

# PRESCRIPTION FOR PROGRESS

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## THE CRITICAL PATH TO DRUG DEVELOPMENT

A WORKING PAPER OF THE  
21ST CENTURY FDA TASK FORCE

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## EXECUTIVE SUMMARY

The biopharmaceutical industry can bring new medicines to market in a faster, safer, and less expensive way than current government and industry policy allows. Recognizing this reality, the U.S. Food and Drug Administration (FDA) has taken a dramatic step to streamline drug development by incorporating new technologies. The FDA's Critical Path Initiative, announced in March 2004, has recommended evaluation of new ways to use genetic tools, faster computers, new imaging techniques, and electronic medical records in the drug evaluation process.<sup>1</sup> This ongoing project, while still in its infancy, holds the potential to break down barriers between regulators and industry and to expedite the often complicated journeys of lifesaving medical innovations from researchers to regulators to patients.<sup>2</sup>

In support of the Critical Path Initiative, the Center for Medical Progress at the Manhattan Institute convened 25 experts from industry, government, and the scientific community in a task force on the 21st century FDA. In spirited and wide-ranging discussions, participants considered how advances in genomics and other disciplines might be used to optimize the drug approval process. This working paper distills the problems, principles, and proposals that surfaced during that dialogue.

In our discussions, a general consensus emerged that FDA, scientific researchers, and pharmaceutical companies can collaborate to:

- Integrate biomarker validation into every stage of the regulatory review for drug, diagnostic, and biologic applications.
- Improve clinical trials by creating one standard for collecting and using data from electronic medical records.
- Utilize validated biomarker-based studies to assess the safety and effectiveness of specific drugs for specific subpopulations at specific doses.
- Articulate the importance of congressional appropriations sufficient to implement the FDA's Critical Path activities, as well as providing the \$5.9 million earmarked for Critical Path purposes in the FDA's 2007 budget proposed by President George W. Bush.

This working paper is intended not as the final word on the Critical Path but as a springboard to continuing discussion and debate. Although this paper focuses on drug development, participants in the task force's discussions recognize that the FDA has vital responsibilities in other areas, such as bioterrorism and food safety. Nevertheless, the authors of this report believe that the Critical Path Initiative should be a priority within the FDA and within government. By steering us toward a drug approval process that is driven more by science and restricted less by regulation—by unleashing the powers of American enterprise and pathbreaking science—the Critical Path Initiative can improve health and save lives.



## THE CRITICAL PATH TO PERSONALIZED MEDICINE

The biopharmaceutical industry has the means to bring revolutionary new medicines to market faster, more safely, and less expensively than current industry or government policy allows. Yet the FDA, drug developers, and scientific researchers have only begun to evaluate the new technologies that may optimize testing-and-approval of new drugs.

We are living in a period of enormous innovation in the biological sciences. New fields like genomics, proteomics, and other “-omics” sciences are being linked to powerful new computers and statistical modeling that allow researchers an unprecedented view into the inner workings of human biology.<sup>3</sup>

Biopharmaceutical companies have embraced this knowledge and are rushing to translate new discoveries into powerful, safer, and more effective therapies that can treat diseases based on their underlying genetic roots, hastening the day when patients will, as a matter of course, receive individualized or targeted drug therapies.

The scientific challenges facing the development of personalized medicine are considerable. The current system of drug development and approval is outdated, inefficient, and expensive. It often uses technological standards developed in the 1960s to evaluate drug candidates identified using the latest advances in basic science. Under the FDA’s current framework, the development of personalized therapies remains more expensive and less efficient than it could be, slowing the translation of new knowledge into new treatments.

The current regulatory and industry approach is focused on ensuring that every product is safe and effective for the general population. At a presentation on drug safety convened at the Institute of Medicine, senior FDA staffers remarked that current drug development technologies are “largely empirical in nature” and that “this tradition focuses on population means and observations of outliers” that result

in “trial and error” clinical medicine.<sup>4</sup>

The FDA and its stakeholders recognize that this approach makes failure likely for products that otherwise might be safe and effective for specific subpopulations or individuals. The challenge facing industry and regulators is to develop valid standards for identifying these “high responders” at earlier stages in the drug development process. The goal is to speed development of important new drugs to market and ensure that people receive the medicines that are best for them.

To its great credit, the FDA is taking a dramatic step to catalyze the use of new technologies to focus and streamline drug development. The FDA’s Critical Path Initiative, announced in March 2004, aims to use genetic tools, faster computers, new imaging techniques, and electronic medical records in the drug evaluation process.<sup>5</sup> This report breaks new ground by bringing together the analyses and ideas of experts and stakeholders to identify serious challenges to the Critical Path and to suggest solutions for those challenges.

Many task-force participants believe that the media creates a false dichotomy between “bad” drugs (which reach the market, but shouldn’t have) and “good” drugs (which are, at least in the public’s mind, “safe”). In truth, “bad” drugs with unacceptable safety profiles are usually weeded out by the development process before they reach market. It is true, however, that the development process focuses on a new drug’s broad-based safety and efficacy profile. Consequently, drugs that have bad effects on small subsets of patients may slip through these screens.

In fact, physicians need better knowledge about how to use medicines safely and effectively in individuals and subpopulations. Some drugs, such as Vioxx, may cause problems for a small subset of people. Others drugs, such as thalidomide, may be

intolerable for broad populations but useful in sub-populations; thalidomide has been widely used to treat certain cancers. Instead of taking “bad” drugs off the market, or plastering them with interminable warning labels, regulators and industry should work together to develop personalized medicines that can better ensure that people who can safely benefit from these drugs get them and that those who are at risk avoid them.

The hope is that scientific advances will eventually enable pharmaceutical companies to use genomic screening techniques linked to biomarkers early in the drug development process to identify drugs likely to cause serious side effects in a substantial number of people.<sup>6</sup> FDA and industry can facilitate this goal by working together to create standards for biomarker validation that can be used in clinical testing to screen for rare, but unavoidable, side effects such as liver, kidney, and heart damage. This technology is not currently available, although these side effects are often the reason that medicines do not reach the market or are withdrawn from the market. A more targeted approach to drug development and evaluation would make medicines more effective and safer. The first step is to find and validate likely biomarkers.

Biomarkers are measures of disease progression, pharmacology, or safety that can identify unique disease mechanisms or responses to medicines. FDA guidelines can specify how biomarker-based tools and alternative drug evaluation techniques can be used for drugs, biologics, and diagnostics as well as a combination of medicines and tests.

Because of advances in our understanding of how genetic variations shape response to medicines and disease, researchers have reason to hope that biomarkers can become an important new tool for the personalization of medicine. But validating these biomarkers will require an unprecedented degree of collaboration and cooperation among many stakeholders in the biopharmaceutical community.

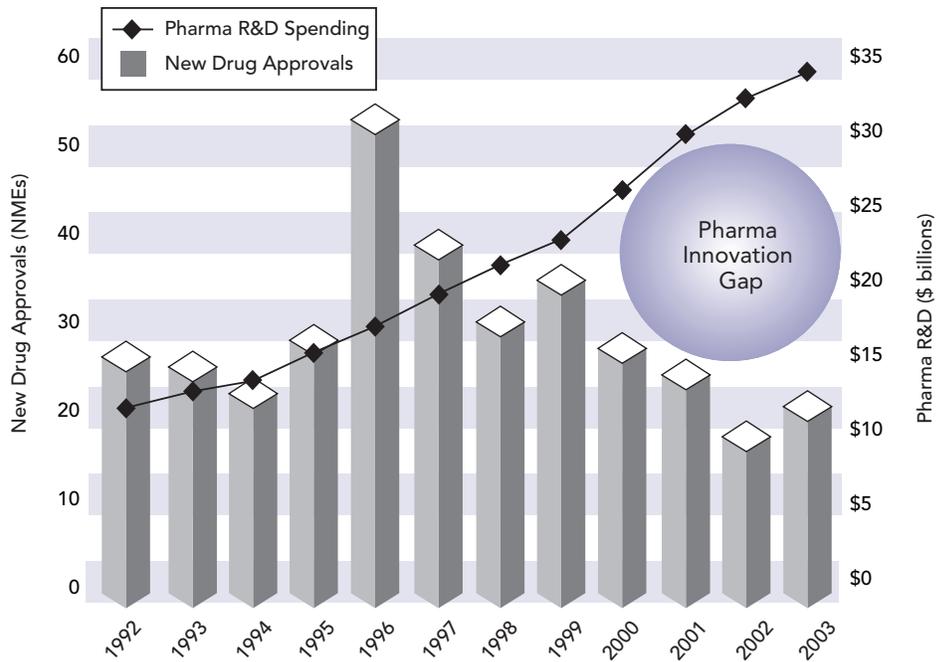
How can the FDA, working with industry and other partners, best promote and advance personalized medicine? That is the vital question confronting policymakers, industry leaders, the scientific community, and the FDA itself.

### PUBLIC HEALTH AND THE CRITICAL PATH

The drive to streamline the drug development and approval process through biomarkers, better animal models, improved surrogate end points, and innovative clinical trial designs has important public health implications, especially for the development of new vaccines and antibiotics.<sup>9</sup> The markets for these drugs are often smaller and much less reliable sources of industry revenue than for chronic ailments like heart disease and cancer. As a result, lengthy and expensive regulatory requirements can act as powerful disincentives for companies to invest in research for these vital public health tools.

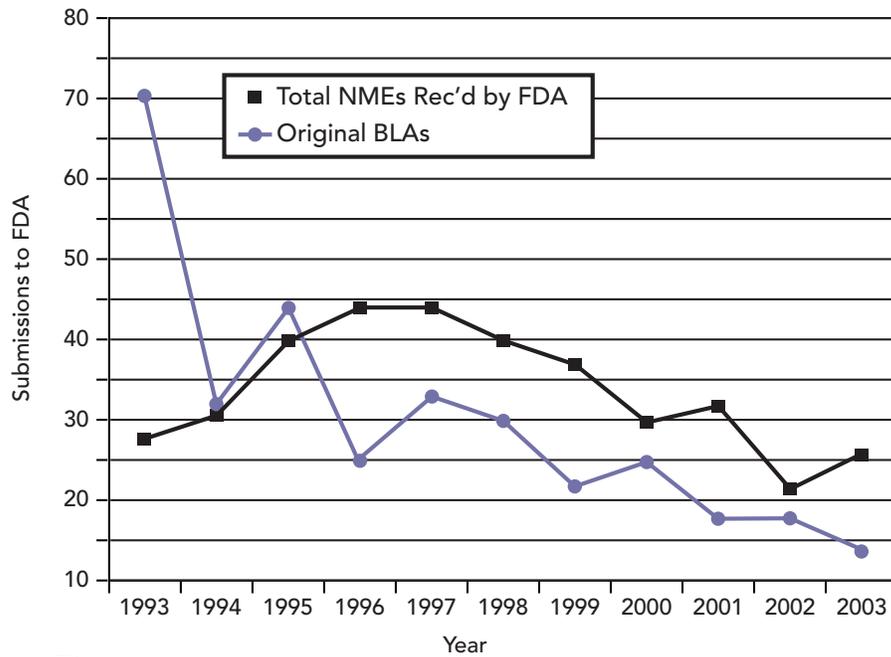
Public health officials actively discourage physicians from prescribing new antibiotics, hoping to delay the evolution of drug-resistant pathogens. This practice may be prudent medically, but it has the side effect of reducing industry revenue for investing in the next generation of antibiotics. Vaccines, on the other hand, can be subject to government price controls<sup>10</sup> and are administered to targeted populations at infrequent intervals. As a result, the annual U.S. sales for a single statin drug, Lipitor, are greater than those of the entire global vaccine industry. Since companies view these products as financially unattractive, the pipeline for new vaccines<sup>11</sup> and antibiotics<sup>12</sup> to combat resistant pathogens, emerging diseases, and potential bioterror attacks has grown worryingly thin. Streamlining the drug development process and lowering development costs should spur additional research into these product areas.

