and FDA Timelines — A Comparative Analysis	Examination of EMEA's Centralized Procedure and a comparative analysis of product approvals by both the EMEA and the FDA.
FDA's Critical Path Initiative Update	Assessment of progress of FDA's Critical Path, in terms of the number and nature of projects, who is conducting them, resource allocation, and outcomes.
China's Biotechnology Industry	Evaluation of the therapeutics pipelines of small and medium sized biotechnology companies in China.
Microdosing and Development Strategy	Assessment of therapeutic area, cost, time, uptake, outsourcing, and other factors affecting the use of microdosing studies in clinical development.

AGENDA 2008

TUFTS CSDD RESEARCH PROJECTS DUE FOR COMPLETION

Biopharmaceutical Innovation and Diffusion	Empirical analyses based on data collected from physicians and payers to assess the factors that determine biopharmaceutical innovation and diffusion.
R&D Innovation in Less Developed Countries	Identification, categorization, and analysis of biopharmaceutical R&D activities and partnering programs worldwide.
Bioterror and Pandemic Countermeasures	Identification, categorization, and analysis of R&D projects focused on bioterror and pandemic countermeasures.
Safety Issues as They Relate to First-in-Class and Follow-on Compounds	Comparison of safety issues (e.g., FDA black box warnings) pertaining to first-in-class and follow-on drugs on the WHO Essential Drug List.
Entry Rates for Follow-on Drug Approvals	Updated analysis of the speed with which competitors in a drug class enter the marketplace and the timing of their development relative to that of the first-in-class drug.
Formulary Decision-Making Process	Empirical analysis of Medicare payer decision-making process underlying formulary determinations (i.e., coverage) of drugs considered "medically necessary" by United States Pharmacopeia.
Biopharmaceutical Company Mergers and Acquisitions	Assessment of the impact of company mergers and acquisitions on development time and cost and R&D productivity.
Drug Reimbursement Decisions	Analysis of the role of budget impact as an emerging factor in drug reimbursement decisions regarding 20 high-impact prescription drugs in the U.S. and Europe.
Investigative Site Landscape	Expanded analysis of factors driving sponsor-site relationship effectiveness and efficiency.
Protocol Design Complexity and Patient Recruitment	Assessment of protocol design complexity and its impact on patient recruitment and retention effectiveness.
The Changing Phase I Environment	Comprehensive analysis of trends, practices, and external forces redefining Phase I objectives and activities.

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.
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 *Orphan Drug Act of 1983*.
1984	Develops first comparison of the rate of drug safety withdrawals in the U.S. and abroad.
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: it now costs $231 million to develop a new drug.
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.
1996-97	Provides data and public testimony at Congressional hearings that led to passage of the *FDA Modernization Act of 1997* (FDAMA).
1997	Completes comprehensive analysis of FDA/sponsor meetings, showing that meetings reduce the time of new drug development.
1999	Publishes analysis showing impact of the *Prescription Drug User Fee Act of 1992* (PDUFA).
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 (EMEA) and the U.S. FDA.
2001	Updates its ongoing analysis of average cost of pharmaceutical R&D. It now costs $802 million to develop a new drug and bring it to market.
2003	Provides first assessment of the impact of FDA's new fast track program on total development times.
2004	Completes analysis on the economics of follow-on drug development and incremental innovation.
2005	Provides quantitative evidence demonstrating the lack of correlation between drug safety withdrawals and speed of regulatory approval.
2006	Publishes first comprehensive estimate of the average cost of developing a new biotechnology product, and pegs it at $1.2 billion.
2007	Publishes extensive analyses on oncology drug R&D. Overall approval success rate is 8%.
2007	Provides comprehensive analysis of gender, ethnic, and racial disparities among clinical investigators.

GLOSSARY OF TERMS

Adaptive clinical trials — A process for improving the efficiency of clinical trials based on interim analyses of clinical data, which allow for mid-course corrections for trials that are off target.

