Accelerating the Development and Delivery of Safe and Effective Cures for Patients in the United States

Key Considerations for the Food and Drug Administration User Fees Reauthorization

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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 FDA's ability to carry out its mission;
- Using digital technology to improve health and health care; and
- Increasing investment in medical products to address unmet and public health needs.

ACKNOWLEDGMENTS

This effort is chaired by former Senate Majority Leader William H. Frist, MD and former Representative Bart Gordon. Andrew von Eschenbach, MD serves as an advisor to this effort. Janet Marchibroda, BPC's Health Innovation director, serves as the staff director for this 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.

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Introduction

With passage of the bipartisan 21st Century Cures Act with nearly unanimous support in Congress in December 2016, tremendous progress has been made to accelerate bringing safe and effective treatments and cures to patients in need. The 21st Century Cures Act included several provisions that will improve the discovery, development, and delivery of medical products for millions of Americans and improve U.S. global competitiveness, including those related to bringing the patient voice to the development process; increasing the use of real-world evidence and drug development tools to modernize how drugs are developed, evaluated, and approved; advancing precision medicine to tailor treatments for patients; improving the regulation of regenerative and other advanced therapies; enhancing the Food and Drug Administration's (FDA's) capacity and scientific expertise to keep up with new scientific advances; and providing significant funding for research on diseases for which there is no cure.[1]

Congress is now poised to take additional action to advance biomedical innovation in the United States through "must-pass" legislation reauthorizing user fees for prescription drugs, devices, and biosimilars, which must be in place before September 30, 2017, when current programs expire. On April 14, 2017, the leaders of the U.S. Senate Committee on Health, Education, Labor, and Pensions (HELP) and the U.S. House of Representatives Committee on Energy and Commerce released a discussion draft of the Food and Drug Administration Reauthorization Act of 2017 (FDARA Discussion Draft)—bipartisan legislation reauthorizing FDA user fee agreements.[2,3,4] The FDARA Discussion Draft references and implements formal agreements negotiated between the FDA and industry in 2016—commonly referred to as commitment letters.[5,6,7,8] Timely completion and passage of FDA user fee reauthorization legislation before August 2017 is a crucial and necessary next step toward helping Americans in need and realizing the promise of the 21st Century Cures Act.

This policy brief provides BPC insights and recommendations to inform Congress as it finalizes and passes user fee reauthorization legislation in the coming weeks. Such recommendations draw from the BPC's work over the last several months, including recommendations from the report *Advancing Medical Innovation for a Healthier America*, a technical assistance letter provided to the Senate HELP Committee, and the report *Using Real-World Evidence to Accelerate Safe and Effective Cures*, developed through BPC's Advancing Medical Innovation effort under the guidance of former Senate Majority Leader William H. Frist, MD, and former Rep. Bart Gordon.[9,10,11] These recommendations are also consistent with BPC comments shared during several patient/consumer stakeholder meetings convened by FDA to inform the development of the Prescription Drug User Fee Act (PDUFA) commitment letter, BPC's August 2016 formal comments to FDA on the PDUFA commitment letter, BPC's September 2016 formal comments on FDA draft guidances on cell therapy, as well as other research performed by BPC's Health Innovation Initiative over the last several months.[12,13]

Executive Summary

The April 14, 2017 discussion draft of the FDA Reauthorization Act of 2017 references and implements several provisions included in the FDA commitment letters that will accelerate the delivery of safe and effective cures and treatments to Americans and improve U.S. competitiveness. These include provisions that will increase scientific expertise and capacity at the FDA, accelerate the use of real-world evidence and other drug development tools to improve regulatory decision-making, incorporate the patient voice into the medical product development process, and advance the development of combination products. Such provisions align with BPC's previous recommendations and both complement and support provisions of the 21st Century Cures Act passed nearly unanimously with bipartisan support in December 2016. BPC encourages Congress' speedy passage of user fee legislation that will accomplish these goals, as any delay beyond July 2017 is likely to have a significant, negative impact on the ability for FDA to carry out not only the important elements of the FDA committment letters, but also the 21st Century Cures Act.