### Innovation Gap



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### 10-Year Trends in Major Drug and Biological Product Submissions to FDA



Source: FDA

### SHORTCOMINGS OF THE CURRENT DRUG DEVELOPMENT AND APPROVAL PROCESS

In the last decade, U.S. pharmaceutical research and development expenditures have risen 250 percent, and from 1999 to 2003 the National Institutes of Health (NIH) budget for biomedical research doubled, from approximately \$13 billion to over \$27 billion.<sup>7</sup> Although these expenditures have led to many advances in basic biomedical science, the number of new drug and biologic applications per year submitted for FDA approval over this period has declined.

The Tufts Center for the Study of Drug Development estimates that the industry must spend \$800 million to \$1.7 billion and 12 to 15 years of research and development on average to bring a product to market.<sup>8</sup> These costs must be recouped predominantly during a limited period of patent protection or marketing exclusivity if drug development is to remain financially viable. With such great amounts to recoup in such a limited time, the drug industry is forced to charge increasingly higher prices. Because of rapidly escalating prices for branded prescription medications, national drug policies and price controls are being considered, which would threaten the future of the research-based pharmaceutical industry in the United States. Higher development costs also limit accessibility of medications and discourage development of medications for orphan diseases and diseases that affect primarily low-income populations.

Individual companies have devoted enormous resources to identifying potential biomarkers that

**Bioinformatics** is a branch of clinical research that analyzes biological information using computers and statistical techniques. An ever-growing discipline, it includes analyzing data from drug studies, evaluating and mining clinical data of patients in the real world, collecting and storing genetic material, and combing patient health records to develop predictive models of health care.

would help streamline the development and approval process. To date, however, critical improvements have proved elusive. Many biomarkers have been discovered, but the task of validating them is laborious, and many do not prove reliable in the validation process. For instance, there is still no biomarker to predict hepatic injury (liver damage), nor is there a good animal model available. Achieving even one of these goals would represent a major breakthrough.

The FDA has concluded an analysis of the causes for the delays in drug development and has called for collaborative research to develop and validate new tools and methods for testing new medicines. The FDA is confident that this research and the resulting new tools will enable more rapid and informative drug development, such as occurred for AIDS drugs in the 1980s and 1990s. In response to the AIDS crisis, the FDA worked closely with the pharmaceutical industry to develop innovative methods for the rapid development of new drugs for AIDS and HIV,<sup>13</sup> resulting in development times as short as two years for these drugs. During the same period, the average development time for all drugs slowed to less than twelve years. This experience clearly demonstrates that it is feasible to accelerate drug development without taking unnecessary and dangerous shortcuts.

It is clear that FDA leadership is committed to the Critical Path Initiative. It is increasing the number of training sessions for reviewers on new statistical and drug study methods. The Interdisciplinary Pharmacogenomics Review Group (IPRG) advises and educates reviewers on how drug evaluation can utilize pharmacogenomics (the study of how variations in the human genome affect the response to medications).

But the agency needs new organizational mechanisms and additional resources to implement the Critical Path Initiative fully and to ensure that drug advisory committees utilize its tools. While the amount of this additional funding should be determined through consultation with the FDA, Congress, and FDA stakeholders, there is a glaring need for additional funding. The FDA is unable to routinely send staff to important collaborative scientific activities in such areas as bioinformatics, biomarker development, nanotechnology, clinical trial design, and imaging. For example, a recent meeting on storing, collecting, and analyzing tissue samples drew scientists and

managers from the National Cancer Institute, the army, CDC, private companies, and academia, but no one from the FDA attended, despite the fact that the agency will be one of the single biggest repositories of genetic samples in the world. Similarly, there is no FDA office responsible for ensuring that companies adopt Critical Path Initiatives.

## PROMOTING COLLABORATION

The FDA's senior management has collaborated with industry, other government agencies, community-based research, and academia to develop new ways to evaluate drugs during and after the development process. The Critical Path process will be most successful, however, when collaboration expands beyond senior management and FDA reviewers are comfortable using validated Critical Path tools. Medical reviewers, for example, within drug divisions could actually begin to use non-frequentist trial designs (such as Bayesian models) or virtual

clinical trials for diseases where small treatment populations make traditional clinical trials extremely time-consuming or expensive. Although the agency is developing guidances that implement new science-based standards, industry can do much more to share the clinical data necessary to validate the standards. Safety biomarkers, for example, have the potential to expedite the creation of new guidances.

Through conferences, consortia, and other means, the Critical Path Initiative has encouraged collaborative efforts in the following areas:

- Testing and development of molecular and imaging biomarkers for regulatory approval and use
- Specific directions for use of biomarkers in clinical trials during drug development (a clear regulatory framework for evaluation)
- Collection and evaluation of genomic and molecular information to develop assays for predicting the toxicity of drugs at given doses and identifying who benefits most from which treatments

## BAYESIAN ANALYSIS

Bayesian analysis is an important statistical tool for confirming that smaller groups of patients are benefiting from new drugs and devices and identifying the connection between how a product works and clinical outcome.

When comparing two hypotheses using the same information, traditional statistical methods would typically result in the rejection or non-rejection of the original hypothesis with a particular degree of confidence, while Bayesian methods would yield statements that one hypothesis was more probable than the other. Rather than assuming that we know nothing prior to conducting an experiment and then conducting an experiment to see if a cause and an effect (drug and clinical outcome) happen so frequently that it is most likely not a matter of chance, Bayesian analysis presumes that we have knowledge about other causes and effects and uses that knowledge to shape the experiment and come up with an estimate of whether the cause and effect are the result of chance. Such estimates and experiments are continually updated in light of new knowledge.

The FDA recognizes that Bayesian computations can be used in combination with these two forms of data. The FDA has used Bayesian statistics to accelerate the approval and improve the safety of coronary stents. Harvard statisticians used Bayesian statistics to analyze seven randomized trials of FDA-approved stents involving 5,806 patients stored at the Harvard Clinical Research Institute (HCRI) to develop an "objective performance criterion" for medical device clinical trial.<sup>15</sup>

- Evaluation of the impact of drugs in the real world through the use of electronic patient records

With input from stakeholders, the FDA is working to clarify standards and guidelines for the application of these new tools in the regulatory process. In that spirit, the FDA and stakeholders can continue to employ statistical measures that identify smaller groups of patients more likely to benefit from a product compared with those less likely to do so.

Such approaches incorporate the sort of confirmatory evidence encouraged and allowed under the FDA Modernization Act of 1997.<sup>14</sup> The act allows drugs to be approved with data from one adequate and well-controlled clinical trial investigation and with confirmatory evidence to establish effectiveness for risk/benefit assessment. Under this model, validated biomarkers will be combined, as reliable data emerge, with existing studies to speed up drug development and narrow the group of patients for whom a medicine works best.

In the past, when the FDA granted “accelerated approval” of a drug, it was based on the results of one or more adequate and well-controlled studies establishing that the drug has an effect on a surrogate end point that is reasonably likely to predict clinical benefit. Thereafter, the FDA requires studies, once the drugs are available, to re-establish clinical benefit. The Critical Path Initiative accelerates approval and, in theory, makes it available to drugs and diagnostics or a combination of the two. Combining a genetic test that identifies who responds best to a drug could become more widespread as collaborative efforts identify benchmarks that can accelerate the development of products targeted to particular populations.

### *Recommendations for Promoting Collaboration*

- A new cross-centers products task force can, in collaboration with relevant review communities within the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), and the Center for Drug Evaluation and Research (CDER), review the agenda of advisory committees for biomarker-based diagnostics, biologics, and drugs.
- The Interdisciplinary Pharmacogenomics Review Group can develop guidelines for the use of biomarkers in combination with small and adaptive trial designs. It should develop specific training,

## GENOMICS AND POSTMARKET DRUG SAFETY

The fast moving field of genomics can also impact drugs on the market now, which may not have benefited from the use of validated biomarkers during their development and regulatory approval. Novel DNA markers may provide an important contribution to postmarket drug safety by helping to quantify an individual’s risk of suffering an adverse events from the use of currently approved medications. Yet research into this field also raises questions on how to apply genomic pharmacosurveillance data to drug labeling. It also raises questions about how to best coordinate the roles of the pharmaceutical industry, the research community, and insurance providers in dealing with novel diagnostic tests that may be developed post approval for marketed drugs.

recruitment, and reorganization goals to be funded through the Prescription Drug User Fee Act (PDUFA) budget increases.

- Standards can be set for small and adaptive trial design and promoted throughout the divisions to replace, where appropriate, Phase 3 pivotal trials.
- The agency can separately build upon the exploratory IND (investigational new drug) guidelines and work with consortia, such as the Critical Path Institute’s biomarker safety consortium, to improve and increase computerized simulations of drugs to complement Phase 1 human testing. Consistent with the rationale of the exploratory IND, the FDA can collaborate to develop guidelines for the use of these computerized models. An organization such as the Critical Path Institute could sponsor meetings to help the FDA develop methods for doing so. Such a program would allow reviewers to work

more closely with their scientific peers outside the agency.

- To encourage familiarity with Critical Path tools throughout the FDA's rank and file, FDA senior leadership can make knowledge of the Critical Path an integral part of performance and incentive reviews. Without this performance review, there may be wide variance in the use of Critical Path tools among different product reviewers, even within the same center.

## EXPLORATORY INDS AND VALIDATING BIOMARKERS

The FDA and industry share responsibility for developing better tools for clinical evaluation. To that end, early in 2006, the FDA announced a new method for early stage pharmacokinetics (drug metabolism over time) and pharmacodynamics (the effect that the drug is having over time) clinical testing. This new approach, called the exploratory IND, was developed by the Interagency Oncology Task Force (IOTF). An exploratory IND study, sometimes called a "Phase 0 trial," involves "very limited" human exposure to a compound and has no therapeutic or diagnostic intent. The exploratory IND process increases the number of potential drugs that can be tested in micro-doses in small numbers of patients instead of testing pill-size quantities in large clinical trials. While unexpected and serious adverse reactions may still arise, the IND process may allow companies to identify promising drugs—or reject drugs with poor safety or efficacy profiles—before entering into a Phase 1 clinical trial.

As FDA Deputy Commissioner Dr. Woodcock has noted, "The purpose of an exploratory IND [study] is to learn about new discoveries before embarking on extensive human trials.... Thus, we think eventually not only will this lead to new knowledge about many new discoveries, it will save people from being exposed to higher doses of compounds that ultimately turn out not to be useful."<sup>16</sup>

Many companies, in association with the FDA, are seeking to identify and validate potential biomarkers. For example, the FDA and BG Medicine, a Massachusetts-based biotechnology research company, are seeking to validate biomarkers to discern signs of human liver toxicity in the beginning of the drug development process.<sup>18</sup>

**The Critical Path Institute** is a nonprofit organization<sup>17</sup> created in 2005 to support the FDA in its effort to implement the Critical Path Initiative. Based in Tucson, Arizona, the C-Path Institute has been given \$10 million in public and private seed funding for five years. The institute is working with the FDA, drug companies, and other scientific stakeholders to collaborate on a variety of biomarker activities:

- The Cardiovascular Safety Biomarkers Initiative will develop tools for assessing and preventing idiosyncratic adverse cardiac events.
- A QT biomarker initiative aims to assist the FDA in accelerating approval by increasing the likelihood of effective safety screens and risk management programs.
- The Toxicogenomic Biomarkers Initiative will explore ways to incorporate new technology into methodologies for evaluating general toxicity related to the drug development process.

