Using Real-World Evidence to Accelerate Safe and Effective Cures

Advancing Medical Innovation for a Healthier America

Executive Summary

June 2016

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FDA: ADVANCING MEDICAL INNOVATION EFFORT

The Bipartisan Policy Center's initiative, FDA: Advancing Medical Innovation, is developing viable policy options to advance medical innovation and reduce the time and cost associated with the discovery, development, and delivery of safe and effective drugs and devices for patients in the United States. Key areas of focus include the following:

- Improving the medical product development process;
- Increasing regulatory clarity;
- Strengthening the Food and Drug Administration's (FDA) ability to carry out its mission;
- Using information technology to improve health and health care; and
- Increasing investment in medical products to address unmet and public health needs.

This effort is chaired by former Senate Majority Leader William H. Frist, MD and former Representative Bart Gordon. Members of the advisory committee include Marc Boutin, CEO, National Health Council; Mark McClellan, MD, PhD, director, Robert J Margolis Center for Health Policy, Duke University and former FDA commissioner; Patrick Soon-Shiong, MD, chairman and CEO, Institute for Advanced Health; and Andrew von Eschenbach, MD, president, Samaritan Health Initiatives and former National Cancer Institute director and former FDA commissioner. Janet Marchibroda, BPC's Health Innovation director, serves as the staff director for the effort.

The initiative also taps into the expertise and views of a broad range of experts and stakeholders through one-on-one interviews and roundtable discussions.

AUTHORS

This paper was developed by BPC based on a review of the literature, interviews with a broad and diverse range of experts and stakeholders, and roundtable discussions. BPC acknowledges Janet Marchibroda, Tim Swope, Sam Watters, Michael Ibara, PharmD, Marc J. Scheineson, J. Marc Overhage, MD, PhD, and Ann Gordon for their contributions in research and writing.

ACKNOWLEDGMENTS

BPC would like to thank the Jayne Koskinas Ted Giovanis Foundation for Health and Policy for their generous support.

BPC would like to thank its co-chairs and advisory committee for their general guidance and leadership on medical innovation. BPC would also like to thank the number of individuals who participated in interviews and roundtable discussions. A full list of interviewees and roundtable participants is provided in Exhibit I.

DISCLAIMER

The findings and recommendations expressed herein do not necessarily represent the views or opinions of the Bipartisan Policy Center's founders or its board of directors.

Letter from the Co-Chairs

We are fortunate to live in an age of continuous discovery and scientific breakthroughs, especially when it comes to treatments for disease. New and highly effective medications are available today that treat conditions considered incurable just a decade ago, such as Hepatitis C.

But while scientific discovery is moving ahead rapidly, the pace of moving new drug discoveries to patients in need remains quite slow. It takes an average of ten years and two billion dollars to bring a new drug to the marketplace. With so many diseases and conditions that still lack effective treatments—such as Alzheimer's disease, which affects more than five million Americans—the need to accelerate the search for tomorrow's cures is clear.

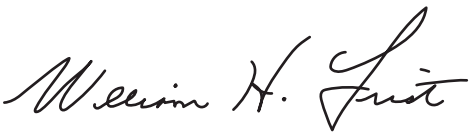
Modernizing the entire life cycle of drug development and regulatory review is the focus of this report. Congress and the administration are moving forward with efforts that demonstrate their strong support for improving the development and delivery of medical products. This report includes recommendations to inform this progress.

Bringing safe and effective cures and treatments to patients in a timely and cost-effective manner will require new processes and new policies to support them. Using real-world evidence—data that reflects the actual experience of patients during real-world situations—in addition to relying on data derived from conventional randomized controlled trials will enhance the nation's ability to advance the safety and effectiveness of drugs in a wider population.

Real-world data is available through electronic medical records, claims databases, laboratory and pharmacy systems, registries, and even from patients' own health-monitoring devices.

Our recommendations focus on defining how real-world data can be used to support more efficient and effective drug development and strengthen the FDA's ability to oversee such progress.

Improving and streamlining the process of bringing new drugs to market will enhance U.S. global competitiveness. But more importantly, an approval process that maintains the highest standards of safety and brings new medications to the market faster will help tens of thousands of Americans who are waiting for treatments and cures. Many cannot wait much longer. For these patients especially, it is time to act.



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Introduction

Despite recent medical breakthroughs such as the cure for Hepatitis C, significant unmet medical needs remain. For the approximately 10,000 known molecular-based diseases, there are approved treatments for only 500 of them.[1] The urgency of finding the next generation of cures is clear.

It takes too long—an average of ten years—and costs too much—an estimated $2 billion—to bring one new drug to market.[2,3,4,5] Modernizing the drug discovery, development, and approval of new cures and treatments plays a critical role in addressing this issue and should be a key priority for the United States.