BPC also recommends that Congress consider legislation in 2017 on other issues identified by BPC in its previous recommendations, including those related to clarifying and increasing the sharing of scientific information with clinicians to support off-label use of approved medical products, clarifying regulatory authority associated with laboratory-developed tests, and supporting implementation of a national registry for regenerative cell therapies.

A recap of BPC's recommendations, outlined in more detail in the report, is provided below.

1. Assure adequate capacity and scientific expertise at the FDA by improving methods, systems, and infrastructure for hiring and retaining key staff.

2. Accelerate the use of real-world evidence to inform and improve regulatory decision-making by publishing guidance on the use of real-world evidence for approval of new supplemental indications and fulfillment of post-marketing commitments and requirements; evaluating, improving, and promoting transparency of methods; and both exploring and laying the groundwork for adoption of new adaptive pathways that take advantage of evidence.

3. Incorporate the patient voice into the medical product development process by strengthening staff capacity, developing guidance on approaches and methods, publishing tools, conducting workshops, and enhancing benefit-risk assessment.

4. Enhance the use of drug development tools—such as biomarkers—by increasing staff capacity, developing a taxonomy of biomarker usage, publishing general evidentiary standards for qualification, and publishing biomarker qualification submissions.

5. Advance development of combination products by improving capacity and training, streamlining review processes, effectively evaluating and allocating resources, establishing policies and procedures, clarifying points of contact, establishing timelines, and publishing guidance.

6. Clarify and allow increased sharing of scientific information with physicians to inform off-label use of approved medical products.

7. Clarify regulatory authority associated with laboratory-developed tests.

8. Advance the development and use of a registry to support regenerative cell therapies.

Detailed Recommendations

As outlined in BPC's recent report *Advancing Medical Innovation for a Healthier America*, accelerating the discovery, development, and delivery of safe and effective treatments for patients requires improvements in and modernization of the medical product development process; greater regulatory clarity; and increased capacity and scientific expertise at the FDA. The FDA commitment letters referenced and implemented through the FDARA Discussion Draft take important steps to achieve these goals, complementing the foundation laid by the 21st Century Cures Act.

As Congress moves forward on legislation reauthorizing FDA user fees, BPC recommends that it consider the following recommendations, detailed below.

Advancing Recommendations in Priority Areas Contained in PDUFA Commitment Letter

1. Assure Adequate Capacity and Scientific Expertise at the FDA

The FDA oversees the safety and effectiveness of products that account for one out of every $5 spent by consumers each year, including drugs, devices, food, and tobacco. Carrying out its important public mission to promote and protect the public health—including the activities outlined in this report—requires a strong FDA that has adequate scientific expertise and sufficient capacity.

Over the last ten years, the FDA budget has more than doubled, from $2.01 billion in FY 2007 to $4.75 in FY 2016.[14,15] At the same time, the number of full-time, permanent employees has increased—although at a somewhat slower pace—from 8,105 in FY 2007 to 14,441 in FY 2016.[16,17]

Nearly ten years ago, the FDA Science Advisory Board concluded that the FDA lacked both sufficient scientific expertise and capacity and an adequate IT infrastructure to keep pace with both current and emerging scientific and technological advances and related regulatory responsibilities.[18] In November 2012, the Partnership for Public Service released the results of its follow-up study indicating that while steps had been taken since the 2007 Science Board Report, several challenges associated with workforce recruitment, hiring, management, and development remain.[19]

The FDA's challenges associated with attracting, hiring, and retaining talented staff with scientific expertise are well documented. The total number of vacancies as of December 2016 was 1,764, representing about 11 percent of the budgeted workforce.[20,21] The average time to hire individuals not currently employed by the federal government is 132 days.[22]

Challenges highlighted by the FDA in a January 2015 letter response to a congressional request for information include outside competition for qualified applicants, challenges in offering competitive salary packages that compete with industry to individuals with the necessary technical knowledge, and challenges in enticing qualified, interested individuals to relocate to the Washington, DC area, given the high cost of living.[23] Expanding the FDA's direct hiring authority and enabling exceptions to federal salary caps can assist in helping the FDA to fill open positions and expand its capacity and scientific expertise.

