One of the most pressing issues that confronts the Food and Drug Administration (FDA) is learning how to better address and assist in medical product development. FDA needs to prepare today so the agency can efficiently evaluate the technologies of tomorrow. Clearly, this is an area that impacts not only health care consumers but also our economies and financial markets. If the FDA can be a more aggressive part of the solution, they can help not only ease some of the pressures that are driving up health care costs but also help all of us to maximize the value of medical innovations.

The high cost of research and development is forcing many companies to make the short-term business decision to focus product development on those molecules that have a much higher potential to recoup expenditures. Unfortunately, this trumps attempts to develop potentially risky but breakthrough products for diseases affecting smaller populations, the orphan drugs. FDA’s critical path initiative will enable innovative growth companies to better and more efficiently attack the steep hurdles facing them, allowing them to compete more effectively against the bigger, better-funded players in the market on a more level playing field. That means a real change in the risk/benefit equation for both the emerging growth companies and the public health.

**Keywords:** FDA, innovation, medical devices, pharmaceuticals, research and development

I. INTRODUCTION

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The new sciences of genomics and proteomics have the very real potential to result in a new kind of medicine—personalized medicine—capable of tailoring highly effective treatments against the underlying causes of specific diseases in individual patients—and perhaps even preventing those diseases from occurring or progressing in the first place.

New engineering applications of nanotechnology can get the right treatment to the right place in discrete individuals with far fewer side effects and complications than in the past. And next-generation information technology can turn the explosion of health information into a life-saving database at the fingertips of health care providers and patients, facilitating better informed, far more effective decisions that improve health and safety and do so cost-efficiently.

But the hard truth is that many of the most dramatic scientific advances in basic research are difficult to translate into safe and effective medical treatments for patients. A disturbing trend is unfolding. Despite the increase in research and development (R&D) spending, the number of new innovative products being submitted to the FDA for approval is decreasing. In fact, output of new products has been dropping since 1997. FDA is now receiving fewer applications for new drugs than in mid-1990s. The number of new device applications is also decreasing (FDA, 2004).

And the rate of failure is increasing. Almost 50 percent of applications are failing in late-stage Phase 3 trials (DiMasi, Hansen, and Grabowski, 2003). This costs companies millions of extra dollars and is driving up the cost of successfully bringing a new drug to market. In 2003, researchers at Tufts Center for the Study of Drug Development estimated these costs to be $802 million, and some sources suggest that the total cost is closer to $1.7 billion (Singh and Gilbert, 2002).

As the late U.S. Senator Everett Dirksen once said, “A billion here and a billion there, and pretty soon you’re talking about real money” (Dirksen Center, 2006).

The high cost of R&D is forcing many companies to make the short-term business decision to focus product development on those molecules that have a much higher potential to recoup expenditures. Unfortunately, this trumps attempts to develop potentially risky but breakthrough products for diseases affecting smaller populations, the orphan drugs.

- Net/Net, this means fewer new products are reaching patients who desperately need them.
So, despite all of the wonderful science, challenges to therapeutic development are preventing us from fully realizing the promise of the Biomedical Century.

Much of the problem can be summed up in one word—uncertainty.

II. FDA IS WORKING ON A REMEDY—PREDICTABILITY

The agency has taken some unprecedented steps over the past year and a half to help address this problem, working to improve the pathways along which medical innovation must travel from bench to bedside.

On the top of the list are various initiatives to speed review times. FDA has publicly committed to reducing total review time for new drugs and biologics across the board by approximately 10.5 percent. FDA’s initiatives also incorporate efforts to improve the processes that researchers and manufacturers use to develop innovative products. The tools of the translational trade so to speak.

The agency is making good headway in various key elements of their innovation initiative.

First is the development of “quality systems” for review procedures. The plan is to build on FDA’s professional staff expertise to identify and apply best management practices. FDA is moving forward not only to reduce the time it takes to review new treatments but also to help product developers get their applications right the first time—to do the R&D work that demonstrates safety and effectiveness as quickly and efficiently as possible.

