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Citation:
R. M. Califf, S. Ostroff, FDA as a catalyst for translation. *Sci. Transl. Med.* **7**, 296ed9 (2015).

10.1126/scitranslmed.aab2404

REGULATORY SCIENCE

FDA as a catalyst for translation

BIOMEDICINE HAS ENTERED A TRANSFORMATIVE ERA, ONE IN WHICH ADVANCES IN mechanistic biology, bioengineering, data management, and health policy promise to deliver unprecedented benefits for public health, such as precision and preventive medicine, theranostic imaging techniques, and mobile health. The U.S. Food and Drug Administration (FDA) has a critical role to play in supporting the timely development of new products and technologies for the prevention and treatment of disease and improvement of human and animal health. The FDA's mission to protect the public health includes ensuring the safety and efficacy of drugs, biological products, and medical devices, as well as the safety of our nation's food supply, cosmetics, and products that emit radiation (www.fda.gov). As such, FDA represents an integral part of the process by which scientific discoveries are translated into medical products with a favorable balance of benefit and risk. But whereas the public readily understands the essential protective mission of FDA, its role in facilitating, assisting, and guiding technology development is less obvious and requires strategic coordination across the many different sectors that make up biomedicine's translational ecosystem.

To strengthen and speed translation, we require a new focus on key areas of an emerging discipline now called regulatory science—the development and application of new tools, standards, and approaches for the assessment of medical product safety, efficacy, and quality—not only at FDA but also among many other stakeholders—academia, the nonprofit community, policy-makers, and industry. In 2007, a subcommittee of FDA's Science Board released a report that provided a compelling rationale for investing in the development of the body of evidence and accompanying methodological toolsets that form the FDA's science base (*1*). With broad support from government, patient groups, academia, and the private sector, the Office of the Chief Scientist was formed, and in 2011, a strategic plan was published that outlined eight priority areas in regulatory science (*2*).

Dramatic recent advances in biological, engineering, and information sciences have fueled intense interest in technology development across the spectrum of stakeholders and other interested parties (*3*, *4*). However, taking advantage of this unprecedented opportunity to accelerate the translation of discovery into approved health products will require the successful implementation of several crucial conceptual elements.

ADVANCES ACROSS OUTCOME MEASURES

Great strides in the measurement of genes, proteins, metabolites, and a growing array of "omics" are being matched by new computational capabilities that enable the measurement, storage, and analysis of vast amounts of data pertinent to multiple dimensions of biological, behavioral, and social systems. These measures, known as biomarkers, are generally defined as characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (*5*). Biomarkers can have substantial value in diagnosing disease, predicting disease outcomes, monitoring response to therapy, and identifying people most likely to benefit or suffer harm from a proposed treatment. When a biomarker predicts the effects of a treatment with a high degree of accuracy, it may be used as a surrogate for a clinical outcome measurement when assessing the balance of benefits and risks in a controlled clinical trial. Unfortunately, many of the biomarkers that are useful in the context of diagnosis, prognosis, or insights into biological mechanisms cannot be used as surrogates for clinical outcomes, because measured changes in biomarkers attributable to the use of a therapy are seldom adequately predictive of a corresponding change in the clinical outcome (or outcomes) of interest. This reality underscores our need for more effective approaches for developing and qualifying biomarkers and for deciphering their appropriate uses in translational science (*6*).

Recent advances in technology and methodology are rapidly and systematically transforming the field of patient-reported outcomes, which are, in essence, outcome measures derived directly from consumers or patients (www.nihpromis.org). A related but distinct approach that forms one facet of the emerging discipline of "regulatory science" seeks to evaluate patient preferences on the basis of increasing knowledge that, given the same ar-

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ray of benefits and risks, different people will make different decisions because of personal preferences or circumstances. Most recently, the creation of wearable, minimally invasive measurement devices is enabling the continuous capture of vital signs and other physiological measures, thereby opening up entirely new capabilities in terms of assessing behavioral and social interactions. In the midst of this "data deluge," we are also refining the ability to measure health outcomes that have always been important (for example, survival or clinical events such as myocardial infarction or cancer recurrence) on a much broader scale and with greater clarity as a result of capabilities afforded by electronic health records and clinical assessment tools such as advanced imaging techniques.