The NIH, CDC, FDA, National Institute of Technology Standards, Department of Energy, companies, and Department of Defense are working independently of one another and are not sharing information with nonprofit centers and companies.

The FDA currently lacks the resources to be a full partner in these important activities. There is not enough staff to be part of all the relevant committees or the meetings and scientific programs within government or the scientific community as a whole.

Absent FDA leadership, the various federal agencies involved in genomic research sometimes find it difficult to work together. For example, the NIH, CDC, FDA, and companies have been meeting about the development of a biomarker for a rare drug side effect

called QT prolongation that causes heart failure.<sup>19</sup>

But the FDA currently lacks the resources to send the relevant medical reviewers to these meetings. In this case, Duke University would like EKG data to identify genetic variations linked to the heart problem. Companies are ready to share EKG data, but the absence of the FDA is stalling progress.<sup>20</sup> Similarly, the FDA's Clinical Pharmacology and Biopharmaceutics office, which is responsible for receiving genomic data, and scientists who review drug and diagnostic applications are unable to fully participate in collaborative efforts to create genomic analysis platforms and to evaluate pharmacogenomic data.

### *Recommendation for Validating Biomarkers*

- The FDA should be given additional funds sufficient to sustain its Critical Path activities, particularly for maintaining a leadership role in biomarker development and use.

## POST-MARKET DRUG EVALUATION

The FDA and the entire biomedical community recognize that prior to marketing, with current tools and technology, there is no way to detect rare, unexpected side effects short of performing studies with sample sizes that exceed tens of thousands of patients. Such massive clinical trials are not practical or sustainable and would bring drug development to a halt. Nor does it make sense to rely on doctors and patients to submit reports of possible problems when information technology permits real time and continuous reporting of such events.

Rather, as the Critical Path report notes, “[S]afety issues should be detected as early as possible, and ways to distinguish potential from actual safety problems should be available. Unfortunately, in part because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing.”<sup>21</sup>

The goal of post-market drug evaluation need not be limited to safety but can also include the ability of doctors and patients to choose medicines and treatments that are best. Further, computerized analysis of clinical data can help pinpoint which patient subgroups will be more likely to benefit from one medicine or avoid side effects from another. In short,

post-market data can be the source of information to develop faster studies that more accurately predict and measure safety and benefits.

To achieve this goal, the FDA, consumers, health plans, and companies must use disease registries, biobanks, and electronic patient records to coordinate medical information that can be used to further personalize medicine (see sidebars). Several agencies are already banking DNA samples using various approaches and standards. The FDA is cooperating with the National Cancer Institute to adopt NCI standards for DNA submissions. Such collaboration is critical to create a common platform for the evaluation of genetic materials and for the establishment of best practices in the future. At present, the FDA's participation in the creation of this important source of post-market information is limited by resource constraints. Congressional approval of the FDA's requested \$4.7 million for drug safety evaluation would facilitate the agency's participation in these collaborative efforts.

Biobanks are “actual repositories of collected human tissue—blood, bone, serum, or sometimes just individuals' DNA. But they become ... valuable because of the clinical ... information captured about the patient and the molecular data generated from the sample. When this data is integrated in a robust, secure fashion—or a clinical genomics environment—researchers can use biobanks for many different purposes, such as hunting for reasons for the underlying genetic processes that cause different diseases or identifying molecular markers that may provide early warning signs.”<sup>23</sup> Larger health plans and hospitals, as well as the Medicare program, are switching to electronic patient records that contain information on many individuals' characteristics, their medical diagnoses, the medicines they took, and how they fared. The health systems of the Mayo Clinic, Kaiser Permanente of Northern California, and several disease-specific patient registries together comprise millions of patients' records with information that can be useful for proactive post-market drug evaluation.

The Mayo Clinic used electronic patient records earlier than many large health systems did. It has a base of 4.4 million electronic records that can generate outcome data using standardized entry criteria. Mayo has a full-scale program for the development of biomarkers in adjusting drug dosing and safety

## DISEASE REGISTRIES, BIOBANKS, AND ELECTRONIC PATIENT RECORDS

Disease registries have become a powerful tool to identify populations of patients most appropriate for a given clinical trial. Disease registries are computerized systems that capture and track key patient information. They are longitudinal, ongoing databases that collect and maintain information on patients with specific diseases. Registries keep track of patients' signs and symptoms, what medications they may be using, various alternative therapies that they may have tried, and such issues as psychosocial aspects of the disease and functional status. All data are collected from physician visits or encounters with the health system.

Each patient's privacy is maintained by coding his or her history. Many registries are simply lists of patients with the disease or disorder, and some provide enough clinical data to provide a "snapshot" of the characteristics of the clinical expression of the disease. Few registries actually provide an up-to-date assessment of the natural history of the disease needed for the design of prospective clinical trials, most likely because of the difficulty in obtaining the required clinical data on an ongoing basis.

One example of a comprehensive approach to patient registries is the C-Path Institute's Orphan Drug Registry, which will create an electronic medical record (EMR) with additional specific modules for each disease. The EMR will automatically be updated from the medical-care providers and include a portal for patients or their families to submit their own data on the course of the disease and how it is being managed. It will identify the standards for accurate diagnosis and characterization of these and other rare diseases. It will also identify a population of patients who are readily available for participation in clinical trials, and it will provide a basis from which to conduct post-market safety surveillance.<sup>22</sup>

profiling. With the help of IBM, Mayo will be able to link its outcomes data to very large external sources of genomic and proteomic data such as the National Cancer Institute. Mayo is also generating its own genomic data by collecting genetic samples and integrating with outcome data. These efforts provide a promising model for the future use of medical records in post-market surveillance.<sup>24</sup>

Use of these data sources—with appropriate safeguards to protect patient privacy and prevent the abuse of medical information—holds great promise for improving drug safety, health outcomes, and the reliability of drug development studies.<sup>25</sup> If a safety problem emerges, it will be more precisely identified in terms of patient characteristics, dosing, and genet-

ic variations. Such information can be used to update and further refine medical treatments to avoid safety problems as well as to maximize benefit.

The next step is to use electronic medical record systems to mine patient data in new ways and to compare outcomes among patients with similar disease characteristics and genomic makeup. Because researchers can look at dozens of patient characteristics and hundreds of treatment steps, observational studies designed to detect individual differences in response to medicine or other treatments can be fairly small but still yield powerful conclusions. Studies have found that carefully designed post-market trials have the same explanatory power as randomized, controlled trials.<sup>26</sup>

The FDA, however, must weigh the need for a complete overhaul of its bioinformatics operation against other pressing agency priorities. For now, it is seeking to create standards that make FDA data easily available to researchers outside the agency and to establish common formats that allow the sharing and pooling of data from registries and electronic medical records systems.

In addition to better data, researchers and the agency must work with other organizations in an open way to develop terminology standards and interoperability standards for use in animal and human studies. The FDA is part of the Clinical Data Interchange Standards Consortium (CDISC) HL7 (standards for electronic interchange of clinical, financial, and administrative information among health-care computer systems) to ensure that FDA bioinformatic activities are consistent with those in the private sector. The National Cancer Bioinformatics Grid, Centers for Medicare and Medicaid Services, FDA, and Centers for Education and Research on Therapeutics (CERTS, a program of the Agency for Health Quality Research in the Department of Health and Human Services) have taken important strides toward data sharing but do not work together on a regular basis.

### *Recommendations for Preclinical and Post-Market Drug Evaluation*

- Create a Center for Clinical Bioinformatics within the FDA and a corresponding Bioinformatics Interagency Task Force. This center could allow stakeholders to create a single standard for collecting and using information from electronic patient records, which would improve medicines and clinical trials. This could include companies, Medicare, health plans, employers, NIH, and CERTS.
- The FDA should become a full participant along with NIH and NCI as part of the NCI's Biospecimen Coordinating Committee and NCI's Wide Repository Committee.
- Companies submitting genomic data should establish specific protocols for the collection, storage, and sharing of tissue samples and serums from which genomic, protein, and metabolic profiles information is generated. One approach that should be considered is the forthcoming NCI best-practice standards. The FDA can require companies

A practical driver for personalized medicine and the study of drug response variation is the realization that extremely rare and catastrophic side effects that require drug withdrawals from the market may be tractable for formal study. The process would include monitoring the epidemiological occurrence of adverse events and correlating the cases with a higher frequency of certain genetic markers, which result from genome screens. The utilization of genomic data for surveillance constitutes a powerful application of personalized medicine, which is now feasible with the advent of array diagnostic technologies. By focusing on both common and rare side effects, the practice of personalized medicine should accept the challenge of drug safety and in the process could relieve some of that burden from the clinical trial process.

to contribute all relevant clinical trial data and biospecimens in standard format by a date set by the agency. The Center for Clinical Bioinformatics can develop partnerships with large health systems such as the Mayo Clinic and integrate its post-market program with larger efforts to mine data for genetic and clinical patterns. If this is implemented, there must be changes in the legal and intellectual property infrastructure to allow the FDA to share data among pharmaceutical companies, and pharmaceutical companies must agree on which data can be shared and which are proprietary.



## ACCELERATING APPROVAL

It is important to let the public know what personalized medicine would look like from the standpoint of the Critical Path Initiative. These new tools could accelerate approval for a wide range of drugs, diagnostics, and devices targeted to specific sub-populations.

Critical Path activities and tools leading to targeted approval of a drug could go through a process such as the following:

- 1 An exploratory and confirmatory phase (up to targeted approval) to determine the safety and effectiveness of a drug for a specific group of patients at a specific dose. This would occur in Phase 2 testing and would include biomarker-based studies to identify how specific groups of people respond to medicines. Tools used to develop targeted subgroups would include gene-expression profiling, gene sequencing, proteomics, and molecular imaging.
- 2 At this point, a medicine could be granted targeted approval. Access could be limited to the specific subpopulation to control early market access.
- 3 Drug safety and effectiveness could be monitored in a registry-type setting or in cooperation with the NIH, academic medical centers, or health plans with acceptable EPR systems.

- 4 Companies could replace direct-to-consumer advertising with a communications plan designed to improve prescriber and individual knowledge of the relative risks and benefits of the product for that defined patient population while prospective and confirmatory trials were conducted.
- 5 Expanded approval could be given to other patients after updated safety assessment and clinical outcome. Any uses for broader patient groups could be applied through a streamlined process similar to the drug's original targeted approval mechanism.

### *Recommendations for Accelerated Approval*

- Companies that rely upon validated biomarkers in Phase 2 testing to identify drugs that work for sub-populations with increased benefit and smaller risk or provide an unmet medical need should be able to make their medicines available to people who meet the pharmacogenomic criteria of their clinical trials on the basis of one study with convincing proof of efficacy in the relevant population.
- Companies can participate in registries or in post-market monitoring of their products within a national interoperable electronic medical records program also used by the FDA.

### THE 21ST CENTURY FDA

The key to making medicines safer and more effective is to make them more personalized and targeted. Moreover, the way to personalize medicine is to transform the FDA from an organization of rule-based regulators to a public health-focused agency staffed with 21st century science-based standard setters. By collaborating with academic institutions, private companies, and other government agencies, the FDA can utilize genetic information and better bioinformatics to create a template that will allow us to move from trial and error or one size fits all medicine to predictive and personalized care.

