BIPARTISAN POLICY CENTER

July 23, 2015

The Honorable Lamar Alexander
Chairman, Committee on Health,
Labor & Pensions
United States Senate
Washington, DC 20510

The Honorable Patty Murray
Ranking Member, Committee on Health, Education,
Education, Labor & Pensions
United States Senate
Washington, DC 20510

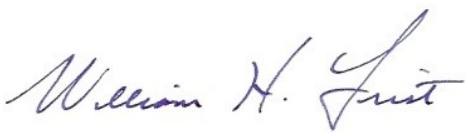
Dear Chairman Alexander and Ranking Member Murray:

On behalf of the Bipartisan Policy Center (BPC), thank you for the opportunity to provide input in response to your request for technical assistance on bipartisan Senate Health, Education, Labor, and Pensions (HELP) Committee efforts to support and advance the pace of medical research, innovation, development, and delivery of treatments and cures in America.

Earlier this year BPC launched *FDA: Advancing Medical Innovation*, to identify the major challenges associated with advancing medical innovation and develop a set of policy recommendations for addressing them. We are proud to lead this initiative with the support of advisory committee members Marc Boutin, JD, CEO, National Health Council; Mark McClellan, MD, PhD, senior Fellow and director, Health Care Innovation and Value Initiatives, Center for Health Policy, Brookings Institution; and Patrick Soon-Shiong, MD, chairman and CEO, Institute for Advanced Health.

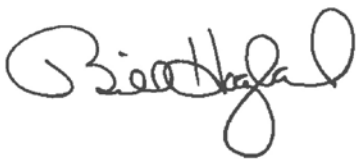
Given intensive ongoing HELP Committee efforts and your request, we have attached to this letter our preliminary input for your consideration. We hope that you find it helpful, and look forward to an ongoing and productive conversation with you and your staff as our respective efforts continue.

Sincerely,



Senator William H. Frist, MD
Former Senate Majority Leader
Co-Chair, Bipartisan Policy Center Initiative
on FDA: Advancing Medical Innovation

Congressman Bart Gordon
Former Member, U.S. House of Representatives
Co-Chair, Bipartisan Policy Center Initiative
on FDA: Advancing Medical Innovation



G. William Hoagland
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INTRODUCTION

The past two decades have been marked by unparalleled advances in science and technology. Public- and private-sector investment in biomedical research has exceeded $100 billion per year over the last ten years.[1]

In this century alone, the nation has witnessed a number of significant breakthroughs—most notably the recent cure for Hepatitis C, a disease that according to the U.S. Centers for Disease Control and Prevention (CDC) currently affects more than three million Americans.[2,3] Americans have also seen advances in oncology, through new treatments based on new genetic understanding. However, even the most bullish proponents of pharmaceutical, biotechnology, and medical device innovations acknowledge that the United States has only scratched the surface when it comes to addressing unmet medical needs. Furthermore, progress across all therapeutic domains has been inconsistent.[4]

The notable progress in oncology and virology has not been matched by similar breakthroughs in many other therapeutic areas. Few novel treatments for mood disorders and other brain-based diseases have emerged over the past several decades, despite considerable investment and the enormous impact of these diseases on patients, their loved ones, and the communities where they reside.[5,6,7,8] A number of promising drugs and biologics developed to arrest the course of Alzheimer's disease have yielded disappointing results.[9,10] America's wounded warriors continue to lack demonstrably effective treatments, let alone cures, for their invisible wounds.

Many substantial unmet medical needs remain and tens of millions of Americans have neither cures nor effective treatments for what ails them.

There are literally hundreds of examples, including:

- In 2015, there will be an estimated 1,658,370 new cancer cases diagnosed and 589,430 cancer deaths in the United States.[11]
- An estimated 5.3 million Americans suffer from Alzheimer's disease.[12] It is the only disease among the top ten causes of death in the United States that cannot be prevented or cured.
- Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this number does not reflect the thousands of cases that go undetected. An estimated seven to ten million people worldwide are living with Parkinson's disease.[13]

- Heart disease (which includes heart disease, stroke, and other cardiovascular diseases) remains the No. 1 cause of death in the United States, killing nearly 787,000 people alone in 2011.[14]

The personal and familial challenges generated by these diseases—and the more than 10,000 other known diseases for which fewer than 500 approved treatments exist—tell only part of the story.[15]

The extraordinary cost of care for those for whom neither cures nor effective treatments are available threatens to overwhelm America's social safety net and significantly constrain the capacity to address equally pressing challenges at home and abroad.

For example, Americans spend more than $250 billion annually to care for people with Alzheimer's disease. Absent a cure or an effective treatment that alters the course of the disease, this figure is expected to exceed $1.2 trillion by 2050.[16] But that cost could be cut by a third and could reduce the number of Americans with Alzheimer's by 42 percent in 2050 by delaying the average onset of the disease by just five years. And those figures don't even account for the benefits of alleviating the physical and emotional toll on families and loved ones; dementia caregivers had $9.7 billion in additional health care costs of their own in 2014.[17]

While the United States has invested more than $1.5 trillion in research and development (R&D) over the past two decades, it is not clear that such investments have given rise to a commensurate level of progress in the discovery, development, and approval of medical products.

As noted in Figure 1, the level of R&D efficiency, defined by the number of new drugs brought to the market per billion U.S. dollars of R&D spending, has declined fairly steadily over the last 60 years.[18] BPC's extension of Scannell et al's analysis of R&D efficiency shows slight improvements over the last year.[19]

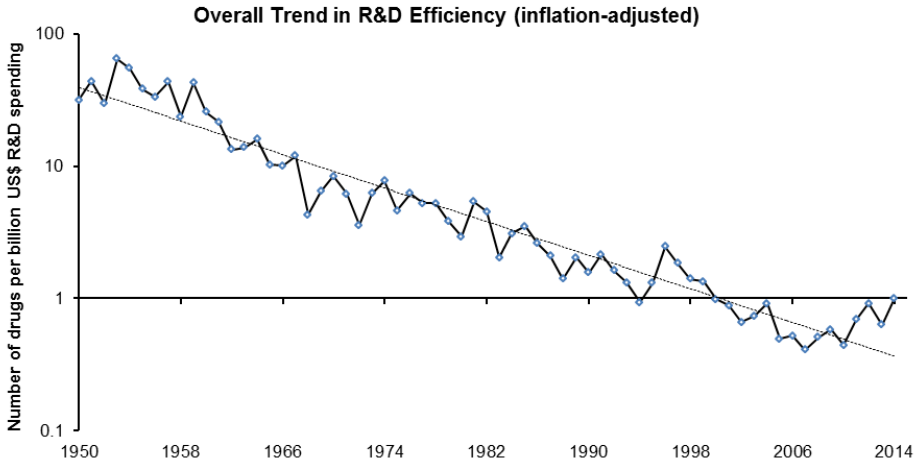

Figure 1: Overall Trend in R&D Efficiency (inflation-adjusted)[18,19]

The most reliable studies suggest it costs approximately $2 billion and takes more than a decade to bring a new drug to market.[20,21,22,23] The average cost of successfully launching a new molecular entity differs little between large pharmaceutical or small biotechnology companies.

Improving the efficiency of R&D and development of safe and effective medical products requires significant action on the part of academic researchers, the life sciences industry, and government regulators throughout the phases of discovery, development, and evaluation. Congress plays a critical role in removing barriers and creating an environment that accelerates the development and delivery of safe and effective medical products.

