PART SEVEN

New Wine in Old Bottles

FDA's Role in Regulating New Technologies

Introduction

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THE BEST word to describe the U.S. Food and Drug Administration's (FDA) role in regulating new technologies is "complicated." Perhaps the words "very complicated" would be better, modified by terms like "difficult," sometimes "controversial," and on occasion even "fraught." Many of the regulatory stakeholders are organized, powerful, and politically sophisticated, and can constitute a potential impediment to the scientific integrity on which the agency prides itself. On a bad day, contemplating stumbling blocks like congressional gridlock, one could think the best descriptive word for FDA's regulatory role vis-à-vis some innovations might be "impossible." But on a good day, you could say that emerging technologies are simply challenging FDA to come up with creatively forward-thinking processes that fit the demands and opportunities presented by ground-breaking twenty-first century medicine.

The five chapters in this part, dealing with such disparate subjects as computerized medical devices, regenerative medicine, direct-to-consumer genetic testing, e-prescribing, and the appropriate use of racial and ethnic categories in biomedical contexts, share a common

theme: FDA's current regulatory approach to medical technology leaves something to be desired. The first three chapters examine technological advances already in play, where the agency is trying to adapt existing legislation and rulemaking to innovations undreamed of when they were enacted—new wine in old bottles, as it were. The last two chapters, suggesting improvements in FDA's stance regarding pharmacovigilance and the role of race in research, are more sui generis.

Computerized medical devices have been around in one form or another for decades but lack an explicit regulatory categorization. FDA's method for regulating them has been quite different from its recent attempts to rein in direct-to-consumer (DTC) genetic testing and regenerative medicine, the new kids on the innovation block. As Cortez points out in his chapter, the agency has long been a "reluctant regulator" with regard to electronic device oversight, even though almost half of all medical interventions now involve computers. It has proceeded cautiously and deferentially on unfamiliar technical terrain, using nonbinding guidance documents to guide enforcement rather than straightforwardly adopting regulatory standards. With regard to regenerative medicine and DTC genetic testing, however, FDA has come out much more aggressively in what looks like an attempt to shut down at least some purveyors of these technologies.

Specifically, in 2010 FDA moved to enjoin Colorado physicians and their company from performing regenerative medical procedures wherein patients' stem cells are removed, manipulated, combined with an antibiotic, and then returned to their bodies. Although the defendants claimed their procedure, Regennex-C, was merely the practice of medicine and therefore beyond the agency's reach, FDA maintained that these treatments in fact constituted unapproved and misbranded drugs under the FDCA. The D.C. Circuit agreed with the agency's position in its 2014 *United States v. Regenerative Sciences* opinion, and permanently enjoined the defendants from utilizing the procedure. The court found that the agency also had regulatory authority under the Public Health Service Act to enjoin it because the defendants were manipulating the cells in question more than minimally. By giving FDA a clear win in this case, however, the D.C. Circuit left it with a big problem: how *should* the agency go about regulating "personalized medicine," which is destined to become far more widespread as stem cell science progresses?

Similarly, in 2013 the agency declared personal genome services to be Class III devices (i.e., those medical devices raising the most serious potential patient safety problems). It ordered 23andMe, a high-profile DTC genetic testing company, to discontinue marketing genomic information because it had neither applied for nor received premarket approval (PMA) as required by the FDCA. Distinguishing raw genomic data from genetic information, which can be used to predict propensity for illness and thus fits the definition of a medical device, FDA came down hard on the company; 23andMe can no longer provide what it still advertises as "health results," such as whether the purchaser carries the gene for Parkinson's disease or BRCA, although the company's website predicts that those results soon will be available. That will depend on whether it comes up with a strategy to safeguard patient safety (i.e., diminish the risks of inappropriate or unnecessary treatment, and of depression and/or suicide accompanying potentially upsetting medical information) that will be sufficient to satisfy FDA's concerns.