Much of 21st century health care might be shaped by policies and actions that are outside the realm of science. If we are not vigilant, third-party payers and the tort system could force drug companies and the FDA to shift investment away from personalized medicine. We recognizes the scientific and regulatory challenges, as well as the impact, that personalized medicine will have on the manufacturing and marketing of medicines. Steering drug development to smaller, even orphan markers will require a significant investment on the part of companies, without a certain return for their efforts. The marketing methods of the past, geared to broad populations and after the fact detection of safety problems, will give way to informing and educating small groups of pa-

tients and physicians whose understanding of the mechanisms of new medicines and participation in data collection will be critical. To the extent that the FDA evolves into a science-based standard setter for translating genetic knowledge into medicines, great progress is possible.

The task force strongly commends the FDA's Critical Path Initiative and the scientists in government, academic, and private settings whose insights made it possible. We share their commitment to personalized medicine as a template for both drug development and public health in the twenty-first century. These reforms will help promote a future where treatment is predictive, rather than haphazard and empirical. They will help usher in an era in which drugs are targeted by biomarkers and diagnostics rather than marketed to large, and perhaps inappropriate, populations.

The sequencing of the genome has made possible a revolution in human health. Personalized medicine is a possibility that depends ultimately on our ability to create the tools and marshal the will to make its many benefits a reality. The recommendations of the task force are intended to promote the Critical Path with a positive discussion of the specific resources and actions needed to achieve this goal. We look forward to making them, and the vision they seek to sustain, a reality in the years ahead.

## APPENDIX I

### A BRIEF HISTORY OF THE FDA<sup>27</sup>

The Food and Drug Administration's origins date from the Civil War, when President Lincoln appointed Charles M. Wetherill, a chemist, to test agricultural products at the newly created Department of Agriculture. Eventually, Wetherill's laboratories grew into the Bureau of Chemistry. In 1883, Dr. Harvey W. Wiley, considered the patron saint of the modern FDA, was appointed to lead the bureau and began a crusade against adulterated foods and "patent" medicines that claimed to be cure-alls.

The FDA gained influence with the growth of the national economy. For most of U.S. history, states retained power over food and drug products. In the nineteenth century, after America became an industrialized nation where consumer products moved rapidly across state borders, reformers became concerned that dozens of fraudulent firms were hawking fake or even dangerous foods and medicines to an unsuspecting public. Demands for more stringent federal labeling requirements and safer products flowed out of a series of tragic events and muckraking exposés—Sinclair's *The Jungle* being among the most famous—and led to the Food and Drugs Act of 1906.

Even after passage of the 1906 act, the FDA lacked injunctive power to prevent potentially harmful products from reaching the market. Its ability to restrain manufacturers was limited to launching a lawsuit in federal court, a very expensive and uncertain tool for setting public policy. Additional regulatory powers, particularly in the area of drug safety, came after a national tragedy, when a Tennessee firm marketed a syrup-based antibiotic called Elixir Sulfanilamide, which contained a highly poisonous solvent that killed more than a hundred people, including many children. The resulting public outcry led to the congressional passage of the 1938 Food, Drug, and Cosmetic Act, requiring companies to submit a pre-market application proving the safety of their products and giving the FDA power to prevent dangerous products from being marketed.<sup>28</sup>

In 1962, the FDA's regulatory power assumed the form that we know today after another scandal, this time involving thousands of birth defects in Europe and Japan caused by the anti-nausea drug thalidomide. The law that was passed in response to the thalidomide tragedy, the 1962 Kefauver-Harris Amendments, added the requirement that manufacturers prove efficacy as well as safety in clinical trials. The amendments also gave the FDA greater control over drug trials, mandated informed consent for patients in clinical trials, gave the agency the ability to police drug advertising, established manufacturing standards for the pharmaceutical industry, and gave the agency the right to inspect production facilities and records.<sup>29</sup>

The 1970s were rife with criticisms of the FDA's new regulatory powers and with claims that the FDA's drug approval process was unduly slow and cost American lives. Nevertheless, there was little movement on FDA reform until the advent of the AIDS crisis in the 1980s. In response to public and often highly controversial tactics from groups like ACT UP, the FDA instituted "treatment INDs," where investigational new drugs for AIDS could be sold after Phase 1 trials (provided that research regarding safety and efficacy was ongoing) and "parallel track," which allowed patients who were excluded from clinical trials to receive experimental drugs.

The AIDS controversy led to the growing realization that drug approval policies designed to protect the general population from unforeseen dangers might be causing more harm to small groups of seriously or terminally ill patients. In 1988, President Reagan's Task Force on Regulatory Relief, led by Vice President George H. W. Bush, commissioned the National Committee to Review Current Procedures of New Drugs for Cancer and AIDS.

In 1992, based on the findings and recommendations of this commission, the FDA adopted its accelerated

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approval program for serious or life-threatening diseases where accelerated drugs demonstrated “therapeutic benefit over existing therapy” based on surrogate end points, provided that company sponsors agreed to conduct Phase 4 or post-market studies that confirmed Phase 2 efficacy findings. Accelerated approval was codified by Congress in the Food and Drug Administration Modernization Act of 1997.

To this day, the FDA’s accelerated approval process has remained a subject of debate. While AIDS drugs have sailed through the FDA, some patient advocacy groups still believe that drugs for serious illnesses are approved too slowly; other critics assert that the surrogate end points used by the program are unproven and that they allow pharmaceutical companies to market expensive drugs that may have significant toxicity profiles but only marginal value for patients. It can be hoped that the Critical Path initiative will alleviate some of this controversy by creating objective benchmarks for drug safety and efficacy based on a more mechanistic understanding of human biology.

## APPENDIX II

### RECENT FDA BUDGETS

#### FDA'S FY 2007 BUDGET REQUEST HIGHLIGHTS MISSION PRIORITIES AND FISCAL RESPONSIBILITY<sup>1</sup>

The Food and Drug Administration (FDA) Fiscal Year (FY) 2007 budget request to Congress totals \$1.95 billion, a 3.8 percent increase over FY 2006. The FY07 request, which covers the period of October 1, 2006, to September 30, 2007, includes \$1.55 billion in budget authority and \$402 million in industry user fees.

The proposed increase of \$70.8 million over the current budget will enable FDA to focus its staff and resources on priority initiatives, including:

- Preparedness for the potential threat of pandemic influenza
- Protection of the food supply from bioterrorism
- Diverse initiatives to realize the promise of molecular medicine
- Strengthening the safety of drugs and human tissues for transplantation
- Meeting statutory obligations under the animal drug and medical devices user fee programs.

The following are FDA's key proposed budget increases:

#### *Pandemic Preparedness (\$30,490,000)*

To protect the nation against the threat of pandemic flu, the FDA proposes intensifying ongoing preparedness activities and launching additional measures to safeguard the public health from this potential threat. Preparedness activities include the development of viral reference strains that manufacturers require to produce influenza vaccines; acceleration of manufacturing capability to produce and deliver sufficient quantities of safe and effective vaccines; collaboration with the international public

health community on recognizing and responding to emerging pandemic threats; and the development of measures to address the potential pandemic-related impacts on FDA-regulated food and animal feed.

#### *Critical Path (\$5,940,000)*

The FDA proposes funding for its Critical Path for Personalized Medicine Initiative, a major nation wide project designed to make personalized medicine a reality and to translate discoveries in medical science into safe and effective new medical treatments. This is the first time Critical Path funding has been included in the Administration's proposed budget. The Critical Path Initiative will seek to mitigate or eliminate obstacles to medical product development that impede the ability to transform investments in basic medical research into products that benefit patients' health.

#### *Food Defense (\$19,873,000)*

The FDA will expand the network of laboratories that would rapidly and competently analyze samples in the event of a terrorist attack on our nation's food supply. This cooperative effort, which involves states and several federal agencies, will substantially enhance the FDA's capacity to detect and effectively respond to intentional contamination of our food. As part of this effort, the FDA will also expand its program of targeted food defense research.

#### *Medical Product Safety (\$6,435,000)*

To improve patient safety, FDA proposes significant new investments in the agency's safety programs for human drugs and transplantable human tissues. The FDA seeks \$3,960,000 to strengthen its capacity to recognize and act on emerging drug safety issues by modernizing its adverse drug event information systems and broaden the sources of data the agency

## PRESCRIPTION FOR PROGRESS

analyzes for drug safety signals. To increase the safety and effectiveness of human tissue transplants, which are involved in more than a million procedures a year, the FDA is requesting \$2,475,000 for its new risk-based program to detect, analyze, and respond to actual or potential disease transmission involving human tissues.

### *Cost of Living Pay Increase (\$20,267,000)*

The FDA is responsible for protecting the nation against the numerous known and emerging public health hazards; ensuring that the FDA-regulated food for the family table is safe and wholesome; that new human and animal drugs, vaccines, and medical devices are available in a timely manner with demonstrated benefits that outweigh risks; and that equipment that emits radiation and cosmetics do no harm. The agency could not carry out this critical and demanding mission without a highly trained staff of scientists, health care professionals, and support personnel whose salaries make up more than 60 percent of its budget.

### *User Fee "Triggers" (\$7,425,000)*

The FDA is requesting resources to meet statutory requirements, called "triggers." This will enable the agency to continue collecting user fees under the Medical Device User Fee and Modernization Act (MDUFMA) and Animal Drugs User Fee Act (ADUFA). These acts require a minimum level of federal spending for reviewing medical devices, and animal drugs and feed as a condition for the agency's collecting user fees from manufacturers. These additional resources have greatly strengthened the agency's ability to accelerate the review and approval of these products.

### *Other User Fee Increases (\$20,170,000)*

The budget request includes user fee increases statutorily prescribed under the Prescription Drug User Fee Act (PDUFA) (\$15,268,000); MDUFMA (\$3,426,000); ADUFA (\$286,000); Mammography Quality Standards Act (\$349,000); and for drugs and devices export certification (\$661,000) and color certification (\$180,000). These user fees support the Administration's vision of transforming health care and improving access to FDA-regulated products through enhanced agency performance. Since 1993,

when the first prescription drug user fees went into effect, they have enabled the agency to significantly reduce the time needed for product reviews and to upgrade other activities, principally by hiring additional staff and acquiring essential information technology.

### *New User Fees (\$25,536,000)*

In addition, the FDA is proposing two new sets of mandatory user fees. The first, estimated at \$22,000,000, would pay the full cost of reinspection and other FDA follow-up work after the manufacturer fails to meet such major FDA requirements as Good Manufacturing Practices, which ensure high quality standards in regulated products. These reinspection and laboratory analyses, which are currently funded by the agency, are essential to verify the manufacturer's corrective measures. The second new user fee, estimated at \$3,536,000, would cover the cost of issuing an estimated 37,000 food and animal feed export certificates.