We have identified policy actions that Congress should take to accelerate medical innovation, and to reduce both the time and cost of developing and delivering safe and effective drugs and devices to patients.

It is important to note that actions associated with improving medical product discovery, such as increased federal support of biomedical research, are also needed, but are not the focus of this report.

Recommended policy actions fall into four primary areas, details for which are outlined below:

1. Improving the Medical Product Development Process
2. Increasing Regulatory Clarity
3. Strengthening the FDA's Ability to Carry out its Mission
4. Increasing Investment in Medical Products to Address Unmet and Public Health Needs

Together, these recommendations not only reduce the time and cost associated with the development and delivery of medical products, they are also expected to considerably increase the competitiveness of U.S. companies in the global marketplace.

This letter recommends various actions that should be taken to advance medical innovation. Many of these recommendations could require additional resources not now available within FDA's $4.8 billion annual budget. If additional funding is required to implement the recommendations of this report, the FDA budget should be carefully reviewed and assessed to determine if current, existing programs remain priorities relative to these recommendations. If they become lower priorities, then reallocating existing resources within the FDA budget or related health agencies' budgets, should first be considered as additional resources. Second, if a net increase in funding is necessary to fund these recommendations, then additional resources should be provided through reduced federal spending from automatic spending

programs (e.g., entitlements), increased user fees, revenues, or a combination of all three. The goal is to improve the health of the American public, but not at the expense of making the federal ledger less healthy.

Congress has demonstrated significant bipartisan leadership in advancing proposals that will accelerate the development and delivery of both safe and effective drugs and devices to the American people.

The policy recommendations included in this letter will significantly advance medical innovation and support patients in gaining timely access to treatments that can cure their diseases, improve their conditions, and promote their general health and wellbeing.

SUMMARY OF FINDINGS

1. Improving the Medical Product Development Process

1.1 **Congress should accelerate the generation and use of more relevant evidence** to support the development and delivery of drugs and devices, and enable (1) assessment of the full range of factors not easily characterized in randomized clinical trials, (2) more precise design of clinical trials, and (3) better decision making regarding value and coverage, by performing the following (see page 17 for more details):

1. Require FDA to develop a program to evaluate and prioritize the use of real-world evidence—including data from both clinical and patient experience—to support post-approval study requirements, approval of new indications for existing medical products, and ultimately improved clinical trials used for regulatory review. The FDA should engage stakeholders and experts in this process. To support this work, require FDA to develop a detailed plan within 18 months, begin implementation of a program within 24 months, and issue final guidance within 48 months.
2. Direct FDA to develop a framework for modernizing the traditional, randomized, large-scale (Phase III) clinical trials model of evidence development for regulatory review, engaging experts and stakeholders through a collaborative public process. The framework should provide an approach and regulatory requirements for incorporating data from pragmatic, randomized studies of broader populations where care is provided under more typical settings, as well as data from randomized clinical trials.
3. Promote public- and private-sector investment in the development of a broad-based, nationwide virtual infrastructure to obtain more robust real-world evidence on both the safety and effectiveness of drugs and devices.

1.2 Congress should **improve and expand the qualification and use of biomarkers** to facilitate the development of safer and more effective medical products and increase the efficiency and effectiveness of the drug development process, by taking the following actions (see page 22 for more details):

1. Require FDA to establish a framework and process for the submission, review, and qualification of drug development tools.
2. Authorize and strongly encourage FDA to engage with experts and stakeholders through biomedical research consortia, to support the review of qualification submissions.

3. Improve transparency of drug development tool-related activities by requiring FDA to make information regarding the number of qualification-related requests and plans submitted and the number of drug development tools qualified, publicly available.
4. Require FDA to develop—through a collaborative public process—guidance on biomarkers which contains:
    a. A conceptual framework describing appropriate standards and scientific approaches to support development;
    b. Recommendations for demonstrating the predictability of surrogate endpoints for purposes of supporting accelerated approval; and
    c. Description of the requirements for entities seeking qualification, reasonable timelines for FDA review, and processes by which both entities and FDA may consult with biomedical research consortia or others with expert knowledge and insights.

1.3 Congress should **improve and expand the use of patient-reported outcomes (PROs**) through the following actions (see page 25 for more details):

1. Require FDA to develop—through a collaborative public process—guidance on PROs that contains the following:
    a. A standard, consistent process for submission, review, and qualification of PRO instruments;
    b. Description of the requirements for entities seeking qualification, reasonable timelines for FDA review of submissions, and processes by which both entities and FDA may consult with biomedical research consortia or others with expert knowledge and insights; and
    c. A conceptual framework describing appropriate standards and scientific approaches to support the development of PRO instruments.
2. Create a mechanism to improve communication between FDA and sponsors regarding the development of approaches for the use of PRO instruments.

1.4 Congress should **assure the incorporation of patient perspectives into benefit-risk assessment** associated with regulatory decision-making for drugs, by taking the following actions (see page 28 for more details):

1. Require FDA to establish and implement a process under which an entity may submit patient preference data to enhance a structured risk-benefit framework.
2. Require FDA to publish guidance regarding process and timelines for the submission of patient preference data; methodological considerations and approaches for both collection and assessment of such data for benefit-risk; and methodologies, standards, and potential experimental designs for patient-reported outcomes.
3. To provide regulatory clarity and a predictable environment for communications, specify that the exchange of truthful and non-misleading information among patients, patient caregivers, or patient advocates and medical or scientific staff of a manufacturer, the purpose of which is to discover and understand patient or caregiver perspectives related to the specific disease from which a patient suffers, shall not be considered promotion or commercialization of the investigational drug or biologic, or a violation of the Federal Food Drug and Cosmetic Act.

1.5 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 (see page 31 for more details):

1. Require FDA to issue rules which 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.

1.6 Congress should **promote harmonization of international standards**, through the following (see page 32 for more details):

1. Require FDA to establish a clear process for recognizing standards for medical devices and require FDA to publish guidance regarding such process.
2. Encourage FDA's commitment to and actions related to the harmonization of international standards, including, but not limited to, those related to manufacturing facilities.
3. Require FDA and the U.S. Trade Representative to report on progress on international standards harmonization.
4. Encourage FDA to participate in mechanisms that facilitate the sharing of best practices internationally.
5. Encourage FDA to explore reciprocity of approval among highly developed trading partners for well-understood drug or device classes or products for which there is high unmet medical need.

1.7 Congress should **improve the interoperability of health information technology** (IT) by requiring the following (see page 36 for more details):

1. Require the federal government to adopt standards for health IT.
    a. Federally adopted standards should include those required for accurate identification and matching of patient data, provider identification, transport, terminologies, clinical models, clinical data query language, security, and application interfaces.
    b. Federal adoption should encompass inclusion of standards within certified electronic health record (EHR) technology required under the Centers for Medicare and Medicaid Services (CMS) Medicare and Medicaid EHR Incentives Programs, health IT systems procured by federal agencies, various electronic health data submissions required by federal agencies, and health IT systems directly funded through federal agency contracts, grants, and cooperative agreements.
2. To assure that federal agencies comply with federal standards, require each federal agency to report annually on its compliance with federally adopted standards, and require the Government Accountability Office (GAO) to issue a report, every two years, on federal compliance with such standards.