IMPROVING EVIDENCE GENERATION

Human phenotyping and systems biology. The changes in human biology that result from the systemic administration of a drug, biologic, food product, or implanted device reveal information important both for developing medical products and for understanding human biology. The modern disciplines of physiology and pharmacology emerged at a time when biological measures were extraordinarily expensive to obtain and storage and computational capacities were severely limited. Dramatic reductions in the cost of obtaining biological measures, combined with the advent of cloud computing and other advanced computational and analytical tools, are enabling the redefinition of states of health and disease and the treatment of medical conditions according to molecular pathways. As our knowledge of the complexity of biological systems improves, we will be able to apply appropriately a spectrum of inquiry ranging from explorations in animal models to early human studies. The end result will be a much richer and comprehensive understanding of how proposed interventions engage with their biological targets (and also how they contribute "off-target" effects).

Streamlining and optimizing clinical trials. A clear understanding of the benefits and risks of a medical product is best gained through evaluation in a controlled clinical trial. But the costs and logistical difficulties of performing high-quality clinical trials, always considerable, have recently been moving along an unfavorable trajectory. Without a randomized control group, however, the true effect of an intervention relative to the natural course of the disease will remain uncertain. Thus, whenever possible, any attempt to assess the balance of benefits and risks for a therapy should incorporate randomization to ensure an interpretable control group for causal inference. Such evaluations should also include relevant populations in whom the products will be used and should incorporate appropriate time frames for evaluation.

Substantial work by consortia in the drugs and biologics (www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm) and device (http://mdic.org) arenas has yielded a roadmap for implementing a "quality by design" approach to clinical trials. By tailoring the intensity of data collection to optimally support study safety, validity, and efficiency, and by focusing on building in quality from the ground up, there is a strong case to be made that we can not only do more trials but also do them better, quicker, and at a much lower cost. Furthermore, the National Library of Medicine's ClinicalTrials.gov registry provides a powerful tool for portfolio analysis (*7*). With nearly 400 trials now being registered every week, there exists an opportunity to improve the process by which priorities are assigned within the domain of clinical research to produce more trials with significant impact on health and wellness—itself a critical step in ensuring the rational development and dissemination of technologies.

Use of "real-world" clinical data. Although randomized trials perform an essential role in the development of therapies, we should not neglect the crucial and complementary role that can be played by high-quality observational studies. After decades of anticipation, we have now entered an era in which almost every American has an electronic health record (EHR). The accuracy, completeness, and scientific rigor of these records and their associated claims data must be improved if they are to meet the needs and expectations of physicians and scientists. Still, the combination of EHRs, medical-claims data, and disease registries is nonetheless creating a new "data fabric" for biomedical information. The FDA's Sentinel Initiative (*8*) now has claims data derived from the billing records of more than 170 million Americans. These data are being used on a regular basis to understand drug safety issues that emerge from spontaneous reports, social media posts, scientific publications, and news reports. In addition, vital national networks are being built to integrate EHRs and registries

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with data voluntarily contributed by patients to provide the rich, fine-grained detail needed to conduct high-quality observational studies (see www.nihcollaboratory.org/about-us/Pages/default.aspx and www.pcornet.org).

However, truly effective use of this volume of observational data will require considerable methodological development, including whether an observational study can provide sufficient evidence to render a randomized trial unnecessary. Furthermore, the incorporation of randomization into systems already collecting "big data" on populations as well as the use of cluster-randomized trials present the opportunity to blend continuous learning, enabled by observation and analytics, with rapidly implemented randomization. By encouraging new methods for obtaining evidence at the interface of observational studies and randomized trials, FDA is poised to make major contributions to the development of a robust "learning health system."