Why the markedly more aggressive FDA conduct toward these two recent medical innovations than toward computerized medical devices? In the case of 23andMe, the direct-to-consumer nature of the product is undoubtedly a large factor. With no medical professionals involved to interpret potentially worrisome health results for lay purchasers, the possibilities for psychological harm and inappropriate treatment are apparent. Moreover, the high-profile company, a "darling of the tech industry" and recipient of the 2008 *Time Magazine* Invention of the Year award, has never been shy in its marketing efforts. Even today, it uses Groupon coupons to pump up the sales of "ancestry information" and raw genomic data from the vials of spit that purchasers send the company—all that the firm now provides, pending further FDA action. Questions have also been raised about the accuracy of the company's testing methods and about other uses to which consumers' genetic information might be put, which the agency must consider in any application for approval. But categorizing genetic information as a Class III device is probably overkill as a long-run regulatory strategy. As Pike and Spector-Bagdady suggest in their chapter, FDA and the public will be better served by an approach more narrowly tailored to the risks presented by specific types of genetic vulnerability.

With respect to the Regenerative Sciences stem cell procedure, FDA's original 2008 warning was spawned by the company's website claims,

accompanied by patient testimonials, that it employed the patient's own enhanced mesenchymal stem cells to regenerate bone and cartilage. The defendants were apparently the only practitioners of this untested therapy, and not only was patient safety an issue but a whiff of the snake-oil salesman permeated FDA's concern. (The defendant's website sells an "Advanced Stem Cell Support Formula" dietary supplement at $97.99 for a one-month supply.) In one sense, Regenerative was an easy target because it presented as a one-off situation. But the issue it raised about FDA's jurisdiction over regenerative medicine has far-reaching implications, as now buttressed by the D.C. Circuit's decision. In her chapter, Riley sensibly suggests that the agency consider adopting "responsible innovation" as an abbreviated pathway to approval for stem cell therapies, which are sure to proliferate as the science develops.

The fourth chapter in this section departs from the focus on the present and looks to the future in offering an ambitious plan to advance patient safety by combining e-prescribing and electronic medical records technology to improve pharmaceutical use and FDA oversight. Lamenting the agency's less-than-stellar record on pharmacovigilance, Rosenberg et al. advocate better pre- and postmarketing oversight of the way physicians actually employ approved products, including off-label use. They want to make doctors specify *why* they are e-prescribing particular medical interventions and then require them to report the medical outcomes of their treatment choices. FDA would then evaluate these data for further evidence about safety and efficacy. Their proposal is easy to state but gargantuan in its implications. Can doctors really be expected to track down the results of every prescription they write, let alone justify off-label use when it may have become the standard of care?

This far-reaching and nontrivial undertaking would require extensive and expensive physician buy-in to be effective, and doctors' opposition to taking on regulatory responsibilities they consider intrusive and onerous will be a given. Perhaps a better idea would be to start slowly by implementing a pilot program in a field like oncology, where the patient risks associated with inappropriate or ineffective therapy are higher, treatment standards are still evolving, and follow-up about the results of treatment is part of the process. The opportunity to link e-prescribing to electronic medical records to evaluate treatment efficacy and improve patient safety should not be squandered, but trying to do too much too fast seems doomed to failure.

Finally, in the last chapter Kahn uses a broad lens to examine FDA's current approach to the use of racial and ethnic categories across all of biomedicine. Pointing out that "[r]ace is not a coherent genetic concept; rather it is best understood as a complex and dynamic social construct," he compares FDA guidelines for collecting data on race and ethnicity in clinical trials with the International Conference of Harmonization's (ICH) "Ethnic Factors in the Acceptability of Foreign Clinical Data." FDA's guidelines are designed "to ensure consistency in evaluating potential differences in drug response among [U.S.] racial and ethnic groups" but explicitly warn that the categories they establish for purposes of data collection are neither genetic nor biological.

The ICH, by way of contrast, is focused on eliminating national regulatory differences in order to open up global pharmaceutical markets and "constructs race as some sort of component of a larger category of ethnicity." ICH views the more nuanced FDA guidelines as an impediment to harmonization, but Kahn's warning against having the United States adopt a "harmonized conception of race as genetic" simply to facilitate globalization is sound. He cites a memorable editorial in *Nature Biotechnology* to the effect that "[p]ooling people in race silos is akin to grouping raccoons, tigers and okapis on the basis that they are all stripey." Point made. In black and white.

Few knowledgeable people would argue that FDA is not an overworked and underfunded government agency, given its vast regulatory responsibilities encompassing at least a quarter of the U.S. economy. New medical technologies are constantly pushing the regulatory envelope, creating new agency challenges for effective oversight. The five provocative chapters in this part illuminate some of those challenges and offer intriguing perspectives on potential regulatory routes forward in a dynamic and difficult era.