3. Designate responsibility for identification of standards for federal adoption to the Director of the Office of Management and Budget (OMB), with support from the National Coordinator for Health IT.
4. Require that any standards for federal adoption are (1) developed by a voluntary consensus body as defined by the National Technology Transfer and Advancement Act and OMB Circular A-119, (2) tested prior to adoption, and (3) established through formal rulemaking and a collaborative, public process, to assure appropriate public input and transparency.
5. Require that standards for federal adoption be published annually and that effective dates for adoption should not occur until at least 12 months subsequent to publication.
6. Authorize the Director of OMB and the National Coordinator for Health IT to use federal advisory committees to assist with the identification of areas for which standards are needed and evaluation of standards against established criteria for federal adoption, to inform federal decision-making.
7. To promote testing and validation of standards adoption and interoperability of systems, direct the National Institute of Standards and Technology (NIST) to develop and make publicly available methods for testing compliance with federal standards and authorize federal agencies to recognize independent testing and certification bodies that will provide assurance that software complies with federally adopted standards.

2. Increasing Regulatory Clarity

2.1 Congress should provide **further clarity regarding regulatory authority associated with health IT** and assure the implementation of a risk-based oversight framework for health IT that both promotes innovation and protects patient safety, by performing the following (see page 40 for more details):

1. Clarify that health IT should not be subject to regulation as a medical device by FDA, except when determined by the HHS secretary that the product poses a significant risk to patient safety.
2. Require the HHS secretary to recognize independent bodies to develop voluntary consensus standards, evaluate and render decisions on compliance with such standards, and facilitate voluntary patient safety reporting to continually improve the development, implementation, and use of health IT.

3. Clarify that current law enables those who develop and implement health IT to participate in patient safety activities and direct the HHS secretary to extend confidentiality protections to health IT developers to permit them to report patient safety events, view patient safety organization-protected information, receive and analyze patient safety event reports, create and receive quality improvement reports from patient safety organizations, and work with providers to develop strategies for improvement.

2.2 Congress should **clarify regulatory authority related to laboratory-developed tests** (LDTs) by performing the following (see page 44 for more details):

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 including but not limited to those of the Diagnostic Test Working Group and the College of American Pathologists, when developing the risk classification scheme.
3. Notwithstanding the FDA's October 3, 2014 draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests* 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 which 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 (i.e., 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 (e.g., 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 FDA and CMS through its Clinical Laboratory Improvement Amendments (CLIA) authorities.

4. Require FDA to examine its current risk classification scheme for traditional IVDs to ensure that it aligns with the unique nature of risk associated with diagnostic tests. 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.

2.3 Congress should **improve regulatory clarity associated with precision medicine** by establishing a working group that includes the FDA, the National Institutes of Health (NIH), NIST, and the Office of the National Coordinator for Health IT (ONC), to develop and submit a report to Congress. The report should characterize the rapidly evolving precision medicine landscape and develop a risk-based regulatory framework for precision medicine that protects patient safety, promotes innovation, and is flexible enough to accommodate rapid changes in science. The working group should leverage and build upon existing efforts of federal agencies, as well as the President's Precision Medicine Initiative (see page 48 for more details).

2.4 Congress should **improve the consistency of combination product reviews and address delays associated with the development and evaluation of combination products** through the following actions (see page 50 for more details):

1. Amend the Food, Drug, and Cosmetic Act to provide greater clarity regarding designation of combination products.

2. Require FDA to take actions to address the lack of coordination and agreement among collaborative centers regarding requirements, the timeliness of response, and the lack of clarity regarding data requirements.

3. Require FDA to publish a timely list of decisions to requests for designation (i.e., which FDA center has primary jurisdiction) and encourage FDA to abide by precedent when faced with a similar combination product, unless FDA can present a rationale for making a different decision.

4. Require FDA to track and issue reports that demonstrate that milestone meetings involving sponsors and FDA are meaningfully attended by the non-lead FDA center(s), and that reviewers in non-lead centers have completed their reviews within timelines consistent with user fee performance goals of the coordinating center, e.g., the new molecular entity review model expectations and the principles outlined in the Good Review Management Practices.

2.5 Congress should **improve the regulatory framework for regenerative medicine** by performing the following (see page 53 for more details):

1. Require FDA to provide additional clarity regarding the regulation of regenerative medicine, specifically addressing adult autologous stem cell therapy.
2. Encourage FDA's recognition of the unique nature of stem cell therapeutics, in particular autologous or similar therapies, and the fact that they require a different regulatory approach than that applied to traditional drugs or biologics. Explore the creation of a new regulatory category separate from HCT/P 351 or 361.

2.6 To **improve FDA's process for creating guidances and regulations**, Congress should perform the following (see page 56 for more details):

1. Require FDA to seek public input on a guidance prioritization scheme.
2. Clarify that FDA should use formal rulemaking processes when making substantive policy changes.
3. Authorize and encourage FDA to use public-private partnerships to develop and draft guidance documents requiring significant scientific input, while leaving final approval authority with the agency.
4. Explore and address administrative barriers to finalizing guidances.

3. Strengthening the FDA's Ability to Carry Out its Mission

3.1 Congress should **assure adequate capacity and scientific expertise at the FDA** by performing the following (see page 58 for more details):

1. Require the FDA to conduct an organizational review process to identify gaps in scientific expertise, capacity to carry out various aspects of its mission, and opportunities for streamlining and using existing resources more efficiently.

2. Require FDA, working with HHS and the Office of Personnel Management, to modernize human resources practices and systems to address gaps in scientific expertise and capacity, by performing the following and reporting to Congress on progress, within 12 months:
    a. Reviewing and improving recruiting, hiring, and retention strategies;
    b. Implementing direct hiring authority;
    c. Allowing the use of qualified blind trusts or other appropriate mechanisms to address conflict-of-interest concerns;
    d. Exploring and improving personnel policies that support appropriate turnover; and
    e. Implementing additional exemptions from standard federal agency hiring policies (including increasing the number of employees that can exceed federal salary compensation caps).
3. Eliminate barriers that prevent FDA staff from attending scientific conferences and meetings, which are crucial to helping them keep up with the latest scientific developments.
4. Encourage FDA to expand its partnerships with academic institutions to raise awareness of the opportunities at the FDA and build a pipeline of talented graduates who can establish a career at the agency.
5. Encourage FDA to improve its IT infrastructure to support knowledge management and sharing, workflow management, and more effective communications across reviewers and centers, as well as with sponsors.
6. Create for FDA a waiver of the OMB Paperwork Reduction Act to further FDA's ability to more readily collect information from industry, academia, patient groups, and other experts and stakeholders through voluntary surveys and questionnaires, to rapidly expand knowledge and insights.

3.2 Congress should **encourage the effective use of public-private partnerships** at the FDA by performing the following (see page 62 for more details):

1. Reconfirm and encourage the FDA to use its existing authority to use partners and trusted intermediaries to augment FDA internal resources, particularly for novel or complex technologies that may be outside of the FDA's normal expertise.

2. Require the FDA to monitor, evaluate, and report on the outcomes and effectiveness of existing public-private partnerships to determine whether additional investment in these programs and/or further coordination and accountability associated with such programs is warranted, as well as whether outdated or ineffective public-private partnerships should be phased out.
3. Support the launch of a study to both assess current conflict of interest policies associated with advisory groups and develop recommendations that both effectively address conflict of interest concerns and enable FDA to gain input from a broad and representative set of individuals representing patients and academia.