The digitization of biology and the vast increase in the amount of electronic data captured during routine care, or by patients themselves, creates an unprecedented opportunity to modernize and augment clinical trials and improve the post-market monitoring process. More than three-quarters of physicians and hospitals use electronic health records (EHRs); seven in ten American adults say they track at least one health indicator for themselves or someone else.[6,7,8]

This "real-world data" can be used to support a more timely and cost-efficient drug development process. The need to advance the generation and use of real-world evidence was one of the key recommendations of BPC's July 2015 report, *Advancing Medical Innovation for a Healthier America*.

Benefits of Real-World Evidence

The vast majority of the time and cost associated with drug development is devoted to clinical trials, which on average take seven years and cost $1.6 billion.[9,10] While randomized clinical trials (RCTs) are regarded as the gold standard for research, their tightly controlled design does not reflect medication use in the real world. Often missing from trials are representative samples of patients with multiple co-morbidities, concomitant use of other drugs, varying ages, races and ethnicities, and different practice settings.

Supplementing RCTs with real-world evidence—reflecting the actual experiences of a diversity of patients during routine patient care—will improve the generalizability and efficiency of RCTs, and will help support progress toward more personalized, precision medicine. RCTs alone are unlikely to provide the type of data needed in an era of personalized medicine, in which drugs and diagnostics are developed to treat subsets of patients who may respond to one treatment but not another, due to genetic or other factors.

Real-world evidence can support many of the activities during the clinical trial phase. It can expedite the generation of hypotheses; enable identification of sub-populations with higher risk-benefit ratios to target development efforts; support more efficient and targeted patient recruitment; reduce the burden of data collection and reporting; speed the identification of safety and operational issues requiring action; and lead to earlier conclusions about effectiveness and faster decisions about value and reimbursement.

Real-world data can also improve the post-market phase of drug development, during which the Food and Drug Administration (FDA) monitors long-term effects of new drugs and treatments. Real-world evidence can reduce the time and cost of this phase through more efficient methods of data collection. The FDA already uses real-world data to support some post-marketing surveillance efforts, primarily through its Sentinel Initiative.

In addition, real-world evidence, along with new technology now widely adopted, makes possible a new paradigm for closely monitoring the safety and efficacy of drugs prior to and after their approval. This "close-monitoring" during clinical trials, post-approval commitment phase, or after approval of a subset of patients—through a combination of personal monitoring devices, smartphone apps, phone calls and virtual visits, all with patient consent—would benefit patients, researchers and regulators.

Close-monitoring would move safety monitoring practices from a population-based model to a personalized medicine approach. Monitoring would be more frequent, proactive, and individualized, but with less disruption to the patient's lifestyle and without incurring excessive costs. Compliance would likely improve, safety would be strengthened, and development and review cycles would be shortened.

This near-real-time safety monitoring strategy also enables a new adaptive approach to drug development and approval for drugs shown to be safe and effective in well-defined subpopulations. New, adaptive approaches will be necessary in a new era of personalized medicine.

There is a growing consensus that real-world data can and should play a significant role in supporting and strengthening the evidence base for safety and effectiveness across the life-cycle of drug development, encompassing both pre- and post-market regulatory decision-making. Near-term opportunities for use of real-world data include supporting regulatory decision-making associated with label extensions or a new indication for an approved drug; supporting confirmatory studies for drugs approved under FDA's existing expedited programs; and improving the efficiency of Phase IV post-market monitoring and ongoing post-market surveillance. The use of pragmatic clinical trials, which combine the benefits of collecting data from more real-world settings while incorporating elements of randomization, is also ripe for implementation.

Recommendations for Modernizing the Drug Development Process Through the Use of Real-World Evidence

Integrating real-world evidence into today's drug development process will require improving certainty about the types of evidence that will be accepted and under what circumstances, through greater regulatory clarity. It will also require greater transparency of, as well as agreement on, acceptable methods. Improved data quality and changes in policies for information sharing will make the use of real-world evidence easier and less expensive.

To lay the groundwork for a new era of precision medicine, new adaptive approaches for regulatory decision-making will be needed. The following recommendations are intended to support this progress.

I: Improve Regulatory Clarity Regarding the Use of Real-World Evidence

1. The FDA should develop formal guidance regarding the use of real-world evidence to inform regulatory decision-making, including the circumstances under which real-world data could be used, as well as the types of real-world data, methods, and the levels of evidence that would be acceptable for use in regulatory review and decision-making. The guidance should include, but not be limited to, new drug approvals, label expansions, new indications, post-market commitments, and post-market study requirements.

2. The FDA should engage representatives of regulated industry, patient and disease research organizations, academia, experts in the use of electronic data, experts in statistical methods, and experts in privacy policy in the development of the guidance.

