response to genetics and the body’s reaction. Give physicians a larger armory and let them decide which weapon is best for the task.

Larger armories are also useful for a second problem. Many diseases are resistant to a silver bullet but succumb to silver bullets. The heterogeneity of patients, diseases, and drugs and their multi-factorial combinations makes efficacy testing on final outcomes like mortality or life expectancy problematic. If we test three drugs against a disease each may fail to improve life expectancy even if all three drugs when used together or in sequence might cure the patient. But testing all possible combinations is far too costly to be reasonable. Combination therapies are best discovered in the field where knowledge can evolve and where individual circumstances of time and place can be adjusted for. The medical discovery process is why combination therapies and gold-standard treatments are often off-label treatments. Thus, we should be shifting our approval standards away from final-outcome mortality and toward safety and efficacy measured against the disease. Give physicians a larger armory and let them decide on tactics.

Philosophically I support a more libertarian approach to drug approval, one that offers greater respect for patient autonomy. I have deemed this a Consumer Reports model of the FDA. Consumer Reports evaluates products and gives recommendations but it doesn’t forbid consumers from making choices given their own values and constraints. Consumer Reports helps consumers to make better choices. Similarly, a less paternalistic FDA would provide more information to patients and doctors, but it would also leave more choices in their hands. In addition to offering greater respect for patient autonomy, I believe that such an approach would lower costs and increase the number of new drugs and devices offering tremendous value to patients in the United States and the world.

ACKNOWLEDGMENTS

Conflict of Interest: None declared.

Biostatistics (2017) 18, 3, pp. 404–407
doi:10.1093/biostatistics/kxx019
Advance Access publication on 12 June 2017

Discussion: New directions for the FDA in the 21st century

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The Food and Drug Administration (FDA) is a remarkable agency, one of the crown jewels of the US government. Its staff and structure are dedicated to safeguarding American public health, and although we sometimes complain about its role as gatekeeper, we all sleep better knowing that our foods and drugs have passed the FDA’s careful scrutiny. Its regulatory scope and process reflect the technical demands of
its responsibilities, and the FDA is one of the very few federal agencies that have taken a lead in defining and developing the new field of regulatory science (FDA, 2016).

Although no regulator can or should attempt to anticipate every innovation that might require new approaches to regulation, in the case of healthcare, there are three areas of opportunity that may call for equally innovative responses from the FDA. The first is in making more use of predictive analytics to inform the FDA’s deliberations. As the trusted third party charged with the mandate to review clinical evidence for all drugs and devices marketed in the USA, the FDA is privy to enormous amounts of valuable data. More aggressive rates of data collection will require more investment in data science, but this is only appropriate since such data is paid for with the flesh and blood of courageous patients enrolled in clinical trials. The array of potential new therapies today is dizzying, in immuno-oncology, gene therapies, and the growing number of applications of gene editing. To meet this torrent of potential new applications, the FDA will need to expand its information technology base, not only to include new forms of data, but also to integrate its earlier collections of clinical trial information.

Recent advances in data science using machine-learning techniques such as support vector machines and deep learning networks have transformed several other data-intensive industries such as consumer credit provision, insurance, marketing, and online retail sales (Khandani and others, 2010; Butaru and others, 2016). Given the magnitude and scope of data entrusted to the FDA, a host of insights regarding the viability of certain therapeutic lines of development should be available if the right estimation methods are used. These insights can lead to better decisions in the approval process, and can also allow the FDA to provide more refined guidance to the industry regarding unmet needs, overcrowding in certain therapeutic domains, and factors most predictive of clinical success and failure. The Information Exchange and Data Transformation (INFORMED) initiative in the FDA’s Office of Hematology and Oncology Projects (Health and Human Services Idea Lab 2016) may be just the beginning of a broader effort to bring data science to the agency.

The second area of opportunity for the FDA is in information sharing. While it would be a violation of trust for the FDA to release any of its data into the public domain, there may be a middle ground in allowing certain aggregated information to be shared so as to benefit the public good. For example, more accurate estimates of the probabilities of success of clinical trials by indication could lead to more efficient allocation of scarce resources, and such estimates are unlikely to jeopardize the proprietary information of any single industry sponsor. Recent advances in well-known methods developed by computer scientists for sharing selective portions of data—known as secure multiparty computation—may be particularly relevant for improving knowledge sharing while preserving privacy and protecting intellectual property (Abbe and others, 2012). INFORMED may be an ideal testbed to evaluate the feasibility and desirability of such algorithms for the biopharma industry.