3.3 Congress should **improve the FDA's internal review processes** by performing the following (see page 64 for more details):

1. Direct FDA to both conduct and implement strategies in response to an organizational study of its review and approval processes; this study should evaluate review times, identify root causes of delays, identify best practices, and recommend measurable goals and actions to support faster turnaround times. As part of this effort, FDA should conduct a best practices study of review divisions to identify best practices that can be applied across divisions.
2. Direct FDA to develop an inter-agency education and training program to implement best practices across centers and divisions.
3. Direct FDA to establish a monitoring system to track and report progress against implementation goals and impact on drug and device review times.

4. Increasing Investment in Medical Products to Address Unmet and Public Health Needs

4.1 Congress should **accelerate the development and approval of antibiotics** by performing the following (see page 67 for more details):

1. Require FDA to establish a program to expedite the approval of certain antibacterial and antifungal drugs for use in limited populations of patients at the request of the sponsor, which includes the following:
    a. Requires prominent labeling of the limited population antibacterial and antifungal drugs that indicates it is for a limited and specific population and requires the sponsor to submit promotional materials to the FDA for approval; and

   b. Allows the FDA to remove labeling and promotion restrictions if the drug is approved for broader use.

2. Require FDA to publish guidance describing criteria, process, and other considerations for demonstrating the safety and effectiveness of antibacterial and antifungal drugs approved for use in limited populations.
3. Require the FDA to publish an assessment of the program, hold a public meeting, and consider expansion of the limited use pathway and program beyond antibacterial and antifungal drugs.

4.2 Congress should **improve processes for early patient access to medical products** by performing the following (see page 70 for more details):

1. Require sponsors to make their policies on expanded access during clinical trials publicly available, including procedures for requests, qualification criteria, and single point of contact.
2. Require FDA to finalize guidance regarding how it interprets and uses adverse drug event data resulting from drug use under expanded access programs.

4.3 Congress should **increase incentives for the development of medical products with unmet medical needs** by creating a new regulatory pathway for dormant therapies, by performing the following (see page 71 for more details):

1. Give the FDA the authority to designate a new treatment as a “dormant therapy” if intended to treat an unmet medical need. A dormant therapy must not contain active ingredients that have been previously approved by the FDA.
2. Determine a fixed period of protection from generic and biosimilar competition for dormant therapies.
3. Require sponsors of approved dormant therapies designation to waive certain rights to patents of the approved dormant therapy at the end of the protection period.

SECTION 1: IMPROVING THE MEDICAL PRODUCT DEVELOPMENT PROCESS

1.1 Accelerating the Generation and Use of More Relevant Evidence to Improve the Development and Delivery of Drugs and Devices

Background

Clinical trials are the most critical and expensive phase of the drug development process, accounting for about $1.5 billion of the approximately $2 billion spent on bringing a new drug to market.[24] FDA's ultimate approval decision is largely based on data from clinical trials.

The vast increase in the amount of data collected electronically from both the clinical experience and the patient represents a new and significant opportunity to improve clinical trials. This holds true particularly for Phase III trials, which are relatively large trials involving thousands of participants with the disease and/or condition that the molecule is designed to treat, as well as for Phase IV trials and postmarket observational studies of safety, which are conducted after a drug is already on the market to determine if an approved molecule is effective for other potential indications or to provide additional data on safety.

Prior to approval, drugs and some devices are typically tested in several controlled settings using randomized controlled trials (RCTs). The use of biomarkers, adaptive trial designs, and other tools has improved RCT methodology, resulting in stronger evidence and improved clinical development efficiency. The tightly controlled nature of RCTs brings strong evidence, but only in a relatively small and narrowly defined population, limiting generalizability. Often missing from trials are representative samples of patients with multiple comorbidities, concomitant use of other drugs, varying races and ethnicities, ages at both the low and high ends of the spectrum, and different practice settings. Studies with relatively small sample sizes (e.g., 5,000-7,000 patients on average) and study durations that only allow for assessment of shorter-term outcomes further limit the evidence. As a result, clinical trials are limited in their ability to bring FDA (as well as clinicians and payers) desired evidence on both the benefits and the risks of products across those patient populations that actually use the products upon approval. Uncertainty remains regarding safe and effective use of products outside of the parameters of the RCTs. These limitations are particularly important for precision medicine, where information is needed about the effects of a new drug or device in specific subgroups of patients based on patient preferences, genomics, and other clinical factors.

FDA also reviews drugs and devices *after* approval through a combination of post-market reporting requirements and surveillance programs designed to offer continued confidence associated with the safety of a medical product once it hits the market.

Evidence gathered outside of carefully controlled trials—so-called "real-world evidence" captured from the actual experiences of patients during routine patient care—can significantly strengthen the evidence base for approval, safety, and effectiveness. Real-world evidence, including data about the use, benefits, and risks of a drug or device, can be derived from sources such as "pragmatic" randomized trials (i.e., large simple trials that mimic routine care in the real world setting) that can leverage both a virtual data infrastructure and non-randomized observational studies (e.g., prospective registries, retrospective database studies, etc.).

The considerable increase in the use of EHRs in the clinical setting, combined with the surge in the number of Americans recording health information through wearable devices or other electronic health tools, is significantly increasing the volume of real-world evidence available to support pre-market and post-market decision-making.

The introduction of real-world evidence into the clinical trials process will:

- Improve the generalizability of research findings to broader populations and real world clinical settings;
- Support the earlier evaluation of effectiveness to help with decision-making associated with payment and value;
- Bolster methods for post-market surveillance; and
- Improve confidence in methods designed to accelerate the development and approval of medical products, including those that fill serious, unmet medical needs.

FDA and the field in general have gained considerable experience and made significant progress in the development and use of real-world evidence to support post-market drug safety surveillance, including the experiences of FDA's Sentinel Initiative, the Observational Medical Outcomes Partnership, the Innovation in Medical Evidence Development and Surveillance program at the Reagan Udall Foundation for FDA, and the Observational Health Data and Sciences Initiative. FDA's work in this area is supported by the FDA Amendments Act enacted in 2007, which mandated FDA to establish an active surveillance system for monitoring drugs, using electronic data from health care information holders.[25] The Sentinel Initiative is FDA's response to that mandate. After five years of development, the Sentinel Initiative is being used by FDA as an integral component of their tools for monitoring the safety of medical products—mainly drugs, vaccines, and biologic products. Congress enacted legislation in 2012 mandating that FDA expand its surveillance work to include medical devices, but to date it has not directed specific resources to support this work.[26] Recently, the

National Medical Device Postmarket Surveillance System Planning Board released recommendations on how such a system could be implemented.[27]

The Patient Centered Outcomes Research Institute (PCORI) and the NIH have continued to make progress in developing a national infrastructure for conducting randomized and non-randomized observational studies. Their work holds promise for creating more opportunities to fill evidentiary gaps as drugs and devices are used in clinical practice.

In its *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation*, the President's Council of Advisors on Science and Technology (PCAST) recognized that the traditional binary approach to drug approval "fails to adequately acknowledge and signal evolving knowledge about risks and benefits." The report also highlighted the potential value of harnessing accumulating evidence from clinical experiences with medical products over time to support regulatory approval. PCAST advised that further "research and multi-stakeholder discussion" was needed and that FDA, under its existing regulatory authorities, should establish pilot projects to explore such approval mechanisms to develop evidence across the life-cycle of a drug from the pre-market through the post-market phase.[28] New pragmatic clinical trial designs that can augment Phase III clinical trials may offer important opportunities to explore such discussions and pilot designs.