Second, FDA is working on new guidance documents in critical medical areas. The idea is to bring together experts in government, academia, and the private sector to design a better pathway for developing new treatments—to make sure that the clinical end points for studies, the study designs themselves, and the whole clinical development process is as clear and predictable as possible for both scientists and clinicians. Over the past year, the agency introduced new guidances on integrating pharmacogenomic testing into the drug development processes, and on investigational new drug (INDs) exemptions for studies of lawfully marketed cancer drugs and biological products, as well as a draft guidance for reviewers of human somatic cell therapy INDs.

Efforts also include updating the way that medical products are manufactured. Best practices in manufacturing methods throughout the global economy have undergone historic progress over the past 25 years, particularly in the high-tech industries, through their implementation of “six sigma” and other quality improvement methodologies. Regulators should not be too proud to learn from the best because health care consumers deserve the best. New regulations must encourage quality improvements in medicine. New regulatory approaches must be designed to encourage companies to
continuously seek out and apply cost-reducing and precision-enhancing innovation in manufacturing and technology.

FDA is also conducting a root cause analysis for product approvals that require more than one review cycle and many months of additional development time. Evidence shows that upfront, focused communication with product developers about FDA expectations can help developers get their applications right the first time around. And there are several new pilot programs underway to pursue earlier communication with product manufacturers. Predictability is a team effort.

Twenty-five years ago, the success rate for a new drug used was about 14 percent (FDA, 2004). Today, a new medicinal compound entering Phase 1 testing—often after more than a decade of preclinical screening and evaluation—is estimated to have only an 8 percent chance of reaching the market (FDA, 2004). For very innovative and unproven technologies, the probability of an individual product’s success is even lower. “We have got to work together to turn that around.”

For all that modern science has to offer, developing new treatments is still very much an art—in which hunches, intuition, and luck play a critical role. The odds are long. For medicine that is affordable and innovative, we need more well-understood science and we need regulatory predictability. Which brings us to a discussion of the FDA “Critical Path” program.

“Critical Path” refers to the translational hurdles that medical products such as drugs, biologics, and devices must negotiate as they move from laboratory concept to the actual commercialized treatments that make a real difference in patients’ lives. The critical path encompasses not only the science of developing drugs and devices and other medical products but also the know-how for turning an experimental medicine into a finished product that can be used safely and effectively.

Better, more current and predictable scientific research and standards must be developed and devoted to streamlining the critical path. Investment in basic research is not enough. Specifically, new development tools are needed to improve the predictability of the drug development cycle and to lower the cost of research by helping industry identify product failures earlier in the clinical trials process. When Thomas Edison was asked why he was so successful, he responded, “Because I fail so much faster than everyone else.”

The FDA’s critical path report finds that updated development tools are needed in three critical areas: product safety, medical utility, and manufacturing (FDA, 2004). New development tools in these areas will enable better throughput to commercial product development and will act as a productivity multiplier, increasing the returns on public and private investment in basic research.

With improved scientific methods and a new, shared effort by all of us, I believe we can develop and improve standards for product characterization and product safety testing, for both traditional and innovative products. For example, by applying genomic and proteomic techniques, we can develop
FDA and Critical Path to Twenty-first-century Medicine

safety assessment programs for new biomaterials. With better scientific methods, we can develop better animal models, new biomarkers, and surrogate end points for clinical safety and effectiveness.

Today only about 1 percent of the proteins in blood have been identified (Crawford, 2004). Of that 1 percent only 20 percent have FDA-approved diagnostic utility (Crawford, 2004). These proteins, after we understand them, could help accurately predict disease remission. Currently, academics and private companies collect data and establish correlations, but no one is responsible for organizing this information into the broader knowledge that could lead to generalized principles for industry and FDA could use for broader, faster, and more accurate product evaluation.

Think about the millions of Dollars, Pounds, and Euros that would be saved by all types and sizes of companies and governments if publicly discussed and vetted biomarkers could be used predictably in the drug approval process.