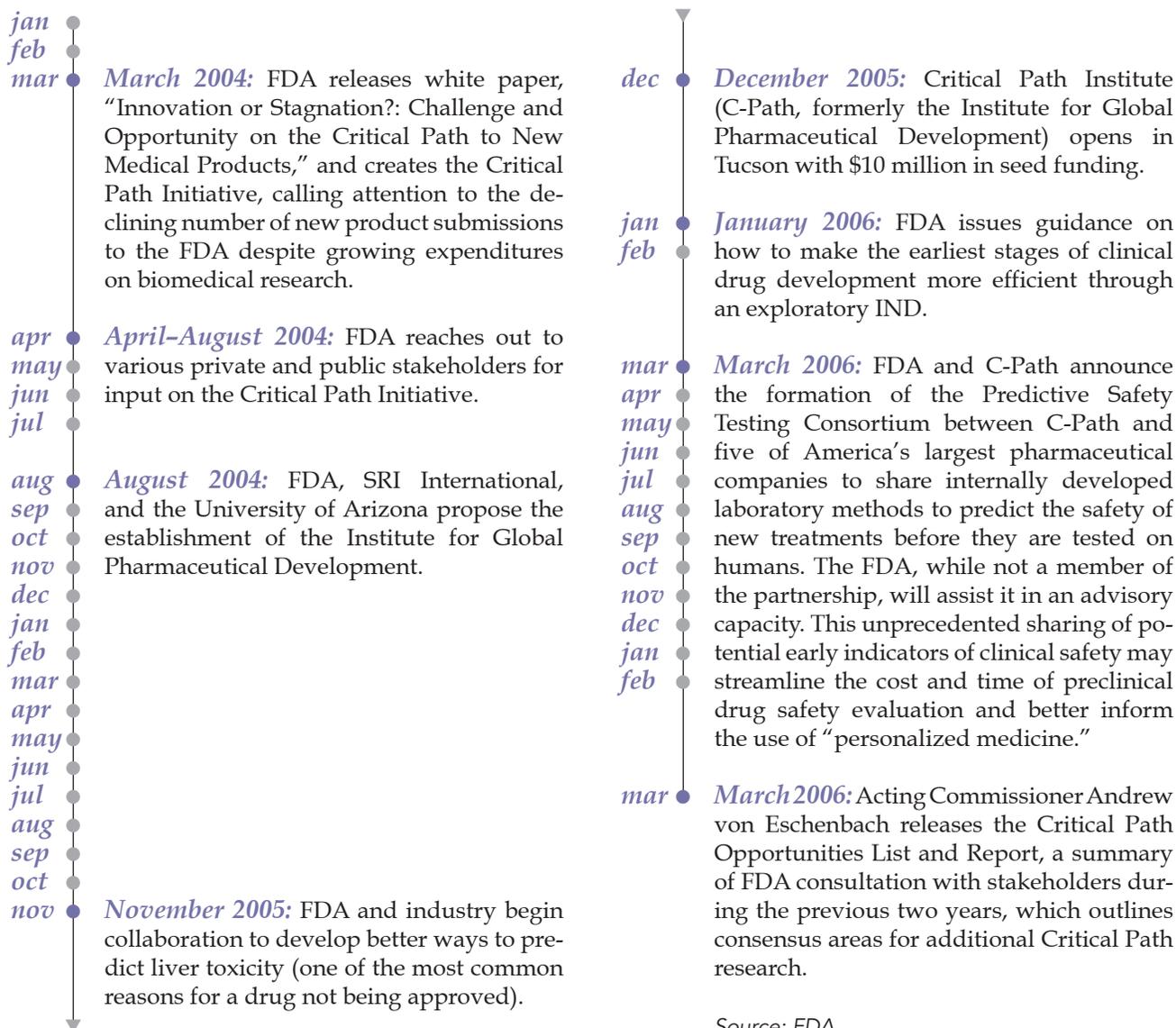
The FDA's budget request for FY 2007 is future-oriented, a characteristic reflecting the agency's performance strategy since its founding 100 years ago. As it is preparing to enter its second century of service to the nation, the FDA will intensify its efforts that have made it the world's premier regulatory agency, and an accomplished and steadfast protector of the nation's health.

**OVERVIEW OF THE FDA BUDGET  
NUMERIC TABLE  
(DOLLARS IN MILLIONS)**

	2005	2006	2007	2007 +/- 2006
Foods	\$436	\$439	\$450	+\$11
Human Drugs	496	518	535	+17
Biologics	172	195	210	+15
Animal Drugs and Feeds	98	99	105	+6
Medical Devices	250	261	272	+11
National Center for Toxicological Research	40	41	34	-7
Other Activities	115	117	120	+3
GSA Rental Payments	129	134	146	+12
Other Rent and Rent Related Activities	36	36	36	0
FDA Consolidation at White Oak	21	22	26	+4
Export/Certification Fund	7	8	8	+1
<b>Subtotal, Salaries &amp; Expenses</b>	<b>\$1,801</b>	<b>\$1,869</b>	<b>\$1,942</b>	<b>+\$74</b>
Buildings and Facilities	0	8	5	-3
<b>Total, Program Level</b>	<b>\$1,801</b>	<b>\$1,876</b>	<b>\$1,947</b>	<b>+\$71</b>
<b>Less Current Law User Fees:</b>				
Prescription Drug User Fee Act (PDUFA)	-\$284	\$305	-\$321	-\$15
Medical Device User Fees (MDUFMA)	-34	-40	-44	-3
Animal Drugs User Fee Act (ADUFA)	-8	-11	-12	0
Mammography Quality Standards Act (MQSA)	-17	-17	-18	0
Export/Certification Fund	-7	-8	-8	-1
<b>Subtotal, Current Law User Fees</b>	<b>-350</b>	<b>-382</b>	<b>-402</b>	<b>-20</b>
<b>Total Discretionary Budget Authority</b>	<b>\$1,450</b>	<b>\$1,495</b>	<b>\$1,545</b>	<b>+\$51</b>
<b>Less Mandatory Proposed Law User Fees:</b>				
Reinspection User Fee	0	0	-22	-22
Export/Certification Fund (Foods and Feeds)	0	0	-4	-4
<b>Subtotal, Mandatory Proposed User Fees</b>	<b>\$0</b>	<b>\$0</b>	<b>-\$26</b>	<b>-\$26</b>
<i>Mandatory BA (Scorekeeping Adjustment)</i>	\$0	\$0	-\$26	-\$26
<b>Total Net Budget Authority*</b>	<b>\$1,450</b>	<b>\$1,495</b>	<b>\$1,520</b>	<b>+\$25</b>
<b>Biodefense (non-add):</b>				
<i>Food Defense</i>	\$150	\$158	\$178	+\$20
<i>Medical Product Countermeasures</i>	57	57	57	0
<i>Security</i>	7	7	0	0
<b>Subtotal, Biodefense (non-add)</b>	<b>\$214</b>	<b>\$222</b>	<b>\$242</b>	<b>+\$20</b>
FTE	9,992	10,176	10,209	+33

\* Net budget authority is contingent upon enactment of proposed mandatory user fees and receipt of estimated collections.

## APPENDIX III TIMELINE OF THE CRITICAL PATH



Source: FDA

## APPENDIX IV

### THE FDA'S ENABLING STATUTE

United States Code<sup>30</sup>

TITLE 21 – FOOD AND DRUGS

CHAPTER 9 – FEDERAL FOOD, DRUG, AND  
COSMETIC ACT

SUBCHAPTER IX – MISCELLANEOUS

#### Sec. 393. Food and Drug Administration

##### (a) In general

There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this section referred to as the “Administration”).

##### (b) Mission

The Administration shall –

- (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
- (2) with respect to such products, protect the public health by ensuring that –
  - (A) foods are safe, wholesome, sanitary, and properly labeled;
  - (B) human and veterinary drugs are safe and effective;
  - (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;
  - (D) cosmetics are safe and properly labeled; and
  - (E) public health and safety are protected from electronic product radiation;
- (3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal

arrangements; and

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

##### (c) Interagency collaboration

The Secretary shall implement programs and policies that will foster collaboration between the Administration, the National Institutes of Health, and other science-based Federal agencies, to enhance the scientific and technical expertise available to the Secretary in the conduct of the duties of the Secretary with respect to the development, clinical investigation, evaluation, and post-market monitoring of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.

##### (d) Commissioner

###### (1) Appointment

There shall be in the Administration a Commissioner of Food and Drugs (hereinafter in this section referred to as the “Commissioner”) who shall be appointed by the President by and with the advice and consent of the Senate.

###### (2) General powers

The Secretary, through the Commissioner, shall be responsible for executing this chapter and for –

- (A) providing overall direction to the Food and Drug Administration and establishing and implementing general policies respecting the management and operation of programs and activities of the Food and Drug Administration;
- (B) coordinating and overseeing the operation of all administrative entities within the Administration;

- (C) research relating to foods, drugs, cosmetics, and devices in carrying out this chapter;
- (D) conducting educational and public information programs relating to the responsibilities of the Food and Drug Administration; and
- (E) performing such other functions as the Secretary may prescribe.

### (e) Technical and scientific review groups

The Secretary through the Commissioner of Food and Drugs may, without regard to the provisions of title 5 governing appointments in the competitive service and without regard to the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates, establish such technical and scientific review groups as are needed to carry out the functions of the Administration, including functions under this chapter, and appoint and pay the members of such groups, except that officers and employees of the United States shall not receive additional compensation for service as members of such groups.

### (f) Agency plan for statutory compliance

#### (1) In general

Not later than 1 year after November 21, 1997, the Secretary, after consultation with appropriate scientific and academic experts, health-care professionals, representatives of patient and consumer advocacy groups, and the regulated industry, shall develop and publish in the Federal Register a plan bringing the Secretary into compliance with each of the obligations of the Secretary under this chapter. The Secretary shall review the plan biannually and shall revise the plan as necessary, in consultation with such persons.

#### (2) Objectives of agency plan

The plan required by paragraph (1) shall establish objectives and mechanisms to achieve such objectives, including objectives related to—

- (A) maximizing the availability and clarity of information about the process for review of applications and submissions (including petitions, notifications, and any other similar forms of request) made under this chapter;
- (B) maximizing the availability and clarity of information for consumers and patients concerning new products;
- (C) implementing inspection and post-market

monitoring provisions of this chapter;

(D) ensuring access to the scientific and technical expertise needed by the Secretary to meet obligations described in paragraph (1);

(E) establishing mechanisms, by July 1, 1999, for meeting the time periods specified in this chapter for the review of all applications and submissions described in subparagraph (A) and submitted after November 21, 1997; and

(F) eliminating backlogs in the review of applications and submissions described in subparagraph (A), by January 1, 2000.

### (g) Annual report

The Secretary shall annually prepare and publish in the Federal Register and solicit public comment on a report that—

- (1) provides detailed statistical information on the performance of the Secretary under the plan described in subsection (f) of this section;
- (2) compares such performance of the Secretary with the objectives of the plan and with the statutory obligations of the Secretary; and
- (3) identifies any regulatory policy that has a significant negative impact on compliance with any objective of the plan or any statutory obligation and sets forth any proposed revision to any such regulatory policy.

(June 25, 1938, chap. 675, Sec. 903, as added Pub. L. 100-607, title V, Sec. 503(a), Nov. 4, 1988, 102 Stat. 3121; amended Pub. L. 100-690, title II, Sec. 2631, Nov. 18, 1988, 102 Stat. 4244; Pub. L. 105-115, title IV, Secs. 406, 414, Nov. 21, 1997, 111 Stat. 2369, 2377)

### References in Text

The provisions of title 5 governing appointments in the competitive service, referred to in subsec. (e), are classified generally to section 3301 et seq. of Title 5, Government Organization and Employees.

### Codification

Another section 903 of the Federal Food, Drug, and Cosmetic Act was renumbered section 904 and is classified to section 394 of this title.

### Amendments

1997—Subsec. (b). Pub. L. 105-115, Sec. 406(a)(2), added subsec.(b). Former subsec. (b) redesignated (d).

Subsec. (c). Pub. L. 105-115, Sec. 414, added subsec. (c). Former subsec. (c) redesignated (e).

Subsecs. (d), (e). Pub. L. 105-115, Sec. 406(a)(1), redesignated subsecs. (b) and (c) as (d) and (e), respectively.

Subsecs. (f), (g). Pub. L. 105-115, Sec. 406(b), added subsecs. (f) and (g).

1988—Subsec. (b)(2). Pub. L. 100-690 substituted “shall be responsible for executing this chapter and for “shall be responsible.”

#### **Effective Date of 1997 Amendment**

Amendment by Pub. L. 105-115 effective 90 days after Nov. 21, 1997, except as otherwise provided, see section 501 of Pub. L. 105-115, set out as a note under section 321 of this title.