Over time, FDA should consider the design, evaluation, and adoption of an alternative approval structure with a revised model that includes the use of a conditional or provisional release of a product into a controlled, real world environment. This would enable the evaluation of key effectiveness and safety endpoints under more real world circumstances. Real-world evidence plays a key role in this work.

In order to effectively leverage real-world evidence to improve the effectiveness and efficiency of the development and delivery of medical products, the following actions are needed:

To advance the use of real-world evidence in clinical trials within a regulatory context:

1. Improve the methods, tools, and infrastructure for developing real-world evidence to support clinical trials and inform regulatory decisions.
2. Develop a program to begin evaluating the methodologic gaps and appropriate approaches for using real-world evidence within clinical trials; and
3. Begin exploring a modernized approach to reform the traditional Phase III model to incorporate earlier evidence from more relevant patient populations under real-world conditions through the development of a framework and a pilot program.

To continue to advance the use of real-world evidence to support post-approval study requirements and approval of new indications for existing medical products:

1. Explore the strengths and weaknesses of systems and tools developed to capture, validate, and analyze real-world evidence for post-market studies; and
2. Identify and prioritize approaches to fill methodologic gaps to support uses of these data for such studies.

Finally, investment in a consensus framework and broad-based, reusable virtual data infrastructure is also needed for the implementation of new and efficient opportunities to develop more relevant evidence to support regulatory decisions. Such an infrastructure should be distributed and build upon the experiences of the multiple pilot projects conducted to date, to support the use of real-world evidence from randomized, pragmatic trials and observational studies for both pre-market and post-market efforts associated with drugs and devices.

Section 2062 of the 21st Century Cures Act (H.R. 6) passed by the House of Representatives on July 10, 2015, establishes a program to evaluate the potential use of evidence from clinical experience to support the approval of a new indication for an existing drug, or to help support or satisfy post-approval study requirements. The Act also requires the establishment of a framework within 18 months of enactment and the implementation of the program within 24 months. Finally, the Act requires the HHS secretary to issue draft guidance within 36 months and final guidance within 48 months of enactment and authorizes the secretary to make appropriations of $3 million to execute pilot demonstrations.[29]

Policy Recommendations

Accelerating the generation and use of more relevant evidence to support the development and delivery of drugs and devices will require the following actions:

1. Congress should require the FDA to develop a program to evaluate and prioritize the use of real-world evidence—including data from both clinical and patient experience—to support post-approval study requirements, approval of new indications for existing medical products, and ultimately improved clinical trials used for regulatory review. The FDA should engage experts and stakeholders, including representatives of regulated industry, academia, patient advocacy and disease research organizations, and others in the development of the program.

   Such a program should be designed to do the following:

   a. Evaluate the use of potential sources of data including EHRs, registry data, patient-generated health data, and administrative claims data;

b. Identify gaps in current data collection activities and development of strategies to fill those gaps;

c. Evaluate and agree upon standards and methodologies for data collection and analysis;

d. Identify priority areas, remaining challenges, and pilot opportunities that the program will address; and

e. Describe the context in which real-world evidence would enable more relevant evidence to support regulatory decisions.

FDA should develop the following to support implementation of the program and framework:

a. Within 18 months, develop a detailed plan for how the program would be implemented;

b. Begin implementation of the program within 24 months; and

c. Within 48 months, develop final guidance for industry on appropriate standards, methodologies, circumstances, and processes for which sponsors of drugs and FDA may incorporate real-world evidence in support of regulatory approval decisions, including expanding labeled indications and post-market study requirements.

2. Congress should require FDA to develop a framework for modernizing the traditional randomized, large scale Phase III clinical trial model of evidence development for regulatory review. The new model should provide an approach and regulatory requirements for incorporating data from pragmatic, randomized studies of broader populations where care is provided under more typical care settings (in addition to data from traditional RCTs) to support regulatory approval decisions. Such a framework should consider provisional, conditional, or adaptive approval options.

   The FDA should engage experts and stakeholders, including representatives of regulated industry, academia, patient advocacy and disease research organizations, and others in the development of the framework.

   The design of this framework would enhance the evidence for approved drugs and devices by providing a pathway—to be developed over time-for more evidence on populations and settings that are traditionally unaccounted for in RCTs.

Such a framework should include processes that will:

a. Identify regulatory approval approaches that serve as an alternative to the traditional binary approach that currently exists, enabling more opportunities to develop and use data on broader populations;

b. Identify new ways to develop evidence from pragmatic, randomized studies during the clinical development of drugs and devices used during the regulatory review process;

c. Identify mechanisms and processes for collecting data on safety and effectiveness on an ongoing basis, including through randomized controlled studies, pragmatic randomized studies, and other designs after initial approval;

d. Create mechanisms to ensure the market removal or label modification of products when required follow-up studies and monitoring are not completed or demonstrate an unfavorable risk-benefit balance for certain populations; and

e. Create pilot projects to test assumptions and demonstrate feasibility of new approval pathways.

3. Congress should promote public- and private-sector investment in the development of a broad-based, nationwide virtual infrastructure for use by FDA and others, to obtain more robust real-world evidence on both the safety and effectiveness of drugs and devices. The nationwide infrastructure should leverage existing pilot projects. Such investment should serve the needs of FDA, as well as the broader learning health care system.

1.2 Improving and Expanding the Use of Drug Development Tools: Biomarkers

Background

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.[30] 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.[31]

Biomarkers are believed to be able to reduce the time, cost, and uncertainty of drug development. They also hold great promise for advancing precision medicine.

The biomarkers most commonly used in drug development are described below:[32]

- *Diagnostic Biomarkers* distinguish between patients with a particular disease and those who do not have the disease.
- *Prognostic Biomarkers* provide information on the likely course of disease in an untreated individual.
- *Predictive Biomarkers* provide a forecast of the potential for a patient to respond, in some identified manner (either favorable or unfavorable) to one or more specific treatments.
- *Response Biomarkers* dynamically show biological responses in patients after having received a therapeutic intervention.

Recognizing the positive impact of biomarkers and other drug development tools on the efficiency and effectiveness of the drug development process, more than a decade ago, FDA called for the development of new, publicly available scientific and technology tools, including biomarkers.[33] Since then, FDA has released guidance for industry and FDA staff on the qualification process for drug development tools, including biomarkers.[34]

There are generally two pathways through which biomarkers can be accepted by FDA for use in drug development: (1) through submission of biomarker data during the approval process associated with a single drug and (2) through the qualification of a biomarker for a particular context of use through FDA's Biomarker Qualification Program.[35] To date, only five biomarkers have been qualified.[36]

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 science and consistent evidence, methodological challenges, lack of regulatory clarity, and logistical and operational issues associated with implementation.[37,38,39,40]

Additional actions are needed to advance the development, qualification, and use of biomarkers in the drug development process, including expansion and improvement of methods to further the science and development of evidentiary standards, creation of greater transparency around current activities, and development of additional guidance to improve regulatory clarity. FDA has recently called for academia, industry, government, and consortia to work together to advance this science and develop the evidence for biomarker qualification.