In partnership, regulators, industry, and academia can apply modern engineering and cutting-edge scientific knowledge to medical product manufacturing. In partnership, we can improve standardization and automation of clinical research. And in partnership, we can develop novel and improved clinical trial designs and analytical methods for evaluation of safety and effectiveness that can reduce costs. Currently, 50 percent of drugs that undergo large-scale Phase 3 trials turn out to be too unsafe or not effective enough for marketing (Lesko, 2004). That is not a sustainable model for the twenty-first century.

Consider the implications if FDA could help companies to fail faster. Using the lower end of the Tufts drug development number:

- A 10 percent improvement in predicting failure before clinical trials could save $100 million in development costs.
- Shifting 5 percent of clinical failures from Phase 3 to Phase 1 reduces out of pocket costs by $15–$20 million.
- Shifting one-fourth of failures from Phase 2 to Phase 1 would reduce out of pocket costs by $12–$21 million.

FDA’s critical path activities and research must complement, not compete with, what industry and other regulatory agencies in the United States and around the world and are already doing.

I believe that FDA should assume an organizational role because FDA is at the crossroads of the translational process. FDA is uniquely suited to take a major role in this effort because of their unique cross-industry and cross-cutting knowledge of the hurdles companies and products encounter that are causing them to fail in late-stage clinical trials. FDA has the technical expertise that can draw together stakeholders, help prioritize research that is most needed, and to partner with others to conduct this research. Obviously, solutions will have to come from sources with the greatest expertise. This
could entail contracting with academic organizations, private industry, and other global translational research groups.

FDA’s critical path initiative will enable innovative growth companies to better and more efficiently attack the steep hurdles facing them, allowing them to compete more effectively against the bigger, better-funded players in the market on a more level playing field. That means a real change in the risk/benefit equation for both emerging growth companies and the public health.

We all know that emerging life sciences companies face substantial obstacles to product development. Smaller firms do not have the luxury of pouring more and more dollars into riskier, potentially breakthrough products. They may have the most innovative science in the world, but if their burn rate is too high and if the money runs out, their breakthrough technologies either (a) get stopped dead in their tracks or (b) get bought by the bigger boys with the deeper pockets.

Consider FDA’s critical path initiative as a revised game of shoots and ladders. Rather than relying on a roll of the dice, FDA can be a bridge over the shoots and a guide to the ladders.

The most important tool is collaboration. Regulators must embrace stakeholders as partners in the public health process.

The bipartisan crown jewel of current FDA reform legislation is the Reagan/Udall Foundation (also known as “the Critical Path Foundation”). Approved by the U.S. Congress and signed into law in September 2007, the Foundation is designed to streamline and improve the development of drugs and medical devices—allowing the FDA work with both industry and academia to accelerate the nascent sciences of genomics and proteomics to help realize the very real potential of a new kind of medicine—personalized medicine—capable of tailoring highly effective treatments against the underlying causes of specific diseases in individual patients—and perhaps even preventing those diseases from occurring or progressing in the first place.

According to Senator Ted Kennedy, a cosponsor of the bill, the Reagan-Udall Foundation “will make new research tools and techniques available to the entire research community, shortening the time it takes to develop new drugs and reducing costs for patients” (quoted in The Associated Press, 2007).

Recently, congressional hearings were held about the growing gap between the scientific resources the FDA has at its disposal and the various responsibilities to both police and improve the public health. The hearings followed a searing report by the FDA’s Science Advisory Board that concluded, “FDA’s inability to keep up with scientific advances means that American lives are at risk.” The problem: Congress adds new responsibilities but not the corresponding resources even as it blames the FDA for falling short of the new regulations it must enforce.

Science Board member Garret FitzGerald, a University of Pennsylvania pharmacology professor, cites a “cabal of congressional majorities and presidential
administrations that has serially stripped the agency of assets.” When politicians even drive away the agency’s private support and voluntary participation, you know that at the heart of the FDA’s problem are pols willing to attack the agency for political gain.

