REGULATION

Biomedical Innovation: A Risky Business at Risk

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Regulatory and financial challenges conspire to stall the development and market approval of breakthrough medical products. Inconsistent parameters are used to assess the safety and efficacy of drugs, biologics, and devices; this glitch in the system introduces uncertainty, slows or blocks product approvals, and increases the costs of product development. Here, we consider how to balance the benefits and risks to the public in the assessment of innovative medical products. We also discuss the Institute of Medicine's recent report on the medical device approval process.

Recently, Aaron Kesselheim at the Harvard University Department of Health Policy and Management noted that U.S. Food and Drug Administration (FDA) approvals for new drugs and biologics have decreased substantially; there was a 39% reduction in approvals during the period from 2005 to 2009 as compared with a decade earlier (1995–1999). Paradoxically, this decrease in approvals occurred despite the investment of billions of dollars in public and private funding for research and development (*1*). The Kesselheim commentary builds on an earlier report from the U.S. Government Accountability Office (GAO) that noted that scientific, business, and regulatory issues all contribute to the challenges associated with the development and ultimately the market approval of novel therapeutics (*2*). In the regulatory arena, an important contributor to the decline in new device approvals specified in the report is the marked uncertainty associated with the medical products approval process. A key recurring challenge is inconsistency, ambiguity, and even discordance in the parameters used to define "effective and safe" drugs, biologics, and devices. Thus, it has become a major societal issue to assess the current regulatory approaches for clinical and translational science and to use this information to redefine and implement a new, consistently applied regulatory framework for the development of innovative products. Here, we discuss why a new framework is needed that weighs and balances the benefits and risks to the public of pioneering medical products.

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IS THE HIPPOCRATIC OATH RELEVANT?

For centuries, the Hippocratic oath, or some pledge derived from it, has guided physicians to "first, do no harm" (*3*). This pivotal instruction, which new physicians publicly pledge to uphold before beginning professional lives devoted to the care of the sick, conveys a responsibility to avoid intentionally harming patients in the quest to heal. Prior to the publication in the early 1900s of the Flexner Report—a treatise that serves as the basis for the modern practice of medicine—(*4*) and the ensuing movement toward a scientific (evidence-based) approach to the practice of medicine, this fundamental obligation was not just philosophical; it was essential to protect patients from some of medicine's popular "cures," such as bloodletting for fever (*5*). In an age of magic, such a pledge likely referred to an abhorrence of pagan ritual and the need to embrace therapies with sound mechanistic basis or empiric support. One wonders, however, whether the oath was meant to imply that complete safety should transcend all other features of a possible cure.

In the era of science-guided therapeutic development, is it realistic to state (or even believe) that one cannot do harm in the quest to discover new drugs, biologics, or devices and define their optimal use? The concepts of respect for the autonomy of patients in decision-making, beneficence (doing what best serves the patient), justice (fair distribution of medical care), and informed consent are all critical constructs in medical research ethics. However, in an age when even the most deadly of cancers can sometimes be cured with highly potent, yet potentially deadly chemotherapeutic agents, it is perhaps time to rewrite the Oath of Hippocrates to state: "on average, try to do more good than harm" (*6*, *7*).

Our aim as innovators is not and should not be to diminish the essential requirement to protect patients' safety but rather to acknowledge that all treatments (both those being developed and those currently being used in clinical care) carry some degree of both risk and benefit. The obligation of clinical investigation is to provide high-quality scientific evidence that permits quantitative assessment of these opposing parameters. With this information, patients and their families, clinicians, and patient advocates can make informed choices among various therapeutic options.

A RISK-BENEFIT BALANCING ACT

As a case study of risk-benefit analysis, let us consider Type 2 diabetes mellitus. Controlling blood sugar in patients with diabetes is a laudable therapeutic goal. Studies have proven that control of serum glucose concentrations is associated with health benefits—for example, lowering the risk of microvascular diseases such as diabetic retinopathy (*8*). Although the optimal level of glucose control is a matter of some debate (*9*), there is little argument that diabetes is best treated through a combination of dietary manipulation, life-style changes, and drug therapies. A number of agents that control blood glucose have been developed, and several recently discovered ones such as the glitazones target specific biological pathways. Regulatory approval of such drugs has largely depended on their ability to demonstrate, in clinical trials, a favorable effect on controlling serum glucose concentrations.

The global obesity and diabetes epidemics are coupled with (and complicated by) a growing public demand for new effective diabetes medications. Partly in response to these pressures, FDA has issued a Draft Guidance document that outlines a development path for new diabetes agents that recognizes the desire for innovative therapies while acknowledging that many of the newer agents are associated with an increased risk of cardiac ischemic events. The document sets out quantitative guidance for the level of cardiac risk that must be excluded as a precondition for approval of new agents (*10*). As an example of what is now required, the draft guidance language from FDA states, "If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (that is, the risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analy-

sis supports approval, a postmarketing trial generally will be necessary to show definitively that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial." The construct accepted in this Guidance reflects the fact that these effective drugs have both benefits and risks.