Section 2021 of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, contains multiple provisions associated with drug development tools generally and biomarkers, specifically, which are summarized below:[41]

- Requires the HHS secretary to establish a process for the submission, review, and qualification of drug development tools.
- Authorizes the HHS secretary to engage and consider recommendations of medical research consortia with respect to drug development tools.
- Requires the HHS secretary to make the following information publicly available related to drug development tools:
    - The number of qualification requests submitted and accepted, as well as the number of requests for which external scientific experts are utilized,
    - The number of qualification plans and packages submitted, and
    - The number of drug development tools qualified.
- Requires the HHS secretary, in consultation with biomedical research consortia and other interested parties through a collaborative public process, to develop draft guidance on biomarkers within 24 months, and final guidance within 30 months, which contain the following:
    - A conceptual framework describing appropriate standards and scientific approaches to support the development of biomarkers,
    - Recommendations for demonstrating that a surrogate endpoint is reasonably likely to predict clinical benefit for the purpose of supporting accelerated approval, and
    - Description of the requirements for entities seeking biomarker qualification, reasonable timelines for HHS review, and processes by which both entities and the HHS secretary may consult with biomedical research consortia or others with expert knowledge and insights.
- Authorizes appropriations of $10 million.

Policy Recommendations

Congress should 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, by taking the following actions:

1. Require FDA to establish a framework and process for the submission, review, and qualification of drug development tools.
2. Authorize and strongly encourage FDA to engage with experts and stakeholders through biomedical research consortia to support the review of qualification submissions.
3. Improve transparency of drug development tool-related activities by requiring FDA to make information regarding the number of qualification-related requests and plans submitted and the number of drug development tools qualified, publicly available.
4. Require FDA to develop—through a collaborative public process—guidance on biomarkers which contains:
    a. A conceptual framework describing appropriate standards and scientific approaches to support development;
    b. Recommendations for demonstrating the predictability of surrogate endpoints for purposes of supporting accelerated approval; and
    c. Description of the requirements for entities seeking qualification, reasonable timelines for FDA review, and processes by which both entities and FDA may consult with biomedical research consortia or others with expert knowledge and insights.

1.3 Improving and Expanding the Use of Drug Development Tools: Patient-Reported Outcomes

Background

A patient-reported outcome (PRO) is defined by the FDA as "a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of the patient's symptoms or functioning without amendment or interpretation of the patient's response by a clinician or anyone else."[42] A PRO instrument is a means to capture PRO data that is used to measure treatment benefit or risk in medical product clinical trials.[43] PRO instruments represent another type of drug development tool and are referenced as such in FDA's recent

guidance document on qualification of such tools.[44] As described in a recent Brookings Institution report, capturing PRO measures is the most direct approach to gaining insights from patients about their symptoms, functional status, treatment preferences, and health-related quality of life.[45] Over the last several years, there has been increasing interest in the use of PRO instruments in the drug development process, particularly to support product labeling claims.

The FDA has existing authority to qualify PRO instruments. The Study Endpoint and Labeling Development team was established at the FDA within the Office of New Drugs to serve as a cross-divisional resource on clinical outcome assessments, including PROs, clinician-reported outcomes, observer-reported outcomes, and performance measures.[46] In 2009, the FDA issued final guidance on the use of PRO measures in medical product development to support labeling claims.[47] A recent study has shown that the number of PRO claims approved by the FDA for inclusion in drug labeling has declined in recent years, falling from 30 percent of drug approvals granted between 1997 and 2002 to 24 percent of drugs approved between 2006 and 2010.[48]

In 2014, the FDA published general guidance regarding the qualification process for multiple drug development tools, including PRO instruments.[49] Once qualified, an instrument may be applied in multiple drug development programs without the need to gather additional data to support its use. Thus far, FDA has qualified one PRO instrument—the Exacerbations of Chronic Pulmonary Disease Tool (EXACT). EXACT was developed in two years, and took an additional six years to generate enough clinical evidence for FDA qualification.[50]

A meeting convened by the Brookings Institution revealed the following barriers to the development and use of PROs:

- **Logistical Barriers**. Ongoing challenges in aligning PRO development timelines with clinical development timelines; burdens associated with applying PRO instruments in multinational clinical trials; lack of harmonization in PRO instrument evidentiary requirements across regulatory agencies; and lack of clear incentives for sponsors to opt out of a qualification pathway for a PRO versus developing a PRO as part of an individual drug development program; [51]
- **Communication Barriers.** Inconsistent interpretation of FDA guidance across review divisions and FDA's Study Endpoint and Labeling Development team; lack of a formal mechanism for sponsors to meet with FDA to discuss development issues prior to an investigational new drug (IND) submission; and lack of early and consistent feedback on PRO development plans; [52,53,54]

- **Methodological Barriers**. Perceived stringency of the agency's evidentiary requirements; lack of clarity on evidentiary requirements for an existing instrument to be "fit-for-purpose" for a given context of use; challenges to PRO instruments for pediatric, orphan, and rare disease indications; and challenges with open label studies which are common in oncology. [55,56,57]

As noted in section 1.2 above, Section 2021 of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015 contains multiple provisions associated with the qualification process associated with drug development tools, including PRO instruments. Key provisions include the establishment of a process for the submission, review, and qualification of drug development tools; new transparency requirements associated with the management and approval of qualification submissions; and authorization of the HHS secretary to engage and consider recommendations of external experts through medical research consortia.[58]

Policy Recommendations

Policy recommendations included in Section 1.2 associated with drug development tools generally are expected to have a positive impact on both the development and use of PROs, including the establishment of a framework and process for drug development tools, authorization of HHS' engagement of experts through biomedical research consortia, and improved transparency and reporting requirements regarding qualification submission and qualification. Additional actions are needed to accelerate the use of PRO instruments to improve the drug development process.

Congress should improve and expand the use of PROs through the following actions:

1. Require FDA to develop—through a collaborative public process—guidance on PROs that contains the following:
    a. A standard, consistent process for submission, review, and qualification of PRO instruments;
    b. Description of the requirements for entities seeking qualification, reasonable timelines for FDA review of submissions, and processes by which both entities and FDA may consult with biomedical research consortia and others with expert knowledge and insights; and
    c. A conceptual framework describing appropriate standards and scientific approaches to support the development of PRO instruments.

2. Create a mechanism to improve communication between FDA and sponsors regarding the development of approaches for the use of PRO instruments.

1.4 Incorporating Patient Perspectives into Benefit-Risk Assessment

Background

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 FDA's acceptance of uncertainty (improving benefit-risk assessment).

The National Health Council identified the following barriers to the integration of patient input into benefit-risk assessment:[59]

- **Defining the Patient Community**. Often the terminology used to describe the individuals and organizations that are known broadly as the patient community is inconsistent or fails to capture the distinctions among them. For example, patients, patient advocates, and consumers are sometimes used interchangeably or are grouped together and caregivers are often excluded altogether;
- **Describing Meaningful Engagement.** Patient engagement can represent a range of activities, from passive engagement (e.g., clinical trial participation) to more active participation (e.g., research development); these elements have yet to be clearly defined;
- **Developing a Framework and Methods for Engaging Patients**. While there are existing reviews of patient engagement methods, they have not yet been fully examined for their application to drug development. Guidance on appropriate methods is crucial; and
- **Identifying and Removing Barriers to Meaningful Engagement.** While many companies actively solicit input from patients, there are barriers to communications between patients and manufacturers. For example, because manufacturers often feel that their interactions with patients are at risk of being construed as discussions of unapproved medicines or unapproved uses of approved medicines, they are inclined to forgo valuable input from patients that might inform earlier stage research decisions, such as endpoint selection and clinical trial design. Encouraging meaningful engagement among patients and manufacturers would require clearer guidance or

policies that create a more predictable environment for manufacturers to engage patients.