3. The FDA should review the results of public and private-sector supported research, studies, and pilots associated with the use of real-world data to inform decision-making regarding the types of real-world data that would be acceptable, appropriate statistical and other methods, data quality requirements, and other factors, as appropriate.

II: Improve Methods and Data Quality for the Generation and Use of Real-World Evidence

1. The FDA should establish a program to promote sharing and evaluation of methods used in the evaluation of real-world evidence for regulatory decision-making. The FDA should invite a broad spectrum of researchers who are active in the generation and use of real-world evidence and methods development, as well as leaders who rely upon such real- world evidence—including regulators and payers—to participate in this program.

2. The U.S. Department of Health and Human Services (HHS) should support research to improve methods for the use of real-world evidence, which take into account the much larger samples of electronic data now available and enable high-throughput methods that produce accurate and well-calibrated inferences that quantify levels of uncertainty more accurately.

3. The FDA should require any researchers who receive federal funding or utilize real world evidence to draw conclusions used for regulatory decision-making to publish and make transparent their methods to support peer-review, promote replicability, and assess validity. FDA should encourage private sector studies to do the same.

4. HHS should continue its efforts to advance the adoption of standards and the interoperability of EHRs and such efforts should extend to other clinical systems beyond the EHR. HHS should develop and publish standards that will improve the accuracy of matching of patient data across health information technology systems. HHS should also continue its efforts to harmonize standards related to data used for clinical research with standards related to data within EHRs and other systems used within health care. FDA should revise and update its guidances to include specific recommendations on technological approaches and modern concepts of data provenance.

III: Improve Policies for Information Sharing to Support Clinical Research

1. Congress should require the HHS Secretary—through the Office of Human Research Participants (OHRP) and the FDA—to issue regulations and guidance to facilitate the broader use of centralized IRBs by clarifying the roles of IRBs in multi-site studies and the risks and benefits to human subjects, standardizing informed consent, and incorporating community values through the use of local IRBs while continuing to use central IRBs.

2. Congress should promote National Institutes of Health (NIH) policies to encourage investigators and institutions to voluntarily utilize single IRBs as part of their grant submissions. NIH should provide additional funds to those grants that agree to utilize single IRB arrangements.

IV: Explore New Adaptive Pathways to Modernize Drug Development and Support a New Era of Personalized Medicine

1. The FDA should develop a new program to develop and test a new adaptive pathway approach to expand the capacity for drug development that has the following key attributes:

a. Iterative phases of development, beginning with initial marketing authorization to a restricted patient population, then expanding to wider populations based on risk-benefit ratios;

b. Gathering evidence through close-monitoring and other real-world evidence, to supplement RCTs; and

c. Early involvement of stakeholders who have a role in determining patient access to the drug, including industry, payers, regulators, clinicians, and patients.

2. The FDA's new program to develop and test a new adaptive pathway approach for drug development should include the following elements:

a. Qualifying criteria for the program, which will determine which types of drugs at what stages could be considered for the adaptive pathway approach;

b. Types and levels of evidence required for initial approval and expansion, including evidence generated from close-monitoring, other real-world evidence, and randomized controlled trials, as appropriate;

c. Methods for early involvement of patients, clinicians, payers, industry, and regulators; and

d. Methods for assuring market removal or label modification of products when follow-up studies and monitoring are not completed or when an unfavorable risk-benefit ratio for certain populations is demonstrated.

3. The FDA should engage experts and stakeholders in developing the program, including representatives of regulated industry, academia, clinicians, patient advocacy and research organizations, and others, as appropriate. The FDA should gain public input on the key attributes and elements of the program.

4. The FDA should launch a pilot program to test the attributes and elements of the new adaptive pathway program for drug development, engaging the participation of multiple consortia and organizations.

5. Upon completion of the pilot program, the FDA should issue guidance for a new adaptive pathway program, including final attributes and elements, that reflects lessons learned from the pilots.

Conclusion

Real-world evidence can play a significant role in modernizing the drug approval process in the United States. The increase in the amount of electronic data available, combined with scientific advances resulting in more personalized and more complex drug regimens, demand a new, modernized approach that spans the entire drug life-cycle.

Implementing the steps outlined in this report will enable the United States to make significant progress in leveraging real-world evidence to help get safe and effective drugs to market faster and more cost-efficiently. Taking these actions will not only improve global competitiveness, but more importantly, will help the hundreds of thousands of patients who are waiting for cures and treatments.

Exhibit I: List of Interviewees and Roundtable Participants

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Yale School of Medicine

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Marcus Wilson, PharmD
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Healthcore, a Wholly-Owned Subsidiary of Anthem

It is important to note that while the interviewees provided important input to the development of the report, the findings and recommendations in this report were not specifically reviewed or endorsed by those interviewed.

Endnotes

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