INNOVATION STALLED

Drugs and biologicals. The regulatory approach described above, which uses clear risk-benefit parameters in guidance documents developed by the FDA, unfortunately has not been widely applied to all areas of therapeutics. The result of this omission is that the product approval process has become very slow, unpredictable, and extremely costly (*11*). In a recent article published in *The Boston Globe* (*12*), Robert K. Couglin, President of the Massachusetts Biotechnology Council, verbalized the vexing problem on the minds of scientists and investors alike: "If it takes a total of 12 years and over a billion dollars to get a drug from the bench to the bedside, it takes too long and it's too costly." In that same article, Senator Scott Brown of Massachusetts accused the FDA of "crushing innovation" and "throwing a wet blanket" on drug and biologics discovery and development in the United States by delaying decisions on new therapies, changing the requirements during the approval process, and being unresponsive to the needs of companies that discover and seek to sell life-saving technologies therapeutics (*12*). James C. Greenwood, President of the Biotechnology Industry Organization, added, "The FDA understands that if they approve a product that's not safe or effective, that's a failure, and we agree with that. But it's not deemed a failure if people die because [the FDA] took too long to approve a product" (*12*).

In another recent article at Forbes.com, Henry Miller, founder and former Director of FDA's Office of Biotechnology, agrees: "The FDA has become so risk-adverse and antagonistic to new drugs and to their developers that companies are moving their testing and manufacturing abroad. Approvals have shrunk to a trickle, and fewer new medicines are available to our aging population" (*13*). Together, these observations suggest that one bottleneck to pharmaceutical innovation is a regulatory process gone awry—an impediment that can be relieved by reassessment of FDA's role in terms of risk-benefit analysis and clear, consistent requirements for therapeutics approval.

Devices. FDA has traditionally separated the regulatory approval pathways for medical devices from those for pharmaceutical and biological therapeutics. The logic behind this division is that the undesired side effects and complications associated with a purely mechanical device typically manifest at the site of device implantation and can be identified fairly easily; furthermore, devices often can be removed if necessary. In contrast, the systemic nature of pharmaceuticals delivery means that these agents have the potential to cause unwanted effects at remote locations in the body (such as teratogenesis or carcinogenesis) that are difficult to identify in short clinical trial periods or small subject populations. Hence, FDA approval of devices has typically occurred on a faster time scale (ranging from several months to 1 to 2 years) than that of pharmaceuticals, which can take 8 to 10 years (*14*, *15*). Furthermore, the criteria for approval of drugs and biologics are safety, efficacy, and quality. (To be of sufficient quality, drugs and biologics must be made reproducibly and with appropriate purity and potency according to good manufacturing practices.) Devices, however, must only be shown to be "relatively safe." In an excerpt from the guidance document for device regulation, the FDA states, "Adequate data from in vitro and animal testing, demonstrating that the device is relatively safe and that it functions as intended, must be submitted before approval for clinical studies in humans will be granted" (*16*).

In fact, with the use of a process known as a 510(k) approval (*17*) FDA has traditionally provided even faster reviews with less-stringent clinical-data requirements for devices that are substantially similar to predicate devices that have been previously approved by the FDA. Novel devices to be used for new medical indications or those that hold the potential for causing major untoward complications have traditionally gone through the standard Premarket Approval Process (PMA) for devices. The PMA for devices requires relatively small, randomized, controlled clinical trials powered to detect major adverse events and assess efficacy (*16*). The main goal of the PMA, however, is to ensure that devices are not overtly harmful to the patients compared with the benefits the technology provides. Over the last 30 years, these requirements were considered to be appropriate by both physicians and members of the medical technology industry. No one wanted to see dangerous or unreliable devices unleashed on the public; yet, Americans insisted on having access to the latest technology that could potentially cure their illnesses (*18*).

This process worked extremely well in the past. Ford *et al.* reported that between 1980 and 2000, new drugs and devices yielded a 40% reduction in mortality from coronary artery disease—the number one killer in the United States (*19*). A review of FDA recalls showed that during a 5-year period from 2004 to 2009, 99.6% of all devices approved by FDA through either the 510(k) or the PMA route yielded products that remained on the market; in other words, FDA issued almost no Class I recalls—those invoked for products suspected of causing serious adverse health consequences or death (*20*). During this era, innovation in medical devices flourished in the United States, making this country the undisputed world leader in medical technology.