To date, FDA's efforts to include patients in the regulatory process have been limited to having patients serve on FDA Advisory Committees and participate in meetings. Since 2012, patient representatives have served on advisory committees for more than 150 medical products and have participated in 22 FDA-sponsored product development meetings.[60]

Section 905 of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 called for the HHS secretary to implement a structured risk-benefit assessment framework in the new drug approval process to facilitate balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs.[61] In addition, FDASIA included provisions on patient participation in medical product discussions. Section 1137 of FDASIA directed FDA to "develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by (1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators and (2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry."[62]

As part of its commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), FDA began its work in the fall of 2012 on the Patient-Focused Drug Development Initiative, which aims to more systematically gather patients' perspectives on their conditions and available therapies to treat their conditions. Through this Initiative and as part of its PDUFA V commitment, FDA is holding at least 20 public meetings, each focusing on a specific disease area.[63,64] The Patient-Focused Drug Development Initiative is meant to help FDA meet its PDUFA V commitment to implement an enhanced structured approach to benefit-risk assessment in regulatory decision-making with more clarity and transparency.[65]

In November 2014, FDA opened a docket to gain public input on patient participation in medical product discussions called for in Section 1137 in FDASIA. The comment period closed on December 4, 2014 with 165 public comments.

There is broad recognition of the need to develop and implement a consistent and systematic approach for the benefit-risk assessment of new drugs. Both patient groups and industry have been frustrated by the lack of transparency regarding FDA's assessment of benefit versus risk in drug development, and perceived prohibition of communications directly between patients

and industry. There is also considerable support for the use of patient experience data to enhance and inform decision-making regarding risks and benefits.

Broad-based and bipartisan support of these concepts are reflected in Section 2001 of the 21st Century Cures Act passed by the U.S. House of Representatives on July 10, 2015. The Act contains several provisions associated with the development and use of patient experience data to enhance a structured benefit-risk framework. For example, the Act: [66]

- Develops and implements a consistent and systematic approach to the discussion of regulatory decision-making with respect to, and the communication of, the benefits and risks of new drugs.
- Establishes and implements a process under which an entity may submit patient experience data that can be used to enhance a structured risk-benefit framework, within two years.
- Publishes guidance within three years, regarding the following:
    - Process and timelines for the submission of patient experience data;
    - Methodological considerations and approaches for collection of patient experience data;
    - Establishment and maintenance of registries to increase understanding of disease;
    - Methodological approaches that may be used to assess patients' beliefs with respect to benefits and risks; and
    - Methodologies, standards, and potential experimental designs for PROs.

Policy Recommendations

Congress should assure the incorporation of patient perspectives into benefit-risk assessment associated with regulatory decision-making for drugs, by taking the following actions:

1. Require FDA to establish and implement a process under which an entity may submit patient preference data to enhance a structured risk-benefit framework.
2. Require FDA to publish guidance regarding process and timelines for the submission of patient preference data; methodological considerations and approaches for both collection and assessment of such data for benefit-risk; and methodologies, standards, and potential experimental designs for patient-reported outcomes.

3. To provide regulatory clarity and a predictable environment for patient communications, specify that the exchange of truthful and non-misleading information among patients, patient caregivers, or patient advocates and medical or scientific staff of a manufacturer, the purpose of which is to discover and understand patient or caregiver perspectives related to the specific disease from which a patient suffers, shall not be considered promotion or commercialization of the investigational drug or biologic, or a violation of the Federal Food Drug and Cosmetic Act.

1.5 Improving Off-Label Dissemination Policies

Background

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.

Life science companies are generally restricted in sharing information on off-label use of their products and may face legal action if they actively promote 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.[67] 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.

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. [68] 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 accrue patients for a clinical trial on such off-label use. However, studies have found that doctors may not always understand what uses of a drug or device are on-label and thus have scientific evidence behind them.[69] In order to balance the risks and benefits of off-label uses, physicians need reliable and up-to-date scientific information concerning such uses.

Many key players support expanded dissemination of peer-reviewed literature. In 1995, former Senator Connie Mack (R-FL) introduced a bill co-sponsored by then-Senator William Frist to allow dissemination of evidence-based peer-reviewed literature. The Coalition for Healthcare Communications represents organizations dedicated to assuring the free exchange of information on medical products and includes several medical societies as members. The Washington Legal Foundation has long supported assuring drug and device manufacturers "First Amendment" legal rights to communicate on off-label uses.

Section 2102 of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, requires the FDA to issue draft guidance within 18 months to clarify how drug and device manufacturers can disseminate truthful and non-misleading scientific and medical information about a drug or device that is not included in the approved labeling for the product.[70]

Policy Recommendations

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:

1. Require FDA to issue rules which 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.

1.6 Promoting International Standards Harmonization and Sharing of Best Practices

Background

The medical products industry is a global industry, with drug and device companies operating across the world. In addition to Europe and Japan, the biotechnology landscape now includes a rapidly growing biomedical industry in China, India, and other emerging economic powers. As a result, the U.S. biomedical industry is facing unprecedented global competition. In 2008,

China announced plans to invest $12 billion in drug development. Three years later, in 2011, the Chinese government named biotech one of seven industries that will receive $1.7 trillion in government funding over a five-year period.[71] Moreover, the European Union's (EU's) Innovative Medicines Initiative (IMI) has allocated $2.65 billion to Europe's biopharmaceutical industry.[72]

Strategies for improving U.S. global competitiveness are summarized across this report. Operating within a global environment also causes other complexities and challenges for U.S. companies, including the burden caused by differing rules and regulations across countries.

The FDA has participated in international harmonization bodies for decades. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 uniting the regulatory agencies and the industry associations of the U.S., Europe and Japan. ICH produces standards for safety, quality, and efficacy of medical products. Similar efforts to "achieve greater uniformity between national medical device regulatory systems" began in 1992 with the inception of the Global Harmonization Task Force on Medical Devices (GHTF), now known as the International Medical Devices Regulatory Forum (IMDRF).[73] Despite issuing many guidances and standards, U.S. regulatory agency officials report that "current processes could benefit from better information sharing among agencies on the implementation of international cooperation activities and lessons learned."[74]

The United States and European Union are engaging in ongoing trade talks called the Transatlantic Trade and Investment Partnership (TTIP) that began in July 2013. The purpose of TTIP is to remove, to the extent possible, differences between the rules and regulations in both the European Union and United States in order to make the markets compatible and to make it easier to sell goods and services in both markets. According to the U.S. Trade Representatives, among America's objectives for TTIP is:

> "*While maintaining the level of health, safety and environmental protection our people have come to expect, we seek greater compatibility of U.S. and EU regulations and related standards development processes, with the objective of reducing costs associated with unnecessary regulatory differences and facilitating trade, by promoting transparency in the development and implementation of regulations and good regulatory practices, establishing mechanisms for future progress, and pursuing regulatory cooperation initiatives where appropriate*."[75]

TTIP potential areas of cooperation for drugs include: recognizing each other's Good Manufacturing Practices (GMP) inspections carried out in the European Union and the United States and in third-world countries; allowing the exchange of confidential information for GMP

and other inspection reports but also for products approvals; agreement on biosimilar authorizations; guidelines on clinical study designs for pediatrics; and continuing cooperation on parallel scientific advice so that the European Medicines Agency (EMA), FDA, and the sponsor of an applications could agree on scientific issues.[76]

On the device side, goals of TTIP are to improve on the base of work from IMDRF. There is significant international work underway on a Unique Device Identification (UDI) System for tracking devices and to ensure that the EU and U.S. UDI systems are compatible. Other TTIP goals for medical devices include form harmonization for product approvals and joint recognition of Quality Management System audits.[77] The Trade Promotion Authority (TPA), also known as "Fast Track", was signed into law June 29, 2015 and increases the possibility of an agreement on TTIP as it grants the President the ability to negotiate trade deals that Congress can then approve or disapprove, but Congress cannot amend the deal.