The 21st Century Cures Act contains several provisions to increase FDA capacity and scientific expertise, including expanding definitions and increasing the number of individuals that can be hired through the Senior Biomedical Research Service; authorizing appointments of qualified candidates with competitive service and enabling the FDA commissioner to fix annual pay rates; requiring the FDA to publish a workforce planning report, including a needs assessment and recruitment and retention plan; requiring a Government Accountability Office report to assess progress on hiring, training, and retention. Section III of the PDUFA commitment letter builds upon the 21st Century Cures Act by requiring that the FDA complete the modernization of its hiring infrastructure, augment its hiring capacity and capability, establish a dedicated function for scientific hiring, set clear goals for hiring, and conduct comprehensive and continuous assessment of hiring and retention.

A strong scientific workforce and sufficient capacity—made possible by the actions outlined above—are crucial if the FDA is to help realize the benefits of new innovations and successfully implement the 21st Century Cures Act. Advancing beyond traditional modes of federal government hiring by enabling more flexibility in hiring to attract individuals with considerable expertise and experience for short-term and/or specific needs—either through part-time offerings or the use of sabbatical authority which would enable the FDA to bring in expertise from academia or industry for term appointments—will also assist with improving scientific expertise and capacity.

BPC commends Congress for implementing provisions contained in the PDUFA commitment letter within the FDARA Discussion Draft, which—together with implementation of the 21st Century Cures Act—will significantly increase the FDA's ability to meet the demands of rapid advances in science and technology.

2. Accelerate the Use of Real-World Evidence in Regulatory Decision-making

Real-world evidence—or data gathered from sources outside of randomized controlled trials reflecting actual experiences of patients during routine patient care—provides many benefits and opportunities throughout the drug development life cycle, particularly within the clinical trials and post-market monitoring phases of development. The greatest benefits and opportunities of real-world evidence are expected in the clinical trials phase, which takes on average seven years and $1.5 billion of the more than $2 billion spent on average to bring a drug to market.[24,25,26,27]

As noted in its report, *Using Real-World Evidence to Accelerate Safe and Effective Cures*, the benefits and opportunities of using real-world evidence are numerous, including that it:

- Expedites the generation of hypotheses to inform the design of clinical studies and enables identification of subpopulations with higher risk-benefit ratios to target development efforts;
- Enables more efficient and targeted recruitment of patients for clinical trials;
- Reduces the burden of data collection and reporting and enables the collection of patient-reported outcomes;

- Helps sponsors identify safety and operational issues requiring action sooner, to help avoid adverse events and unnecessary delays;
- Improves the generalizability of trials by augmenting RCTs with data from a broader, more diverse group of patients in different practice settings than is currently gained through targeted, tightly controlled populations, to gain better insights on safety and effectiveness;
- Makes studies and their findings more relevant to patients and provides information on long-term outcomes;
- Informs decision-making regarding value and reimbursement sooner, which is a goal of both sponsors and payers; and
- Reduces the time and cost of conducting post-marketing monitoring.

The 21st Century Cures Act requires the FDA to implement a program within two years, to evaluate the potential use of real-world evidence to help to support the approval of a new indication for an approved drug or post-approval study requirements. It also requires the FDA to develop a framework for implementation that includes sources, gaps in data collection, standards and methodologies for collection and analysis, priority areas, challenges, and potential pilot opportunities. Finally, the FDA is expected to publish guidance that describes the circumstances under which sponsors and the FDA may rely on real-world evidence and the appropriate standards and methodologies for collection and analysis of real-world evidence submitted.

Building on the 21st Century Cures Act, the PDUFA commitment letter also identifies several steps that the FDA will take over a five-year timeframe to incorporate real-world evidence as a new tool to evaluate product safety and effectiveness, including conducting public workshops, initiating or funding activities, such as pilot projects or methodology development projects, and publishing guidance on the use of real-world evidence for approval of new supplemental indications and fulfillment of post-marketing commitments and requirements. The PDUFA commitment letter also contains provisions to advance postmarketing drug safety evaluation.