In recent years, rather than adhering to the "relatively safe" standard, FDA has become increasingly inclined to treat devices as if they were pharmaceuticals while at the same time expanding still further the regulatory requirements needed for the approval of small-molecule drugs and biologics (*16*). Indeed, as regulators continued not to explicitly define "relative," the loose and perhaps more common translation of relative safety is "absolute absence of toxicity." This aversion on the part of FDA to any degree of untoward complications stemming from the use of an approved product has had a crippling effect on medical innovation. There may be a variety of reasons for the current conservative trend and delays in the approval process, including poor management, personnel and expertise shortages, and an increase in the complexity of therapeutic approaches. But one immediately addressable bottleneck is the excessive fear that the regulatory approval processes will be perceived as lax and failing in its mandate to protect the public.

Very recently, the FDA announced the results of a controversial study that the agency had commissioned from the Institute of Medicine (IOM), which seemed to highlight these fears (*21*, *22*). Among other recommendations, the IOM commission

recommended that the 510(k) clearance process, in place since 1976 for medical devices, should be entirely abandoned and proposed that each new low and medium risk device would need to be evaluated "de novo" with a new clinical trial (both pre and post approval) despite a precedent of predicate devices that showed no untoward clinical outcomes from essentially similar previously approved products. This would, in effect, likely cause all medical devices to undergo the much more rigorous, expensive, and time-consuming steps currently required for a PMA approval.

Among the many critics of this study was the Washington Legal Foundation, a pro-business group, who filed a petition with the FDA arguing that the agency was statutorily barred from adopting any of the report's recommendations because of what it claimed was the panel's bias. The legal foundation argued that the Institute of Medicine had failed to balance the panel by including officials from the device industry, investment community, or patients who had benefited from devices (*21*).

The IOM recommendations also resulted in an immediate reaction from both sides of the aisle on Capitol Hill (*23*). Senator Al Franken (D) said, "Calling for the elimination of the 510(k) process could be very harmful to innovation. The report's recommendations would impose new burdens on the medical device industry, without a clear path to a more effective process." Senator Amy Klobuchar (D) added, "Scrapping the 510(k) process entirely isn't what our businesses want and could limit access to life-saving products" (*23*). U.S. representative Erik Paulsen (R), cochair of the house Medical Technology Caucus, remarked, "The 510 K review process has long been regarded as a safe and effective way to bring much-needed life-saving products to the market. Eliminating it, as the IOM suggests, would … give Europe another leg up in competing for these made-in-America technologies. What the medical devices manufacturers need is consistency in the approval process, not more uncertainty. Instead of replacing 510(k), I intend to work with innovators, physicians, and other stakeholders to streamline the device clearance process at the FDA."

In the European Union (EU), devices are approved through a process referred to as CE Mark ("Conformité Européenne") approval. No more untoward results have been reported for devices approved for commercial release in the EU relative to those approved by FDA. In recent years, however, using CE Mark approval as a benchmark, FDA has become progressively risk adverse, resulting in protracted delays and extreme, often prohibitive, costs to gain approval for commercialization in the United States. This trend has severely delayed and in some cases completely blocked potentially life-saving devices (for example, percutaneous aortic valves) from reaching the American public (*18*).

Two recent articles reported results of a survey of more than 200 medical technology companies with recent experience in attempting to gain regulatory approval in both the EU and the United States (*24*, *25*). These companies represent approximately 20% of all U.S. public and venture-backed medical device manufacturers. Eighty-five percent of survey respondents found the EU authorities to be highly or mostly transparent, whereas only 27% of respondents rated the FDA in this category; similarly, 85% found the EU highly or mostly predictable versus only 22% for the FDA. The quality of being highly or mostly reasonable was characteristic of the EU according to 91% of respondents versus 25% for the FDA. The time required for approval of the respondents' low-risk devices in the EU was on average ~2 years shorter than that required in the United States; for higher-risk devices, the difference was 3.5 years. Some delays at FDA can be blamed on lack of appropriate management. As an example, one-third of respondents reported that crucial FDA staff members or physician advisors missed key meetings with the company, and almost half of respondents experienced untimely changes in key FDA personnel, including lead reviewers of a project or branch chiefs responsible for evaluating a product.

Although this study has limitations—including a potential bias based on who chose to respond to the survey—it represents the most direct comparison of the current regulatory climates experienced by a large number of U.S. device manufacturers. The survey's data and analyses—verified independently by PricewaterhouseCoopers—suggest one impetus for a disturbing current trend: Medical technology companies, entrepreneurs, and physician-innovators, who together over the past three decades made the United States the undisputed world