#### **Effective Date**

Section 503(c) of title V of Pub. L. 100-607 provided that:

“(1) Except as provided in paragraph (2), the amendments made by this title [enacting this section and amending sections 5315 and 5316 of Title 5, Government Organization and Employees] shall take effect on the date of enactment of this Act [Nov. 4, 1988].

“(2) Section 903(b)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 393(b)(1)] (as added by subsection (a) of this section) shall apply to the appointments of Commissioners of Food and Drugs made after the date of enactment of this Act.”

#### **Regulations for Sunscreen Products**

Section 129 of Pub. L. 105-115 provided that: “Not later than 18 months after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services shall issue regulations for over-the-counter sunscreen products for the prevention or treatment of sunburn.”

#### **FDA Study of Mercury Compounds in Drugs and Food**

Section 413 of Pub. L. 105-115 provided that:

“(a) List and Analysis.—The Secretary of Health and Human Services shall, acting through the Food and Drug Administration—

“(1) compile a list of drugs and foods that contain intentionally introduced mercury compounds, and

“(2) provide a quantitative and qualitative analysis of the mercury compounds in the list under paragraph (1). The Secretary shall compile the list required by paragraph (1) within 2 years after the date of enactment of the Food and Drug Administration Modernization Act of 1997 [Nov. 21, 1997] and shall provide the analysis required by paragraph (2) within 2 years after such date of enactment.

“(b) Study.—The Secretary of Health and Human Services, acting through the Food and Drug Administration, shall conduct a study of the effect on humans of the use of mercury compounds in nasal sprays. Such study shall include data from other studies that have been made of such use.

“(c) Study of Mercury Sales.—

“(1) Study.—The Secretary of Health and Human Services, acting through the Food and Drug Administration and subject to appropriations, shall conduct, or shall contract with the Institute of Medicine of the National Academy of Sciences to conduct, a study of the effect on humans of the use of elemental, organic, or inorganic mercury when offered for sale as a drug or dietary supplement. Such study shall, among other things, evaluate—

“(A) the scope of mercury use as a drug or dietary supplement; and

“(B) the adverse effects on health of children and other sensitive populations resulting from exposure to, or ingestion or inhalation of, mercury when so used. In conducting such study, the Secretary shall consult with the Administrator of the Environmental Protection Agency, the Chair of the Consumer Product Safety Commission, and the Administrator of the Agency for Toxic Substances and Disease Registry, and, to the extent the Secretary believes necessary or appropriate, with any other Federal or private entity.

“(2) Regulations.—If, in the opinion of the Secretary, the use of elemental, organic, or inorganic mercury offered for sale as a drug or dietary supplement poses a threat to human health, the Secretary shall promulgate regulations restricting the sale of mercury intended for such use. At a minimum, such regulations shall be designed to protect the health of children and other sensitive populations from adverse effects resulting from exposure to, or ingestion or inhalation of, mercu-

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ry. Such regulations, to the extent feasible, should not unnecessarily interfere with the availability of mercury for use in religious ceremonies.”

### **Management Activities Study**

Pub. L. 102-571, title II, Sec. 205, Oct. 29, 1992, 106 Stat. 4502, directed Comptroller General to conduct a study of management of activities of the Food and Drug Administration that are related to dietary supplements of vitamins, minerals, herbs, or other similar nutritional substances and submit an interim report to Congress, not later than 6 months after Oct. 29, 1992, with a final report to be submitted not later than 12 months after Oct. 29, 1992.

### **Congressional Findings**

Section 502 of Pub. L. 100-607 provided that: “Congress finds that—

“(1) the public health has been effectively protected by the presence of the Food and Drug Administration during the last eighty years;

“(2) the presence and importance of the Food and Drug Administration must be guaranteed; and

“(3) the independence and integrity of the Food and Drug Administration need to be enhanced in order to ensure the continuing protection of the public health.”

### **Section Referred to in Other Sections**

This section is referred to in sections 360m, 374 of this title.

## NOTES

- <sup>1</sup> In March 2004, the FDA released a white paper entitled “Innovation or Stagnation?: Challenge and Opportunity on the Critical Path to New Medical Products,” available online at: <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>. This report is often termed the “Critical Path Initiative.”
- <sup>2</sup> The FDA’s basic statutory authority rests on the Food Drug and Cosmetic Act of 1938 (U.S.C. Title 21, Chapter 9). The FDA’s mission statement describes the agency’s broad mandate: “The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.” The purpose of this paper is to examine and recommend ways to improve a small, but vitally important, part of the FDA’s mission: the regulation and approval of new medicines to treat human disease and disability.
- <sup>3</sup> On December 23, 2004, for instance, the FDA approved a genetic test called the Roche AmpliChip, which may help doctors determine which drugs will have fewer side effects and work better for people. The FDA noted:
- [T]his system uses DNA extracted from a patient’s blood to detect certain common genetic mutations that alter the body’s ability to break down (metabolize) specific types of drugs. The enzyme produced from the gene that is tested, called cytochrome P4502D6 (CYP4502D6), is active in metabolizing many types of drugs including antidepressants, antipsychotics, beta-blockers, and some chemotherapy drugs. Variations in this gene can cause a patient to metabolize these drugs abnormally fast, abnormally slow, or not at all. For example, the same dose that is safe for a patient with one variation might be too high (and therefore toxic) to a patient with a different variation who cannot metabolize the drug.
- Center for Devices and Radiological Health (CDRH) Consumer Information, available online at: <http://www.fda.gov/cdrh/mda/docs/k042259.html>.
- <sup>4</sup> The National Academies Institute of Medicine, Committee on the Assessment of the U.S. Drug Safety System, June 8, 2005. Powerpoint presentation by Janet Woodcock and Steve Galson, Acting Director of the Center for Drug Evaluation and Research. Available online at <http://www.iom.edu/?id=27158>.
- <sup>5</sup> “Innovation or Stagnation?” (see n. 1 above).
- <sup>6</sup> This is the goal of the FDA’s Predictive Safety Testing Public/Private Consortium. Members of the consortium include the FDA and the Critical Path (C-Path) Institute, along with other representatives from government, academia, and industry.
- <sup>7</sup> “Innovation or Stagnation?” (see n. 1 above).
- <sup>8</sup> Tufts Center for the Study of Drug Development, “Backgrounder: How New Drugs Move Through the Development and Approval Process,” November 2001; and J. Gilbert, P. Henske, and A. Singh, “Rebuilding Big Pharma’s Business Model,” *In Vivo: The Business & Medicine Report* 21, no. 10 (November 2003), Windhover Information.

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<sup>9</sup> In its recently released *Critical Path Opportunities Report* (March 2006), the FDA stated: “There is urgent need for successive generations of antibiotics and evolving medical countermeasures (including new vaccines and improved tests for screening donor blood and tissues) against emerging infections and bioterror attacks. Although multiple hurdles to innovation exist, modernizing the Critical Path sciences could play a significant role in solving public health needs.”

<sup>10</sup> As in the federal Vaccines for Children program.

<sup>11</sup> Paul Offit, chief of the Division of Infectious Diseases and director of the Vaccine Education Center at the Children’s Hospital of Philadelphia has stated:

The cost to develop and make many vaccines is greater than that to make most drugs, because products given to healthy people are often held to higher standards of safety than those given to people who are sick. In 1998 the FDA licensed a vaccine to prevent rotavirus, a common cause of fever, vomiting, and diarrhea in young children. After the vaccine had been on the market for one year – and was given to about one million children – the CDC detected a rare adverse event: About one of every 10,000 children who received the vaccine developed intussusception, a blockage of the intestine. As a consequence, the rotavirus vaccine was withdrawn.

Before it was licensed, the rotavirus vaccine had been given to about 11,000 children in placebo-controlled prospective studies. Because intussusception was very rare, studies performed prior to licensure were not big enough to determine that rotavirus vaccine caused the condition. Following the withdrawal of the rotavirus vaccine in 1999, children have continued to be hospitalized for and killed by rotavirus. Although many more children would have been helped by a rotavirus vaccine than hurt by it, the current culture does not allow for any serious side effects from a vaccine. As a consequence, pharmaceutical companies are now asked to disprove even very rare adverse effects prior to licensure. Two companies, Merck and GlaxoSmithKline, are now testing rotavirus vaccines in pre-licensure trials that include more than 140,000 children. The cost of these two large trials is about \$400 million. The added financial burden of now disproving rare adverse events before licensure is another disincentive to making vaccines.

“Why Are Pharmaceutical Companies Gradually Abandoning Vaccines?” *Health Affairs* 24, no. 3 (2005): 622–30.

<sup>12</sup> See also “Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates . . . A Public Health Crisis Brews,” from the Infectious Diseases Society of America (July 2004), available online at: [http://www.idsociety.org/pa/IDSA\\_Paper4\\_final\\_web.pdf](http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf).

<sup>13</sup> Christopher Adams and Van Brantner, “New Drug Development,” Bureau of Economics, Federal Trade Commission, July 7, 2003.

<sup>14</sup> Food and Drug Administration Modernization Act of 1997, Public Law 105-115, 105th Congress.

<sup>15</sup> Carole Cruzan Morton, Focus, “Statistical Approach Speeds Up Stent Trials”, February 7, 2003. Available online at: [http://focus.hms.harvard.edu/2003/Feb7\\_2003/clinical\\_research.html](http://focus.hms.harvard.edu/2003/Feb7_2003/clinical_research.html).

<sup>16</sup> “FDA Exempts Phase-I Drugs from Strict Manufacturing,” American Society of Health System Pharmacists, January 12, 2006. Available online at <http://www.ashp.org/news/ShowArticle.cfm?id=13817>.

<sup>17</sup> According to its website, the Critical Path Institute “is an independent, publicly funded, non-profit organization dedicated to the critical path initiative. C-Path fosters research and educational programs intended to enable the pharmaceutical industry to safely accelerate the development of new medications.” The C-Path Institute was jointly founded by the University of Arizona, the FDA, and SRI International.

<sup>18</sup> Michelle Meadows, “Why Drugs Get Pulled off the Market – Pharmaceuticals,” FDA Consumer, January–February 2002.

- <sup>19</sup> The QT interval is a measurement on an electrocardiogram; QT prolongation is a biomarker for sudden cardiac arrest that is associated with drug treatment.
- <sup>20</sup> Patrick Clinton and Jill Wechsler, "What Ever Happened to Critical Path," *Pharmaceutical Executive*, p. 4, available online at: <http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=282481&pageID=4>.
- <sup>21</sup> FDA Critical Path Report, July 2004.
- <sup>22</sup> "Orphan Disease Registries." The Critical Path Institute. April 3, 2006. <http://www.c-path.org/Programs/ProgramProjectSubPages/OrphanDiseaseRegistries/tabid/81/Default.aspx>.
- <sup>23</sup> Brett J. Davis, "BioBanking 101: Accelerating Personalized Medicine," available online at: [http://healthnex.typepad.com/web\\_log/2005/09/biobanking\\_101\\_.html](http://healthnex.typepad.com/web_log/2005/09/biobanking_101_.html).
- <sup>24</sup> "Mayo Clinic 2004 Highlights." The Mayo Clinic. <http://www.mayoclinic.org/annualreport/highlights-2004.html>.
- <sup>25</sup> For instance, electronic health records could be mined to produce routine adverse event reports scrubbed of personally identifiable information.
- <sup>26</sup> J. Concato, N. Shah, and R. Horwitz, "Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs," *New England Journal of Medicine* 342, no. 25 (June 22, 2000): 1887–92.
- <sup>27</sup> The following information (unless noted otherwise) is adapted from the FDA's "History of the FDA," by John P. Swann, Ph.D., FDA History Office (adapted from George Kurian, ed., *A Historical Guide to the U.S. Government* (New York: Oxford University Press, 1998), available online at: <http://www.fda.gov/oc/history/historyoffda/default.htm>.
- <sup>28</sup> The distinction between prescription drugs (requiring prior physician approval) and over-the-counter drugs was added by the Durham Humphrey Amendment in 1951.
- <sup>29</sup> Medical devices follow a different regulatory track. Swann: "The legislation having failed to develop, the Secretary of HEW commissioned the Study Group on Medical Devices, which recommended in 1970 that medical devices be classified according to their comparative risk, and regulated accordingly. The 1976 Medical Device Amendments, coming on the heels of a therapeutic disaster in which thousands of women were injured by the Dalkon Shield intrauterine device, provided for three classes of medical devices, each requiring a different level of regulatory scrutiny – up to pre-market approval."
- <sup>30</sup> 21USC393, available online at: <http://frwebgate6.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=454824489608+0+0+0&WAIAction=retrieve>.