As it considers user fee reauthorization legislation, BPC recommends that Congress include additional provisions associated with methods to improve the use of real-world evidence in regulatory decision-making.

Through its research, BPC has found that the methods and interpretations traditionally used in customized individual study designs used within randomized controlled trials (RCTs) may not be the appropriate methods for understanding much larger data sets, or data drawn from across a network of disparate databases. Studies have shown that similar questions posted to different data sets have drawn very different conclusions. Other studies have shown that different methods applied by different investigators to the same data sets have also drawn different conclusions. Promoting transparency in methods used and public dialogue about best practices for methods will significantly advance the field and provide more confidence in published results using real-world evidence. Given this, it is imperative that regulatory agencies and those who rely upon such data to inform reimbursement decisions educate themselves and the public about best practices in methods of use and interpretation of real-world evidence for decision-making purposes.

BPC Recommendations on Real-World Evidence:

1. As the FDA establishes its program to evaluate the use of real-world evidence, it should promote both sharing and robust evaluation of methods used in the evaluation of real-world evidence for regulatory decision-making, engaging 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.

2. The Department of Health and Human Services (HHS) should also 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. Such research should focus on issues that include, but are not limited to, mitigating bias, obtaining solutions to better refine outcomes definitions, understanding implications to analyses for integrating observational data across a number of disparate sources, and understanding the contributions of real-world evidence to causal reasoning.

3. Finally, 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. Publication should include the specific methods used to evaluate real-world evidence in the study, along with the data sources and intended results, if applicable. The FDA should encourage private sector studies to do the same.

A growing number of regulators and researchers across the world recognize the need for a more flexible approach to drug approval, and they understand the role that real-world evidence can play in the process. As medicine becomes more personalized and drugs become targeted for smaller populations, traditional, large-scale RCTs will become increasingly less feasible. Additional approaches will be needed to assure safety and efficacy and protect the public's health. Adaptive approaches can be an effective method for some types of drugs. These approaches will improve focus on the entire drug life-cycle and utilize close-monitoring and real-world evidence approaches to augment RCTs conducted within smaller populations.

The 21st Century Cures Act contains provisions related to complex adaptive trial designs, including requiring that the FDA hold a public meeting and issue guidance documents that would assist sponsors in incorporating complex, adaptive designs and novel statistical modeling into new drug applications.

The PDUFA commitment letter also contains provisions that facilitate the advancement and use of complex, adaptive, Bayesian, and other novel clinical trial designs, including development of staff capacity, conducting a pilot program, convening a public workshop, and publishing guidance.

In its report *Using Real-World Evidence to Accelerate Safe and Effective Cures*, BPC recommended that the FDA begin to explore a flexible, adaptive, life-cycle approach to drug approvals that would use continuously generated evidence from close monitoring (now more feasible given widespread adoption of technologies), as well as observational studies and other real-world evidence, to augment data generated from randomized controlled trials, to support approval of drugs that have been shown to be safe and effective for well-defined subpopulations.

BPC Recommendations on Adaptive Approaches to Drug Development

1. The FDA should develop a new program to develop and test a new adaptive pathway approach, engaging experts and stakeholders through a public process, to expand the capacity for drug development, with the following key attributes:
   - Iterative phases of development, beginning with initial marketing authorization to a restricted patient population, then expanding to wider populations based on risk-benefit ratios;
   - Gathering evidence through close-monitoring and other real-world evidence, to supplement RCTs; and
   - 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:
   - Qualifying criteria for the program, which will determine which types of drugs at what stages could be considered for the adaptive pathway approach;
   - 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;
   - Methods for early involvement of patients, clinicians, payers, industry, and regulators; and
   - 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 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.

4. 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.

5. The FDA should develop—or cause to be developed—a report that describes the state of the art in adaptive trial designs, their utility and use, and progress in biostatistical methodologies, artificial intelligence, decision support systems, and other methods.