PERSON-CENTERED TECHNOLOGY

The process of engaging people who are most directly affected by the prioritization, goals, and evaluation of technological development has been transformed by the democratization of information exchange. Through social media, the broader Internet, and personal devices, it is now possible to directly involve patients and consumers in this process on a previously unimaginable scale. The FDA's Centers for Drug Evaluation and Research (CDER), Biologics Evaluation and Research (CBER), and Devices and Radiological Health (CDRH) are all intensely involved in efforts to include patients throughout the life cycle of medical product development. As patient-centered technology development evolves, the entire translational system becomes more efficient. Patients—who once were end users of technology—become actively engaged in the design and conduct of research and in the dissemination of results.

THE SCIENCE OF DECISION-MAKING

Enormous volumes of new data can potentially be distilled into better information for guiding decisions about the health of individuals and populations. At the same time, however, there is ample evidence that, because of cognitive biases and behavioral issues, both the general population and key decision-makers are often poorly equipped to make the most effective use of available information. One perspective on FDA is that its primary purpose is to create standards that will enable all stakeholders—consumers, patients, health care providers, administrators, payers, and policy-makers—to have access to the information they need to make the best possible decisions about health and health care. To this end, the FDA is focusing on research related to interpretable labeling of products, the behavioral economics that drive decision-making, and a generalizable framework for assessing the balance of risk and benefit. The ultimate goal of these efforts is to enable decision-makers to accurately balance complex trade-offs, taking advantage of both the quantitative and qualitative evidence bases regarding relevant options for prevention or treatment.

THINK GLOBALLY, ACT GLOBALLY

The FDA exists within a complex ecosystem that includes other federal agencies; the industries that develop, manufacture, and market medical products; patient and consumer groups; academia; and the professional clinical practice community. The U.S. health system and patient population are complex in and of themselves, but 96% of the world's population lives elsewhere, and each nation has its own distinct culture of interactions among these sectors. Because technology development is a global enterprise and investment is closely tied to prospects in a global market, it is critical for the FDA to help advance harmonization and work with international partners to build a thoughtful strategy for effective engagement on a global scale.

Because FDA's purview includes efforts to develop technologies that are directly applicable to public health, its scientists, engineers, clinical and policy experts, and lawyers possess deep knowledge of the science of translation and how to bring products to market. Although this knowledge is shared in transactions related to specific product-development programs, additional venues for appropriate sharing of generalizable knowledge between the FDA and the rest of the translational ecosystem would be beneficial. The FDA receives a great deal of product-related information that contains trade secrets and confidential commercial information. The dissemination of general knowledge based on that information (for example, "precompetitive") raises complex issues. The FDA will continue to explore the sharing of

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such knowledge in ways that protect privileged information and foster learning so that fewer avoidable errors are made in the translational system.

The roadmap for acceleration of translation described herein is not the work of the FDA alone, but the agency is in an excellent position to leverage its talent, knowledge, experience, and expansive view of the effects of technology on society to improve human health in collaboration with other stakeholders. In the midst of this beckoning opportunity, however, FDA cannot lose sight of its core mission of protecting the American public. Every day, FDA must make many decisions about the regulation of food, tobacco, cosmetics, and medical products—all with potentially enormous impacts on the everyday lives of Americans and people around the world. The themes we describe are elements of an overarching goal: namely, to capture the knowledge and creativity engendered by these many specific interactions in the regulatory sphere and apply them to the task of both accelerating scientific translation and improving the likelihood that translational efforts will yield useful technologies. We encourage the broader scientific community to join us in making the most of this opportunity.

– Robert M. Califf and Stephen Ostroff

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Science Translational Medicine

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Sci Transl Med **7**, 296ed9296ed9.
DOI: 10.1126/scitranslmed.aab2404

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