**PRESCRIPTION FOR PROGRESS**

## FDA TASK FORCE MEMBERS

### ROBERT M. GOLDBERG

Chairman, Manhattan Institute's 21st Century  
FDA Task Force

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Dr. Goldberg is co-founder, vice president and director of programs for Center for Medicine in the Public Interest. Prior to founding CMPI, he was senior fellow at the Manhattan Institute and director of its Center for Medical Progress. Dr. Goldberg's current research interests include FDA reform and the impact of new medical technologies on making health care more predictive, preventive and personalized. Dr. Goldberg is the author of numerous articles and reports including "Vaccinating Against Disaster," "False Economy on Drugs," "Importation Nightmare," and "Fight AIDS With Reason, Not Rhetoric." He has testified before the Senate Special Committee on Aging, the Senate Small Business Committee, and the House Commerce Committee. He has written for *The Wall Street Journal*, *The Washington Post*, the *Los Angeles Times*, National Review Online, and *The Weekly Standard*, and he writes regularly for *The Washington Times*. He received his Ph.D. in politics at Brandeis University in 1984.

**Disclosure:**

None.

### DAVID BLEICH, M.D.

Associate Professor of Medicine, University of  
Medicine & Dentistry of New Jersey

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David Bleich, M.D. is chief, Division of Endocrinology, Diabetes & Metabolism and associate professor of medicine at UMDNJ-New Jersey Medical School. His research interest involves understanding the effects of matrix metalloproteinases and their inhibitors on cell adhesion and migration in type 1 diabetes. He has received research grant support from the NIH and Juvenile Diabetes Research Foundation for

this work. He is also funded by the Almond Board of California to evaluate the metabolic effects of almond consumption in pre-diabetes. Dr. Bleich has authored numerous peer-reviewed publications on type 1 diabetes and is a member of the Research Grant Review Committee for the American Diabetes Association.

**Disclosure:**

Dr. Bleich is a member of the Speakers Bureau for Sanofi-Aventis.

### MARK BRUNSWICK

Director, Regulatory Affairs, Elan Pharmaceuticals

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As regulatory affairs director for Elan, Mark Brunswick directs the group responsible for interactions within Elan and with the FDA for drugs regulated by both the Center for Biologics and the Center for Drugs. He worked as a regulatory affairs consultant for SAIC, dealing with government and commercial contracts, as well as compliance inspection. Previously, Mark accumulated nine years of experience as a reviewer for the FDA, specializing in licensing and facilities inspection. He has conducted extensive research into the human immune system, and holds a Ph.D. in immunology and a B.S. in genetics and zoology from the University of London.

**Disclosure:**

Mark Brunswick is director, Regulatory Affairs, Elan Pharmaceuticals.

### PAUL COPLAN, SC.D., MBA

Senior Director, Risk Management, Global  
Safety Surveillance and Epidemiology, Wyeth  
Pharmaceuticals

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Paul M. Coplan is a senior director of risk management at Wyeth. Dr. Coplan works with cross-functional

teams across Wyeth to develop and implement Risk Management plans for marketed products and investigational compounds. In this role, he works with key stakeholders to apply scientifically based methodologies to identify, assess, communicate and minimize risks throughout a drug's lifecycle so as to establish and maintain a favorable benefit/risk profile in patients.

Dr. Coplan received a Doctorate of Science in Epidemiology from Harvard School of Public Health, a Masters in Business Administration from the Wharton School of Business at University of Pennsylvania, and a Masters of Science in Public Health & Nutrition from the University of Massachusetts. He has over 23 years of experience in the field of public health and drug development. Prior to joining Wyeth, Dr. Coplan was executive director of clinical and regulatory affairs and epidemiology at the International Partnership for Microbicides, a non-profit pharmaceutical company dedicated to the development of microbicides to prevent HIV infection among women in developing countries. In this role he was the leader of the Regulatory Affairs department and in framing the regulatory hurdles for licensure of vaginal microbicides to prevent HIV infection. He also ran several clinical trials in Africa of investigational microbicides and established several new clinical trial sites in developing countries. From 1995 to 2003 Dr. Coplan worked in the Epidemiology and Worldwide Regulatory Affairs departments of Merck & Co. where he worked as regulatory leader for Merck's HIV vaccine, herpes zoster vaccine, and cancer vaccine programs.

**Disclosure:**  
None.

### JOSEPH DIMASI, PH.D.

Director of Economic Analysis, Tufts Center for the Study of Drug Development

Dr. DiMasi has been at the Tufts Center for the Study of Drug Development since the fall of 1987. Prior to joining the Tufts Center for the Study of Drug Development, Dr. DiMasi was a member of the Department of Economics at the College of the Holy Cross. Dr. DiMasi received his Ph.D. in Economics from Boston College in 1984. He received a B.A. with honors in both Mathematics and Economics from the University of Massachusetts at Boston in 1975. Dr. DiMasi has

authored numerous articles published in economics and medical research journals. He has served on the editorial boards of the *Drug Information Journal* and the *Journal of Research in Pharmaceutical Economics*.

**Disclosure:**

The Tufts Center for the Study of Drug Development is supported in part by unrestricted grants from pharmaceutical and biopharmaceutical firms, as well as from companies that provide services and products to this industry. Sponsoring companies have no direct access to any of the Tufts Center's proprietary databases, and they have no direct influence on the group's research agenda.

### ROBERT PETER GALE, M.D.

Senior Vice President Research, Ziopharm Oncology, Inc. and Center for Advanced Studies in Leukemia

From 1993-1999, Dr. Gale was senior physician and corporate director of bone marrow and stem cell transplantation at Salick Health Care, Inc. in Los Angeles. From 2000-2004 Dr. Gale was senior vice president for medical affairs at Antigenics, Inc. in New York where he was responsible for design, implementation and analysis of clinical trials of anti-cancer vaccines. Dr. Gale has published over 800 scientific articles and more than 20 books, mostly on leukemia (biology and treatment), transplantation (biology, immunology and treatment), cancer immunology and radiation (biological effects and accident response). He has written on medical topics, nuclear energy and weapons and politics of US-Soviet relations in articles for *The NY Times*, *The Los Angeles Times*, *The Washington Post*, *USA Today*, and *The Wall Street Journal*. He is presently visiting professor of haematology at the Imperial College of Science, Technology and Medicine (Hammersmith Hospital, London, UK). Dr. Gale lives in Los Angeles with his wife Laura and six children.

**Disclosure:**  
None.

**FREDERICK GOODWIN**

Professor of Clinical Psychiatry,  
George Washington University

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Frederick K. Goodwin, M.D., is research professor of psychiatry at The George Washington University and director of the Center on Neuroscience, Medical Progress, and Society at the George Washington University Medical Center. Dr. Goodwin is the former director of the National Institute of Mental Health (NIMH). Prior to that, he held a Presidential appointment as head of the Alcohol, Drug Abuse, and Mental Health Administration. He joined the NIMH in 1965. He is a member of the Institute of Medicine of the National Academy of Sciences and a fellow of the ACNP. He serves on the editorial boards of key scientific journals, including the *Archives of General Psychiatry* and *The Journal of Clinical Psychopharmacology*, and is a founder of *Psychiatry Research*.

Dr. Goodwin is a recipient of the major research awards in his field. The author of over 430 publications, Dr. Goodwin (with K. R. Jamison, Ph.D.) wrote *Manic-Depressive Illness*, the first psychiatric text to win the Best Medical Book award from the Association of American Publishers. Dr. Goodwin is a Senior Contributor and guest host of the award-winning "The Infinite Mind" public radio show, a weekly public radio program dedicated to issues relating to the mind, the brain, and mental illness. Dr. Goodwin served as host of "The Infinite Mind" for seven years starting with its premiere in 1998.

**Disclosure:**

Dr. Goodwin works in a research support capacity for Abbott Laboratories, Glaxo, Solvay, Janssen, Pfizer, Lilly, Forest, Sanofi, and BMS. He is part of the Speakers Bureau at Glaxo, Pfizer, Lilly, and Bristol Myers Squibb. He also works as a consultant for Glaxo, Lilly, Pfizer, Bristol Myers Squibb, and Solvay.

**SUSAN HORN, PH.D.**

Senior Scientist, Institute for Clinical Outcomes  
Research

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Susan D. Horn, Ph.D., is senior scientist, Institute for Clinical Outcomes Research, and adjunct professor, Department of Medical Informatics, University of Utah School of Medicine, both in Salt Lake City. From 1968-1991, she was a faculty member at The Johns Hopkins University in Baltimore in biostatistics and

health policy and management. From 1991-1995, she was senior scientist at Intermountain Health Care in Salt Lake City. Dr. Horn earned a B.A. in mathematics at Cornell University, and a Ph.D. in statistics at Stanford University. She has published over 150 papers in statistics and health services research and developed the Comprehensive Severity Index, used in the conduct of practice-based evidence studies in over 20 clinical areas including nursing home pressure ulcer prevention, post-stroke rehabilitation, hospice, and pediatrics. Findings from these studies have been implemented successfully to improve clinical and operational outcomes.

**Disclosure:**

None.

**MATHIAS HUKKELHOVEN**

Vice President, U.S. Regulatory Affairs,  
Novartis Pharmaceuticals

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Mathias Hukkelhoven, Ph.D. is senior vice president, global head, Drug Regulatory Affairs of Novartis Pharmaceuticals Corporation in East Hanover, New Jersey. In his current role Dr. Hukkelhoven is responsible for global coordination of all regulatory affairs activities and strategies of development projects and marketed products in the Novartis portfolio. From 1999–2001 he was head of the U.S. Regulatory Affairs Department at Novartis. Before this, he was responsible for Regulatory Affairs in the Immunology and Biotech area of Novartis predecessor company Sandoz in East Hanover and Basel (Switzerland). Before joining Novartis and Sandoz he was a group leader in the Regulatory Affairs Department of Hoffmann-La Roche in Basel, Switzerland where he was responsible for biotechnology, oncology and anti-infective projects. From 1984-1990, he worked in various positions in AKZO Pharma in the Netherlands and Belgium, where from 1996-1990 he was Head of the Regulatory Affairs Department of Organon Teknika. Dr. Hukkelhoven graduated in 1979 from the University of Nijmegen, The Netherlands and received his honors Ph.D. degree in Biochemistry from that University in 1984. He is the author of 35 articles on the metabolism of carcinogenic compounds in human tissues. From April 2006 he will be the Chair of the Regulatory Affairs Coordinating Committee at PhRMA.

### *Disclosure:*

Dr. Hukkelhoven is the Vice President of U.S. Regulatory Affairs at Novartis Pharmaceuticals.