3. Incorporate the Patient Voice into the Drug Development Process

Patients are the ultimate beneficiaries of biomedical innovation as new treatments extend and improve lives. In recent years, patients and their advocates have transitioned from merely recipients of care to drivers of the quest for new cures, through advocacy and collection of the scientific evidence necessary to identify unmet needs for researchers and industry. Patients want to be engaged as partners in the drug development process to accelerate the identification of new targets in their diseases and increase the FDA's acceptance of uncertainty (improving benefit-risk assessment). This involves incorporating patient input and experiences into the drug development process.

The 21st Century Cures Act contains several provisions to support patient-focused drug development including requiring that the FDA make a statement regarding any patient experience data that was used at the time a drug is approved; issue guidance regarding how patient experience data will be used in regulatory decision-making, as well as other guidance regarding both data collection and submission; and prepare a report assessing the use of patient experience data in regulatory decision-making.

The FDA formally engaged consumer and patient stakeholders as part of its user fee reauthorization process. BPC was pleased to fully engage in this process, and the resulting user fee commitment letters clearly reflect an increased focus on the needs of the patient. The PDUFA commitment letter builds upon provisions in the 21st Century Cures Act by increasing staff capacity; developing guidance documents on approaches and methods; creating and maintaining a repository of publicly available tools on the FDA's website; conducting a public workshop to gather patient and caregiver ideas, experiences, and recommendations on approaches; and enhancing benefit-risk assessment.

BPC commends Congress for implementing provisions contained in the PDUFA commitment letter within the FDARA Discussion Draft, which—together with implementation of the 21st Century Cures Act—will assure the incorporation of patient perspectives into regulatory decision-making.

4. Enhance the Use of Drug Development Tools, Such as Biomarkers

Drug development tools, including biomarkers, are methods, materials, or measures that aid the drug development process. A biomarker—which is a type of drug development tool—is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention.[28] Biomarkers can be used to select patients for inclusion in clinical trials, predict or identify safety problems related to a candidate drug, or reveal a pharmaceutical activity expected to predict an eventual benefit from a treatment.[29]

Despite the promise of biomarkers, there are still significant barriers associated with the discovery, validation, regulatory acceptance, qualification, and use of these tools. Barriers include lack of scientific and consistent evidence, methodological challenges, lack of regulatory clarity, and logistical and operational issues associated with implementation.[30,31,32,33]

The 21st Century Cures Act requires the FDA to establish a review pathway for biomarkers and other drug development tools that can be used to help shorten drug development time and reduce the failure rate in drug development.

The PDUFA commitment letter identifies additional steps that the FDA will take to enhance the drug development tools qualification pathway for biomarkers, including increasing staff capacity, developing and publishing a taxonomy for biomarker usage, developing a framework and publishing guidance on general evidentiary standards for biomarker qualification, and listing biomarker qualification submissions on a public website.

BPC commends Congress for implementing provisions contained in the PDUFA commitment letter within the FDARA Discussion Draft, which—together with implementation of the 21st Century Cures Act—will improve and expand the qualification and use of biomarkers to facilitate the development of safer, more effective medical products and increase the efficiency and effectiveness of the drug development process.

5. Advance Development of Combination Products

For historical reasons, the FDA regulates drugs in its Center for Drug Evaluation and Research, devices in its Center for Devices and Radiological Health, and biologics in its Center for Biologics and Research. Some of the most innovative products are hybrids—neither pure devices, nor drugs or biologics. Examples include drug-eluting stents for the treatment of coronary artery disease, inhalation devices with insulin for the management of diabetes, and a transdermal patch for treatment of early Parkinson's disease.

The FDA expects to receive large numbers of combination products for review as technological advances continue to merge product types and blur these historical lines of separation among the FDA's medical product centers. Because combination products involve components that would normally be regulated under different types of regulatory pathways, and frequently by different FDA centers, they raise challenging policy, regulatory, scientific, and review management issues.

The 21st Century Cures Act includes several provisions to improve the regulation of combination products, requiring that the FDA meet with sponsors and agree early in the development process on how best to study the product to meet the standard for approval and clarify how dispute resolution works when the different centers of the FDA do not agree.