The Science Board points to the dire need for the FDA to collaborate with academic and private-sector scientists as part of the agency’s critical path initiative to use twenty-first-century science to make drug development safer and more predictable.

Yet Rep. Rosa DeLauro, chairman of the appropriations subcommittee controlling the FDA budget, stripped $1 million for the FDA’s nonprofit Reagan-Udall Foundation, which Congress created to support such teamwork. The congresswoman, who took home to Connecticut $25 million in earmarks, blocked funding because she thinks certain individual appointments to the Foundation, which has no regulatory authority, have conflicts since they work with industry. Considering the Foundation is designed to promote collaboration, it would be a surprise if they did not have such ties.

Now a program to establish guidelines on how to use genetic tests called biomarkers to predict who responds best to cancer drugs could be delayed for months as the Foundation scrounges for money. Worse, Rosa DeLauro is on record as claiming biomarkers are weak measures of a drug’s effectiveness even as the director of the NIH National Human Genome Research Institute, Dr. Francis Collins, hails them as the next revolution in medicine.

Most Americans agree with Dr. Collins. A recent survey released by the Center for Medicine in the Public Interest found that nearly 90 percent of all Americans support the critical path initiative and the development of biomarkers. But the congresswoman’s attack on the FDA reflects poorly on both her political and her scientific judgment. The FDA cannot meet its responsibilities if it has to protect itself from politicians like Rep. Rosa DeLauro.

We must blaze the critical path together. Regulators and industry, patient groups and legislators, and FDA and European Medicines Agency (EMEA) must work together to help bridge the widening canyon between bench and bedside. As FDA’s bioinformatics and biomarker capability increases, its scientific abilities will be strengthened by being deeply and consistently engaged in collaborative drug evaluation development work. Intra- and extramural work must become one in the same, must meet and help develop scientific standards and be part of a program of creating support for guidance, end points, etc. We must use the mantra of the agency’s current antagonists that FDA must be governed by science not politics and use it to our advantage to create a new gold standard for how evaluation should be conducted. With respect to the overall critical path matrix, we may wish to also consider how the FDA undertakes the process of identifying relevant public health and medical needs and opportunities. Since we expect the initial list of critical path issues from the FDA shortly, this also gives us a
ready-made point of departure. I recently had the privilege of a private meeting with Nobel Laureate Joshua Lederberg. The topic of conversation was the future of the FDA and the agency’s critical path initiative. We talked about the state of applied research and “the texture” of the agency, the prioritization of development science, biomarkers, and a host of other future-oriented issues. He talked. I took a lot of notes. At the end of the meeting, he put everything into perspective in a single sentence. He leaned over the table and said, “The real question should be, is innovation feasible?” I hope so.

III. IMPORTANT TAKEAWAY POINTS

1. Better, more current and predictable scientific research and standards must be developed and devoted to streamlining the critical path. Investment in basic research is not enough. Specifically, new development tools are needed to improve the predictability of the drug development cycle and to lower the cost of research by helping industry identify product failures earlier in the clinical trials process.

2. New development tools in these areas will enable better throughput to commercial product development and will act as a productivity multiplier, increasing the returns on public and private investment in basic research. With improved scientific methods and a new, shared effort by all of us, we can develop and improve standards for product characterization and product safety testing, for both traditional and innovative products.

3. Regulators, industry, and academia can partner with the goal of improving standardization and automation of clinical research— in effect targeting “cures” for the development process itself. Such a partnership—with a forceful mandate for change—would seek to apply modern engineering and cutting-edge scientific knowledge to medical product manufacturing.

4. The critical path must be blazed in partnership. Regulators and industry, patient groups and legislators, and FDA and EMEA must work together to help bridge the widening canyon between bench and bedside. We are in the right place at the right time to make a real difference to global public health in the twenty-first century. One of the most pressing issues that confronts the FDA is learning how to better address and assist in medical product development. FDA needs to prepare today so the agency can efficiently evaluate the technologies of tomorrow.

REFERENCES


