Associate Editor's Commentary: Innovation Nation

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"Change is not required," wrote marketing guru W. Edwards Deming. "Survival is not mandatory."

If we learn nothing else from BP's recent unpleasantness, it is that being able to identify an obvious problem (eg, when oil is gushing uncontrolled into the Gulf of Mexico) is one thing. Identifying a potential problem is tougher. Toughest of all, however, is designing a solution that addresses a need early in the curve. Consider Alzheimer disease, a health care oil spill of draconian proportion. As Gina Kolata (1) wrote in the *New York Times*, "The failure of a promising Alzheimer's drug in clinical trials highlights the gap between diagnosis—where real progress has recently been made—and treatment of the disease." Recent significant steps forward in early diagnosis of the disease are important, and also frustrating, because there is still precious little that can be done when this devastating condition is identified either late in the game or in its nascent stages.

To call the science hard (while true) is not particularly helpful. What needs to be addressed are the twin issues of drug development and regulatory science. Both are lagging. Biomarkers notwithstanding, more needs to be done. We need better tools. Too many development programs (almost 50%) are failing in late phase 3. Too many programs are mired in regulatory treacle. The economics are unsustainable from a corporate R&D standpoint and the impact of Alzheimer disease and other diseases on patients, their families, and American health care economics is devastating. Better, more current, and more predictable scientific research and standards must be developed and devoted to streamlining the critical path. Investment in basic research is not enough.

Twenty-five years ago, the success rate for new drugs was about 14%. 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% chance of reaching the market. 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. The costs of development also continue to escalate. In 2003, researchers at Tufts Center for the Study of Drug Development (CSDD) estimated the costs to bring a new medicine to market to be $802 million (2). More recent authoritative estimates are well over the $1 billion mark, going as high as $1.7 billion.

When Thomas Edison was asked why he was so successful, he responded, "Because I fail so much faster than everyone else." Consider the implications if FDA could help companies to fail faster. Even using the lower CSDD 2003 estimate just noted ($802 million), the following figures are illuminating:

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

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New development tools are needed to improve the predictability of the drug development cycle. 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 better-understood science and we need regulatory predictability, which is precisely the mission of the FDA's still-nascent Reagan-Udall Foundation. To quote the late Senator Ted Kennedy, 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."

A properly funded FDA will be able to do more things with greater ability and alacrity. A properly funded FDA will be able to more aggressively pursue the regulatory science so essential for 21st-century drug development. The Critical Path doesn't come cheap, but it is worth it. Better, more current, and predictable scientific research and regulatory standards must be developed and devoted to streamlining the Critical Path so that we can lower the cost of research and help industry identify product failures earlier in the clinical trials process.

There are some tough but important basic principles when it comes to innovation in health care technologies.

Innovation is slow. As any medical scientist will tell you, there are few "Eureka!" moments in health research. Progress comes step by step, one incremental innovation at a time. Biopharmaceutical companies more often profit by improving existing molecules and making processes more efficient than by revolutionizing the whole field with new miracle products. Discontinuous innovation is the wonderful exception to the rule.

Innovation is hard. Today it takes about 10,000 new molecules to produce one FDA-approved medicine. This observation itself is disconcerting, but, further, only 3 out of 10 new medicines earn back their R&D costs. Moreover, unlike other R&D-intensive industries, biopharmaceutical investments generally must be sustained for over 2 decades before the few that make it can generate any profit.

Innovation is expensive. We have already discussed development costs.

Innovation is under attack. From accusations of the "me-too" variety, to questionable schemes to replace pharmaceutical patents with a prize system, life for innovator pharmaceutical companies is rough and tough. Israel Makov (formerly the Big Abba of generics giant Teva) once told me that he wasn't really in the pharmaceutical business, but rather "in the litigation business," and he made this comment before the reality of biosimilars.

Nonetheless, innovation is important. This is true for more than just biopharmaceutical industry profits. In the United States, increases in life expectancy resulting from better treatment of cardiovascular disease from 1970 to 1990 have been conservatively estimated as bringing benefits worth more than $500 billion a year. In 1974, cardiovascular disease was the cause of 39% of all deaths. Today it is about 25%. Cerebrovascular diseases were responsible for 11% of deaths back then. In 2004 they caused 6.3% of deaths. Kidney diseases were linked to 10.4% of deaths and now are associated with 1.8%.

As Harvard University health economist (and health care advisor to President Obama) David Cutler has noted: "The average person aged 45 will live three years longer than he used to solely because medical care for cardiovascular disease has improved. Virtually every study of medical innovation suggests that changes in the nature of medical care over time are clearly worth the cost" (3). Innovation must not be only about medicines. We have to embrace innovative technologies for medical records and prescribing. We need innovative clinical trial designs and molecular diagnostics so that we can develop better, more personalized medicines faster and for far less then the current $1 billion-plus delivery charge. We need innovation in access and reimbursement policies that rewards speed to best treatment rather than lower-cost patients per hour.

These considerations lead to the conclusion that we must start taking innovation, both in-

cremental and discontinuous, seriously, which means spending more on harder developmental R&D (with concomitant higher investment risks). Currently, lip service is being paid to the need for more robust comparative effectiveness—although this is a battle yet to be either defined (comparative effectiveness, cost effectiveness, or clinical effectiveness?) or fought (do we need a US version of NICE?). It will indeed be a battle royale. In the words of Frederick the Great, "L'audace, l'audace, toujours l'audace."

When it comes to health care reform, this is not even the end of the beginning. We need to keep our eye on the prize, that is, innovation that focuses on creating a chronic health care culture that embraces prevention and prophylactic care. We will not survive as a nation of obese, hypertensive diabetics. Rather than wasting time on Beltway spin, redoubling our efforts on innovation is far preferable.

In December of last year, Eli Lilly & Co president and CEO John Lechleiter was the biopharmaceutical industry's representative at President Obama's business leaders summit on how to encourage US job growth and economic recovery. During the meeting, Lechleiter discussed the life sciences innovation hub in Lilly's home state of Indiana, holding it up as a model for how to advance health care technology innovation across the country and, indeed, around the world. I encourage us to embrace that theme and make the 2011 health care discussion all about innovation, because that is the sine qua non here.

Shortly before his death, I had the privilege of a private meeting with Nobel laureate Joshua Lederberg. We talked about the state of applied science, the prioritization of development science, biomarkers, and a host of other future-oriented issues. 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, and so should we all. Innovation equals hope.

REFERENCE

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