The PDUFA commitment letter also includes several steps that the FDA will take to advance development of combination products, including improving capacity and training, streamlining review processes, effectively evaluating and allocating resources, establishing policies and procedures, clarifying points of contact, establishing timelines, and publishing guidance. The commitment letter also provides for independent third party assessment of current practices.

BPC commends Congress for implementing provisions contained in the PDUFA commitment letter within the FDARA Discussion Draft, which—together with implementation of the 21st Century Cures Act—will improve the consistency of combination product reviews and address delays associated with development and evaluation of combination products.

Advancing Other Policy Priorities

BPC also recommends that Congress consider other provisions not currently included in the PDUFA commitment letter, that support the discovery, development, and delivery of safe and effective medical products, whether in the user fee reauthorization legislation or other legislation this year. Such recommendations—drawn from previous BPC recommendations and reports—are outlined below.

6. Clarify and Allow Sharing of Scientific Information to Inform Off-Label Use

The FDA approves and clears drugs, devices, and biologics generally for a specific use in a specific population. This approved use then goes on a product's label. In approving drugs and devices, and considering a product's overall risk-benefit profile, the FDA weighs the potential for off-label use. Sponsors are generally restricted from sharing information on off-label use of their products and may face legal action if they actively promote such uses.

Off-label use of a drug or combination of drugs often represents the standard of care. Indeed, more than one in five outpatient prescriptions written in the United States are for off-label therapies.[34] This is because to get approval for a new indication, a drug or device must again go through the clinical trial process. The FDA does not regulate the practice of medicine, and nothing prohibits physicians from prescribing drugs and devices off-label. In fact, physicians widely employ off-label uses, particularly in specialties such as oncology and pediatrics. Once off-label use is widespread, it can be very difficult to recruit patients for a clinical trial on such off-label uses. However, studies have found that doctors may not always understand which uses of a drug or device are on-label and thus have scientific evidence behind them.[35] To balance the risks and benefits of off-label uses, physicians need reliable and up-to-date scientific information concerning such uses.

Although the FDA has issued guidance to the industry addressing the distribution of articles and publications on off-label indications, precisely what manufacturers can and cannot say regarding off-label uses for their products remains unclear.[36] The threat of criminal enforcement or civil suits resulting from the dissemination of information on off-label use constrains the ability of drug sponsors to communicate with health professionals. Others have argued that providing truthful and non-misleading information regarding off-label use is legal and is protected commercial speech under the First Amendment. These issues have been debated in the courts. The FDA issued a proposed rule in 2016, *Amendments to Regulations Regarding Intended Uses*, as well as a memorandum in January 2017, *Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*.[37,38] To date, issues have remained unresolved.

In the 21st Century Cures Act, Congress expanded the scope of economic information manufacturers could communicate with payors.[39] In March 2017, Rep. Morgan Griffith (R-VA) introduced legislation that would permit exchange of scientific information between manufacturers and health care decisionmakers regarding off-label use of medical products.[40] Congress should further clarify and allow increased sharing of scientific information regarding off-label use of approved medical products with health care professionals, through the following actions:

BPC Recommendations for Off-Label Communications:

1. Require the FDA to issue rules that clarify how manufacturers can disseminate truthful, non-misleading, scientific information about a drug or device that is not included in the approved labeling for the product.

2. Create a safe harbor for the dissemination of truthful and non-misleading, clinically relevant, peer-reviewed literature and other information on off-label use of drugs to health care professionals.

3. Require drug manufacturers to share data on safety and efficacy for off-label uses with researchers, regulators, and insurers, for the purpose of rapidly validating emerging uses for established therapies.