### **STEPHEN MARTIN**

Senior Vice President & Chief Technical Officer,  
Beyond Genomics

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Stephen A. Martin is senior vice president and chief technology officer at BG Medicine. Prior to joining BG Medicine in May 2004, Dr. Martin was senior director of the Discovery Proteomics & Small Molecule Research Center (DPSM RC) at Applied Biosystems in Framingham, Massachusetts. The team focused on developing complete workflows with collaborators in a variety of applied markets, identifying gaps in these approaches and conducting basic research to better understand the key technologies that would revolutionize these fields. Prior to forming the Research Center, Dr. Martin was responsible for Research and Development in Mass Spectrometry and Chromatography. He joined PerSeptive Biosystems in 1994, which was later acquired by Applied Biosystems. Before joining Applied Biosystems, Dr. Martin held positions at Genetics Institute, Medical University of South Carolina and the Department of Chemistry at MIT. He received his B.A. in Chemistry from Boston University in 1980 and his Ph.D. in Analytical Chemistry from MIT in 1984.

### *Disclosure:*

Stephen Martin is senior vice president & chief technical officer, Beyond Genomics.

### **PAT MCGOVERN**

Associate Director, Regulatory Affairs, Novartis

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Patricia McGovern is a director in Drug Regulatory Affairs at Novartis. Trained in chemistry at Columbia University and the University of California, Berkeley, Patricia worked extensively on dermatology and respiratory projects at Novartis prior to assuming her current role as head of Special Projects. The responsibilities of the Special Projects group include coordinating Novartis' activities related to the Critical Path Initiative, and participating in internal efforts that are focused on developing a vision for the future of drug development and implementing aspects of that vision at Novartis.

### *Disclosure:*

Pat McGovern is associate director, regulatory affairs, Novartis]

### **ULKU OKTEM, PH.D.**

Senior Fellow, Risk Management & Decision Process Center, Wharton School at the University of Pennsylvania

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Dr. Oktem is an adjunct professor at the Operations and Information Management Department and a senior research fellow at Risk Management and Decision Process Center of the Wharton School of University of Pennsylvania. Dr. Oktem's research interests include development of effective near-miss management systems and identification and mitigation of adverse drug effects. She teaches environmental sustainability and value creation at the Wharton School, MBA program. Prior to her academic life she worked at Rohm and Haas Company for 16 years where she managed large scale product development and manufacturing, including agricultural chemicals. Dr. Oktem holds B.S., M.S., and Ph.D. degrees in chemical engineering.

### *Disclosure:*

None.

### **PETER PITTS**

Director, Center for Medicine in the Public Interest

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Peter Pitts is director of the Center for Medicine in the Public Interest, a think tank on public health care policy issues and senior vice president, director for Global Health Affairs for Manning, Selvage & Lee. From 2002-2004 Peter was FDA's Associate Commissioner for External Relations, serving as the agency's chief messaging officer. Before his work with the FDA, Mr. Pitts served as managing partner of *Wired World*, director of marketing at *The New York Post*, director of marketing for *The Washington Times* and *Insight Magazine*, and in numerous other communications positions. He joined the Hudson Institute in 1995 as vice president of marketing and communications. He has also served as an adjunct professor at Indiana University's School of Public and Environmental Affairs and at Butler University. A graduate of McGill University, Mr. Pitts writes a regularly syndicated national column for United Press International

and is frequently interviewed by the business press. His most recent book is *Become Strategic or Die*.

**Disclosure:**

None.

**GUALBERTO RUAÑO, M.D., PH.D.**

President & Founder, Genomas

Dr. Ruaño has been an innovator and entrepreneur in the biomedical industry and advocate of personalized medicine for 20 years. He obtained M.D. and Ph.D. degrees from Yale University. He obtained his B.A. degree from Johns Hopkins University, where he was elected to Phi Beta Kappa. Dr. Ruaño founded Genomas (Hartford CT) in 2003, and is the company's president. Dr. Ruaño is director of genetics research at Hartford Hospital. He also holds adjunct professorships in the medical faculties at George Washington University and the University of Puerto Rico. Dr. Ruaño founded Genaissance Pharmaceuticals in 1997, served as chief executive officer and chief scientific officer, and led the company to a public offering in 2001.

**Disclosure:**

Gualberto Ruaño, M.D., Ph.D. is president & founder, Genomas.

**ELLIS RUBINSTEIN**

President & CEO, New York Academy of Sciences

As president and chief executive officer of the New York Academy of Sciences since November 2002, Ellis Rubinstein is rejuvenating the 187-year-old institution through a series of novel initiatives. Mr. Rubinstein came to the Academy after more than 13 years with the American Association for the Advancement of Science (AAAS), where he served as editor of *Science* magazine from 1993-2002, having previously been news editor. Prior to *Science*, Mr. Rubinstein was editor of *The Scientist* and a *Senior Editor* at Newsweek. He also served as managing editor of *Science 86* (a much-honored publication that reached over 500,000 readers) and *IEEE Spectrum* (the principal magazine of the Institute of Electrical and Electronics Engineers). During his 3 decades as a journalist and editor, he was thrice honored by National Magazine Awards.

**Disclosure:**

None.

**STEPHEN SAMMUT**

Venture Partner, Burrill & Company

Mr. Sammut is venture partner, Burrill & Company, a San Francisco based life science merchant bank, and senior fellow, Wharton Entrepreneurial Programs and Health Care Systems. At Burrill & Company, Mr. Sammut manages Asia -Pacific venture activity. At the Wharton School he teaches venture capital management, corporate development, mergers and acquisitions, biotechnology entrepreneurship, intellectual property strategy, and private equity in emerging markets, and a special seminar on private sector participation in international health. He works actively with a student-alumni organization called Wharton Health International Volunteer Program. Mr. Sammut previously held the positions of vice president of development of Teleflex Incorporated and at S.R. One, Ltd., GlaxoSmithKline's venture capital fund, and also served as managing director of the Center for Technology Transfer at the University of Pennsylvania. He is co-founder and former chief executive officer of the Philadelphia Organ Transplant Program. He holds degrees in biology and humanities from Villanova University, attended Hahnemann Medical College for two years and holds an M.B.A. from the Wharton School.

**Disclosure:**

None.

**DAVID SHLAES**

Executive Vice President, Research & Development, Idenix Pharmaceuticals

Dr. Shlaes has had a thirty year career in anti-infectives spanning academia and industry with a long standing scientific interest in antimicrobial resistance. Dr. Shlaes graduated from Case Western Reserve University of Cleveland with a Ph.D. in 1975 and an M.D. in 1976. After completing post-graduate training in Cleveland in 1980, he joined the faculty of CWRU in the Division of Infectious Diseases. In 1984 he became chief, Infectious Diseases Section and in 1991 he was appointed professor of medicine at Case Western Reserve University. In 1996, Dr. Shlaes

moved to industry where he was vice president for infectious diseases at Wyeth Research for six years. In 2002, Dr. Shlaes became executive vice president, research and development for Idenix, Pharmaceuticals, a company located in Cambridge, MA focused on the discovery and development of antivirals. In 2005, he left Idenix to form a consulting company for the pharmaceutical industry (Anti-Infectives Consulting, LLC). Recent responsibilities have included the IDSA Taskforce on antimicrobial availability, the NIH RCE for Biodefense study section, the Manhattan Institute's Task Force on FDA Reform and the Alliance for Biosecurity of the University of Pittsburgh.

### *Disclosure:*

Currently, Dr. Shlaes consults for a number of pharmaceutical companies and investor groups including Idenix Pharmaceuticals, Actelion Pharmaceuticals, and Novoxel where he is a non-executive director.

### **JOHN SWEN**

Executive Director, U.S. Science Policy & Public Affairs, Pfizer Global Research

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John Swen is executive director, U.S. Science Policy and Public Affairs at Pfizer. He co-chairs Pfizer's Research, Science Policy, and Regulatory team and also represents the R&D organization on the U.S. and Global Policy Coordinating Committees. Prior to joining Pfizer in 2001, John held a series of senior posts in the biotechnology industry, as chief operating officer for Modex Therapeutiques, in the computer industry, and in government, where he served for three years in Governor Lincoln Almond's cabinet as director of economic development. John received his B.A. in English from Columbia College, and his M.S. in Management of Information and Technology and Strategy from MIT's Sloan School of Management.

### *Disclosure:*

Mr. Swen is executive director, U.S. Science Policy & Public Affairs, Pfizer Global Research.

### **MICHAEL WEBER, M.D.**

Associate Dean, Professor of Medicine, State University of New York

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Michael A. Weber, MD is professor of medicine at the SUNY Downstate College of Medicine in Brooklyn, New York. He received his medical degree from

Sydney University in Australia. His career has been focused primarily on hypertension and preventive cardiology. He has published numerous research articles in the medical literature and has authored or edited 16 books. Together with Dr. Suzanne Oparil, he is responsible for the widely used reference volume, Hypertension.

Dr. Weber was one of the founders of The American Society of Hypertension and has served as its President. He also served as chair of the ASH Hypertension Specialists Program. He is a fellow of The American College of Physicians, The American College of Cardiology and The American Heart Association. He has served on the Cardiovascular and Renal Drugs Advisory Board of the Food and Drug Administration, and continues as a consultant to that Agency. He has also served for ten years as Chairman of the Formulary Committee of a major pharmacy benefits provider serving many of the leading health plans in the United States.

### *Disclosure:*

Dr. Weber serves as a consultant and provides medical education services for members of the pharmaceutical industry.

### **RAY WOOSLEY**

President & CEO, Critical Path Institute

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Raymond L. Woosley earned a Ph.D. in Pharmacology from the University of Louisville and an M.D. from the University of Miami. Dr. Woosley specialized in Internal Medicine and Clinical Pharmacology at Vanderbilt University where he rose to the rank of professor of medicine. At Georgetown University he served as chairman of the Department of Pharmacology and associate dean for clinical research. In 2001 he became vice president for health sciences at the University of Arizona and Dean of the College of Medicine. In January of 2005 he assumed the position as president and chief executive officer of The Critical Path Institute (C-Path), a publicly funded, non-profit corporation formed to work with the FDA on the critical path initiative.

### *Disclosure:*

None.

**BRIAN ZAMBROWICZ**

Senior Vice President, Genomics, Lexicon Genetics

Brian P. Zambrowicz, Ph.D. has been the executive vice president of research at Lexicon Genetics since August 2002. Dr. Zambrowicz served as senior vice president of Genomics from February 2000 to August 2002, vice president of research from January 1998 to February 2000 and senior scientist from April 1996 to January 1998. While at Lexicon, Dr. Zambrowicz has been in charge of the large-scale genetics program involving the production and phenotypic analysis of knockouts to identify novel mechanisms for treating human disease. This work has resulted in numerous small molecule and antibody-based drug development programs. Dr. Zambrowicz has been leading Lexicon's antibody drug development efforts. From 1993 to April 1996, Dr. Zambrowicz served as a National Institutes of Health, or NIH, postdoctoral fellow at The Fred Hutchinson Cancer Center in Seattle, Washington, where he studied gene trapping and gene targeting technology. Dr. Zambrowicz received his B.S. in Biochemistry from the University of Wisconsin. He received his Ph.D. from the University of Washington, where he studied tissue-specific gene regulation using transgenic mice.

***Disclosure:***

Dr. Zambrowicz is vice president of Genomics at Lexicon Genetics, a drug discovery company.

CENTER FOR MEDICAL PROGRESS

Paul Howard  
MANAGING EDITOR  
*Medical Progress Today*

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The Center for Medical Progress is dedicated to articulating the importance of medical progress and the connection between free-market institutions and making medical progress both possible and widely available throughout the world. It encourages the development of market-based policy alternatives to sustain medical progress and promote medical innovation.

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