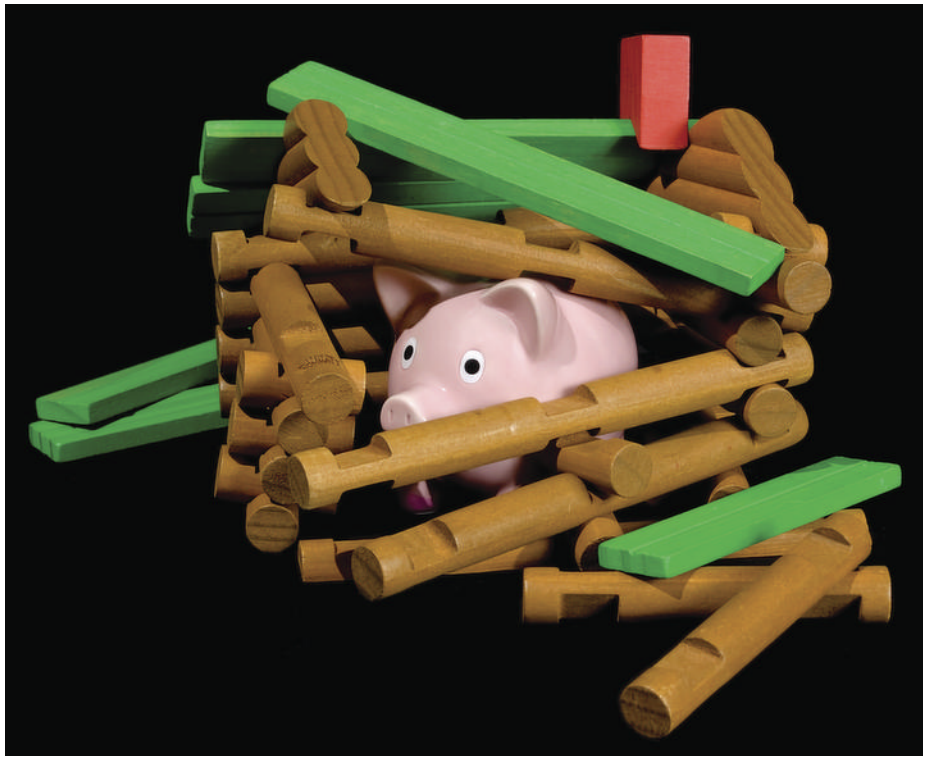

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Fig. 1. Live strong. The thoughtful and industrious little pig—of *Three Little Pigs* fame—had nothing to fear; he weighed the risks and benefits of building a house of bricks and fared better against the wolf than did his neighbors who built their homes of weaker raw materials. Similarly, a strong FDA can properly assess the risks and benefits to the public of new medical products and offer consistent direction to scientists, leading to faster, rather than slower, robust regulatory decisions.

leader in innovation, are now abandoning the American market and its patients in favor of the much more reasonable regulatory approval processes overseas (*12*, *13*).

Robust regulation. A strong FDA with sufficient resources and expertise can properly assess the risks and benefits to the public of new medical products and can provide clear and consistent direction to innovative companies, leading to robust regulatory decisions dispensed in a reasonable timeframe (Fig. 1). The role of FDA as the regulator of health care products is to ensure that they are effective and safe. It ought to be FDA's obligation to rigorously assess the balance between "effective" and "safe," preferably by requiring clinical trials that measure and aggregate meaningful clinical endpoints so that the data can be clearly understood by providers who are considering use of the products in their patients.

ENGAGING THE PUBLIC

It is clear that Americans value having choices and options, including in decisions related to their medical care. Given the complexity of the scientific issues that support diagnostic and therapeutic interventions coupled with the vulnerabilities associated with illness, the health care system can never be completely market-driven. Still, health care providers and the public deserve the opportunity to engage in fact-based discussions around health care choices. Those at the health care–consumer table should assess the scientific evidence in the context of their own state of health and lifestyle choices while also considering society's obligation to pay for health care.

A major challenge to this scenario is the relative lack of sophistication among the American people in understanding even basic quantitative concepts such as probability, estimates, and confidence intervals. Politicians, the public, and the medical community all need education in the area of statistical analysis in order to understand risk assessment and to manage expectations when it comes to medical products. The prevalence of lawsuits directed toward pharmaceutical and medical technology corporations whenever any untoward outcome occurs adds to the perception of the public that any sort of risk is never to be tolerated. Our politicians are also quick to stand before their constituents and loudly accuse biomedical companies of being irresponsible and FDA officials of malfeasance if anything whatsoever goes wrong. All of these realities help to fuel the naïve public notion that life-saving drugs and devices must be no less than perfect agents that cure or prevent illness with no risk of side effects. The truth is that we live in an imperfect world; if there is no risk, there is likely to be no benefit.

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10.1126/scitranslmed.3002459

Citation: R. S. Stack, R. A. Harrington, Biomedical innovation: A risky business at risk. *Sci. Transl. Med.* **3**, 96cm23 (2011).

Science Translational Medicine

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Sci Transl Med **3**, 96cm2396cm23.
DOI: 10.1126/scitranslmed.3002459