7. Clarify Regulatory Authority Related to Laboratory-Developed Tests

Regulatory authority associated with laboratory-developed tests (LDTs) remains unclear, uneven, and duplicative. In October 2014, the FDA issued a long-anticipated draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests*, which was met with significant negative feedback.[41] In November 2016, the FDA announced that it would not finalize the draft guidance.[42] In January 2017, the FDA released a discussion paper outlining its synthesis of feedback from stakeholders, and noted that it wanted to give Congress the opportunity to develop a legislative solution for oversight.[43] Bipartisan activity on this issue has continued recently with Representatives Larry Buschon, MD (R-IN) and Diana DeGette (D-CO) releasing draft legislation building on the discussion draft reviewed during the 21st Century Cures efforts.[44]

Congress should clarify regulatory authority related to LDTs by performing the following:

BPC Recommendations on Laboratory-Developed Tests:

1. Require the development of a risk-based regulatory framework for the regulation of LDTs that promotes innovation, protects patient safety, and avoids regulatory duplication.

2. Require consideration of the relevant proposals of patient, physician, industry, and laboratory stakeholders when developing the risk classification scheme.

3. Require that the framework:

    a. Specify a risk classification for LDTs.

        i. Risk should be defined in terms of the risk that the test produces unreliable or inaccurate information that is used to make a clinical decision; this differs from the risk posed by therapeutic devices that could cause direct bodily harm;
        ii. Such classification should align the risk classification of an individual LDT for a given indication with the risk classification of an IVD for the same intended use; and
        iii. Further, such classification scheme should take into account the control in place for a given LDT (for example, the presence or absence of accreditation, proficiency tests, or other means to ensure laboratory test quality).

    b. Ensure that clinical validity information on LDTs is developed and available for each LDT;

    c. Assure that information on diagnostic errors stemming from LDTs is available to the public (for example, false positives and false negatives);

    d. Leverage the information available in the existing NIH Genetic Test Registry to achieve the framework's goals; and

    e. Address areas of overlap and regulatory uncertainty as it relates to the role of the FDA and CMS through its Clinical Laboratory Improvement Amendments authorities.

4. Require the FDA to examine its current risk classification scheme for traditional in vitro diagnostic devices (IVDs) to ensure that it aligns with the unique nature of risk associated with diagnostic tests. The FDA should be required to provide a report on this examination within two years to Congress. Like LDTs, IVDs do not pose risks of direct harm, in and of themselves, to patients.

8. Advance a Registry for Regenerative Cell Therapies

Regenerative cell therapy—which involves the use of human cells to restore healthy function in the human body—represents the next generation of rapidly emerging, groundbreaking treatments, showing tremendous promise in the areas of cardiology, neurology, oncology, orthopedics, pulmonary, psychiatry, and ophthalmology.[45] The 21st Century Cures Act contained several provisions that are expected to increase the availability of safe and effective regenerative cell therapy treatments for Americans in need.

As the use of such therapies becomes more widespread, there is a critical need to track the types of cells utilized as therapies, methods of administration, and measurement of clinical and safety outcomes on a regular basis through a national registry. These data will be used to monitor safety and inform the development of these novel therapies, as well as to inform clinical and patient decision-making.

A registry is a data collection tool or database that contains information about patients' medical conditions and/or treatments. The use of registries is widespread for a variety of purposes, including research, improving understanding of the natural history of disease, supporting collection of post-market data to respond to FDA post-market surveillance commitments, collecting data for quality improvement programs, supporting understanding of effectiveness of treatments, and the certification of physicians to meet professional requirements.[46] Increasingly, registries are expected to serve as "real-world evidence" to support the medical product development and approval process and are identified as such within the 21st Century Cures Act.

The development and use of regenerative cell therapies is expected to increase considerably over the next several years. There is a critical need to establish a national registry for such therapies to support research, rapidly expand the evidence base regarding effectiveness of treatments, inform safety surveillance efforts, improve practice, and provide additional data to inform patient decision-making.