Biomarker — A characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention.

Blockbuster drug — A drug or biologic that generates at least $1 billion of revenue annually.

Comparative effectiveness — Derived from evidence-based medicine, it entails the evaluation of different drugs, usually from the same therapeutic class, in terms of comparative risks, benefits, and costs.

CRO — Contract Research Organization. An organization that manages various steps in the drug development process, including conduct of preclinical studies, clinical study design and execution, data management, analysis, medical writing, and regulatory submission.

EMEA — European Agency for the Evaluation of Medical Products (recently renamed the European Medicines Agency). A decentralized body of the European Union, based in London, charged with protecting and promoting public and animal health, through the evaluation and supervision of medicines for human and veterinary use. A regulatory agency analogous to the U.S. Food and Drug Administration (FDA).

Monoclonal antibody (mAb) types — Murine mAbs are derived from mouse genes; human mAbs are derived from human genes; chimeric and humanized mAbs are each derived from varying amounts of mouse and human genes, with the humanized products containing more human protein sequence than the chimeric versions.

Pharmacogenomics — The study of the interaction of an individual's genetic makeup and response to a drug.

Post-approval research — Studies conducted on a drug after it has been approved for marketing to improve the prescribing, use, quality, or manufacture of the product or to provide further assessment of safety and effectiveness.

Recombinant protein (rDNA) — Protein produced through the combination of DNA fragments from different sources.

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.

NEW IN 2008!

R&D SENIOR MANAGEMENT ROUNDTABLE SERIES

A program of four, highly interactive one-day roundtable discussions for senior R&D executives, hosted by the Tufts Center for the Study of Drug Development.

ROUNDTABLE I:
Feb. 28, 2008

STRATEGIC OUTSOURCING AND GLOBAL DRUG DEVELOPMENT

Rising R&D costs and competitive pressures are driving research-based pharmaceutical and biotechnology companies to implement new strategies to improve R&D efficiency and boost output. Strategic outsourcing and global drug development programs are two approaches that firms are embracing to enhance performance. This roundtable will explore how companies are using outsourcing and global drug development strategies to improve R&D efficiency and productivity.

ROUNDTABLE II:
May 1, 2008

CHANGE AND OPPORTUNITY IN THE PHASE I LANDSCAPE

The Phase I drug development environment is growing rapidly in response to new global regulations and new programs that research-based pharmaceutical and biotechnology companies are implementing to gather more safety data. The market for Phase I outsourcing is also changing due to sponsor capacity needs. This roundtable will examine the factors driving change in the Phase I environment and explore implications for R&D and outsourcing management strategy.

ROUNDTABLE III:
Sept. 11, 2008

OPTIMIZING PROTOCOL DESIGN — STRATEGIES TO IMPROVE CLINICAL RESEARCH PERFORMANCE

During the past decade, protocol designs have become more demanding and complex, resulting in longer clinical trial cycle times, heavier investigative site work burden, and lower patient enrollment and retention rates. This roundtable will explore how protocol designs vary by therapeutic area, their impact on clinical trial efficiency, and new strategies that research-based pharmaceutical and biotechnology companies can pursue to optimize clinical research performance.

ROUNDTABLE IV:
Nov. 6, 2008

LEVERAGING METRICS AND MARKET FACTORS FOR PORTFOLIO DECISION MAKING

Development metrics and market factors currently favor biopharmaceutical R&D over small molecules. This roundtable will discuss how to leverage metrics and market factors to inform portfolio diversification decisions, taking into account compatibility with core therapeutic areas, the increasing postmarketing study requirements for biopharmaceuticals, and the relative cost and availability of acquisition, in-licensing, and partnering options.

All roundtables will be held 10 a.m. – 3 p.m. at the Tufts Center for the Study of Drug Development, 75 Kneeland St., Suite 1100, Boston, Massachusetts.

For more information, call Charlene Neu at 617-636-2187, or email **charlene.neu@tufts.edu.**

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