The third and most important opportunity for the FDA to explore is to develop a framework for reflecting the patient perspective in its deliberations. Section 3002 of the recently passed 21st Century Cures Act requires the FDA to develop guidelines for patient-focused drug development, which includes collecting patient preference and experience data and incorporating this information in the drug approval process. This is particularly relevant in cases where the FDA is asked to review candidate therapies for terminal illnesses that have no existing treatments. In response to these urgent cases, the FDA has implemented several programs to expedite the approval process.1 In fact, in situations where the clinical

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1 There is the Priority Review designation, which shortens the FDA’s time to take action on an application to 6 months. The Accelerated Approval process allows the use of an intermediate endpoint for candidate therapies for serious unmet medical needs. The Breakthrough Therapy designation is used to expedite the process for a drug that shows substantial improvement over existing therapies for serious conditions. Finally, and most closely related to this proposal, there is the Fast Track process for drugs for serious unmet medical needs, also becoming eligible for Priority Review and Accelerated Approval if appropriate.
evidence of efficacy is overwhelming, the FDA can move extremely quickly. For example, in the case of imatinib (Gleevec), which showed remarkable efficacy in Phase 1 for treating patients with chronic myeloid leukemia, the drug application was reviewed in a mere two and a half months, and went from Phase 1 to FDA approval in two and a half years under the FDA’s Accelerated Approval process (Keng and others, 2013). However, for less clear-cut cases—which comprises the vast majority of candidate therapies—the approval process is not nearly as quick, and even a Fast Track review may lack the sense of urgency that a terminal patient experiences. Moreover, none of the FDA’s programs systematically measure and incorporate patient preferences explicitly in the approval decision, nor do any of these programs call for changing the statistical threshold by which clinical trials are evaluated.

In several recent studies, my co-authors and I propose a formal framework for reflecting patient preferences in the FDA’s approval process using a well-known technique called Bayesian decision analysis (BDA) (Isakov and others, 2017; Montazerhodjat and others, 2017; Harrington and Parmagiani, 2016). Briefly, BDA begins with the recognition that two types of errors are possible in deciding whether to approve or reject a new therapy: rejecting an effective therapy (a false negative) and approving an ineffective therapy (a false positive). The traditional approach for managing these errors is by setting a statistical threshold of 2.5% for the likelihood of a false positive, so that only those therapies exhibiting effects exceeding this stringent threshold in clinical trials will be approved.

In statistical jargon, these are therapies with “p-values” lower than 2.5%. BDA takes a different approach: instead of using the same threshold of 2.5% for all cases, it allows us to compute an alternative threshold that minimizes the expected harm to current and future patients due to the two types of errors. For example, in desperate situations like pancreatic cancer or glioblastoma where death is imminent and no effective treatments exist, patients may be willing to face a greater than 2.5% chance that a drug is ineffective given their alternative. BDA offers a method for computing the approval threshold that minimizes the average harm to current and future patients from false positives and negatives, where harm includes patient-focused input such as quality-adjusted life years lost. In the case of glioblastoma, our application of BDA yields an optimal threshold of 47.5%, a much less restrictive approval threshold that is likely to increase the number of drugs for this terrible disease (Montazerhodjat and others, 2017).

A natural consequence of this laxer threshold is, of course, more false positives—and the potential for a greater number of patients with adverse side-effects. This can be addressed through more vigilant post-approval surveillance by the FDA, and greater requirements for drug and device companies to provide data to the FDA on patient experience following approval. Failure to provide such data or evidence of an ineffective therapy can be grounds for revoking the approval.

However, past experience shows that withdrawing approval of a marketed drug is extremely challenging for several reasons. Therefore, implementing BDA may require legislation to create an entirely new program for “Speculative Therapies” at the FDA. Such a program might involve provisional approval of a candidate therapy consisting of a 2-year license to market the therapy to a pre-specified patient population, no off-label use of the therapy, and regular monitoring and data reporting to the FDA by the manufacturer and/or patients’ physicians during the licensing. At the end of the 2-year period one of three outcomes would occur: (i) the manufacturer can apply for a second 2-year license (only one renewal will be allowed); (ii) the license expires; or (iii) the therapy receives the traditional FDA approval designation. Of course, at any point during the 2-year period, the FDA can terminate the license if the accumulated data suggests an ineffective or unsafe therapy. While such a process may impose greater burdens on patients, manufacturers, and the FDA, it may be worthwhile if it accelerates the development of therapies for patients facing mortal illnesses and extreme suffering. In this respect, a Speculative Therapies program may be viewed as a middle ground between a standard clinical trial and an approval, similar in spirit to the adaptive designs of sophisticated clinical trials with master protocols such as I-SPY 2 (Harrington and Parmagiani, 2016), LUNG-MAP (Steuer and others, 2015), and GBM-AGILE (National Biomarker Development Alliance, 2015), in which patient care and clinical investigations are simultaneously accomplished.
Of course, in practice the FDA considers many factors beyond \( p \)-values in making its decisions. However, that process is opaque even to industry insiders, and the role of patient preferences is unclear. The recent FDA approval of the Duchenne muscular dystrophy drug eteplirsen (Exondys 51) despite mixed clinical evidence suggests that the FDA does take the patient perspective into account. BDA provides a systematic, objective, adaptive, and repeatable framework for explicitly incorporating patient preferences and burden-of-disease data in the therapeutic approval process. As the noted biostatistician Don Berry said, “We should also focus on patient values, not just \( p \)-values” (Berry, 2015).

Acknowledgments

Research support from the MIT Laboratory for Financial Engineering and the Golub Center for Finance and Policy is gratefully acknowledged.

Conflict of Interest: Dr. Lo has personal investments in BridgeBio, ImmuneXcite, KEW, MPM Capital, Novalere, Royalty Pharma, and VisionScope. He is also an adviser to BridgeBio, and a director of Roivant Sciences and the MIT Whitehead Institute. No other disclosures are reported.

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