There is precedence for the establishment of registries for cell therapies. One example is the Organ Procurement and Transplantation Network, a national registry for organ matching established by the National Organ Transplant Act of 1984, and operated by the United Network for Organ Sharing, a private, non-profit organization under federal contract.[47] Another key example is the Stem Cell Therapeutic Outcomes Database, operated by the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin.[48]

The Organ Transplants Amendments Act, introduced in 1987 and passed in 1988, directed the HHS Secretary to establish, by grant or contract, a registry of voluntary bone marrow donors and authorized appropriations (funding) for fiscal years 1989 and 1990.[49] Reauthorization and continued funding were provided by the Transplant Amendments Act of 1990 and the National Bone Marrow Registry Reauthorization Act of 1998.[50,51]

The Stem Cell Therapeutic and Research Act of 2005 created the C.W. Bill Young Cell Transplantation Program as the successor to the National Bone Marrow Program. The program was expanded to include a registry for publicly banked cord blood units and established a network of public cord blood banks through the National Cord Blood Inventory. The 2005 Act also established and authorized funding for the Stem Cell Therapeutic Outcomes Database—defined as a "scientific database of information relating to patients who have been recipients of a stem cell therapeutics product (including bone marrow, cord blood, or other such product) from a donor."[52]

Key provisions of the Stem Cell Therapeutic Outcomes Database (Outcomes Database)—which was reauthorized and provided additional funding through the Stem Cell Therapeutic and Research Acts of 2010 and 2015—are summarized below:[53,54]

- The Outcomes Database shall include information in a standardized electronic format with respect to patients' diagnosis, transplant procedures, results, long-term follow-up, and such other information the HHS Secretary deems appropriate, to conduct an ongoing evaluation of the scientific and clinical status of transplantation involving recipients of a stem cell therapeutics product from a donor;
- The entity awarded a contract for the Outcomes Database shall submit an annual report to the HHS Secretary concerning patient outcomes with respect to each transplant center, based on data collected and maintained by the entity; and
- The Outcomes Database shall make relevant scientific information not containing individually identifiable information available to the public in the form of summaries and data sets to encourage medical research and to provide information to transplant programs, physicians, patients, entities awarded contracts under the broader Program, and cord blood banks.[55]

The Stem Cell Therapeutic and Research Act of 2015 also included provisions requiring the HHS Secretary to review the state of science using adult stem cells to develop new therapies and consider the inclusion of new therapies in the C.W. Bill Young Cell Transplantation Program. By June 30, 2019, the HHS Secretary is required to submit a report to Congress containing recommendations on the appropriateness of such new types of therapies for inclusion in the program.[56]

Currently the Outcomes Database is operating under the authorization of the Stem Cell Therapeutic and Research Act of 2015, which reauthorized and provided $30 million in annual funding to the Database through 2020.[57] Since its inception in 2005, the Outcomes Database has been operating under federal contracts—administered by the Health Resources and Services Administration awarded to the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin.[58]

Congress should consider expanding the scope of the Outcomes Database to include reporting of other regenerative cell therapies. While the definition of the Outcomes Database contained in the Stem Cell Therapeutic and Research Act of 2005 refers to a scientific database

of "a stem cell therapeutics product (including bone marrow, cord blood, or other such product) from a donor," activities conducted under the program since 2005—which focus primarily on bone marrow and cord blood, combined with language contained in the Stem Cell Therapeutic and Research Act of 2015 that calls for the HHS Secretary "to review the state of science using adult stem cells to develop new therapies and consider the inclusion of new therapies in the Cell Transplantation program," create ambiguity regarding whether all regenerative cell therapies can be included in the Outcomes Database. Furthermore, current authorized funding levels are not sufficient to develop and maintain additional cell therapies beyond bone marrow and cord blood.

Finally, the June 30, 2019 deadline for the HHS Secretary to "submit a report to Congress containing recommendations on the appropriateness of such new types of therapies for inclusion in the program," is not timely enough to facilitate the development and launch of an Outcomes Database for the rapidly growing field of regenerative medicine.

BPC Recommendations on Advancing a Registry for Cell Therapy:

1. Congress should clarify that the Stem Cell Therapeutics Outcomes Database referred to in the Stem Cell Therapeutic and Research Act of 2015 is authorized to include other regenerative cell therapies beyond bone marrow and cord blood and authorize additional funding to support the expanded scope of the Outcomes Database.

2. Congress should authorize additional funding to support the expanded scope of the Outcomes Database.

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