Productive international regulatory cooperation can help regulators prioritize resources by learning from each other and leveraging the work of others.[78] Some have suggested that closer regulatory cooperation would reduce costs in drug and device development and promote faster patient access. A 2011 study comparing the approval timing and label wording of FDA with EMA found that approximately half of all drug approval decisions and label contents were the same. However, 20 percent of drugs were approved by one agency and not the other, and 28 percent of drug approvals have variations with the wording of a label. Discussion between the two agencies is increasing alignment.[79]

Former NIH Director Elias Zerhouni, who currently heads Sanofi's R&D organization, noted that in his five years of company experience, he had not seen a regulatory decision that was fully consistent across regulatory agencies. This gap is puzzling given FDA and EMA efforts to harmonize regulatory standards through groups like the International Conference on Harmonization. However, as Zerhouni stated, what have not been harmonized are standards of risk and benefits. Additionally, the United States and Europe require different research and clinical trial data and take different approaches to inspecting manufacturing sites.[80]

Last year outgoing FDA Commissioner Margaret Hamburg announced in a speech to her British counterparts the formation of the International Coalition of Medical Regulatory Authorities (ICMRA). One of the objectives of the new organization is to exchange information and provide synergies and leverage existing efforts. ICMRA builds on the efforts of the International Conference on Harmonization, the Pharmaceutical Inspection Cooperation Scheme, the newly created International Pharmaceutical Regulators Forum, and the Asia Pacific Economic Cooperation's Pharmaceutical Product Supply Chain; it reflects leadership and expertise in standards development and the harmonization of good regulatory practices.[81]

As the standards of advanced regulatory agencies become more aligned, the next step of reducing duplicative regulatory requirements is approval reciprocity, where at the request of a sponsor, a medical product approved by one agency would automatically be considered for approval by the FDA. Reciprocity could be limited to highly-developed trading partners, to well-understood drug or device classes, or to products where there is high unmet need.[82] One example of accomplishing this goal is bipartisan legislation introduced in March 2015 by Representatives Tim Ryan (D-OH) and Steve Stivers (R-OH). The Speeding Access to Already Approved Pharmaceuticals Act (H.R. 1455) would require the FDA commissioner to facilitate the development and expedite the review of a drug, biologic or device within 90 days of EU approval.[83]

Section 2224 of the of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, establishes a clear process at the FDA to respond to and make determinations related to requests for recognition of standards for medical devices. It also requires the HHS secretary to publish guidance identifying the principles for recognizing standards. [84]

Policy Recommendations

Congress should promote harmonization of international standards, through the following:

1. Require FDA to establish a clear process for recognizing standards for medical devices and require the FDA to publish guidance regarding such process.
2. Encourage FDA's commitment to and actions related to the harmonization of international standards, including, but not limited to, those related to manufacturing facilities.
3. Require the FDA and the U.S. Trade Representative to report on progress on international standards harmonization.
4. Encourage FDA to participate in mechanisms that facilitate the sharing of best practices internationally.
5. Encourage FDA to explore reciprocity of approval among highly developed trading partners for well-understood drug or device classes or products for which there is high unmet medical need.

1.7 Improving Interoperability of Health Information Technology

Background

Electronic information sharing among those who deliver, support, and receive care plays a critical role in improving the cost, quality, and patient experience of health care. The interoperability of health information technology systems is necessary to support such information sharing.

Much of the information about a patient's health and health care resides in the many settings in which care and services are delivered. This includes offices of primary care physicians and specialists, clinics, health plans, hospitals, laboratoratories, pharmacies, radiology centers, as well as patients themselves. This information must be delivered to the clinician and the care team, in a usable format, to deliver high-quality, cost-effective, coordinated, patient-centered care. Information sharing can help clinicians avoid duplicative tests, identify and address gaps in care, and avoid medication and other errors—all of which drive higher-quality and more cost-effective care.[85] Health information sharing is also a necessary precursor to rapidly emerging delivery system and payment reforms that reward outcomes and value over volume. The promise of health IT—and much of the rationale for its investments—lies in the value of sharing such information electronically, both among those who deliver care to the patient or with patients themselves.

Unfortunately, despite more than $30 billion in federal investments in health IT enabled by the Health Information Technology for Economic and Clinical Health (HITECH) Act, there is very little electronic information sharing among clinicians, hospitals, laboratories, other service providers, and individuals. For example, only 14 percent of physicians surveyed in 2013 were electronically sharing data with providers outside of their organizations.[86] Only 30 percent of physicians routinely use capabilities for secure messaging with patients, and 24 percent routinely provide patients with the ability to view online, download, or transmit their health records.[87] Finally, a 2012 study indicates that 51 percent of hospitals surveyed were sharing information with ambulatory care providers outside of their organizations, while 36 percent were sharing information with other hospitals outside of their organizations.[88]

Getting to efficient and effective information sharing requires action in two areas: (1) providers and other organizations who deliver health care services must be willing and able to share health information electronically and (2) IT systems within various provider and service delivery organizations must be "interoperable" or have the ability to share information with other systems using agreed-upon standards. Congress can play a significant role in accelerating action in both areas. The focus of our policy recommendations is on the latter.

To date, one of the most significant barriers to electronic information sharing has been the lack of incentives or a business case for such sharing, but the environment is changing. Because most payment in the health care system has been volume based—for example, based on the number of procedures, tests, or visits—there has been little incentive to share information. New models of delivery and payment—which are now rapidly emerging—require providers to focus on outcomes and value versus volume, thereby providing an incentive for information sharing to improve the quality and cost-effectiveness of care and to produce better health outcomes. Other barriers to electronic information sharing include the lack of standards adoption and interoperability of systems, the lack of effective methods for matching patient data across systems, the cost of infrastructure associated with exchange, concerns about privacy, and concerns about liability.[89,90,91,92]

Improving the interoperability of health IT systems requires actions in four general areas:

1. Achieving consensus on a common set of standards for adoption;
2. Assuring federal adoption of agreed-upon standards, which in turn, drives private-sector adoption of such standards;
3. Accelerating methods for testing and validating the interoperability of health IT systems; and
4. Creating a business case and providing incentives for electronic information sharing that drives demand for interoperable systems.

Policy recommendations for addressing three of the four items are outlined below.

Section 3001 of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, contains extensive provisions related to interoperability, many of which are outlined below.[93] The Act:

- Defines standards for interoperability;
- Requires the Health IT Policy Committee—a federal advisory committee—to incorporate policies for updates to interoperability standards;
- Requires the HHS secretary to enter into contracts with health care standards development organizations who will provide to the HHS secretary recommendations for interoperability standards and multiple methods for testing such standards

- Requires the HHS secretary, in consultation with the National Coordinator for Health IT, to periodically conduct hearings to evaluate and review standards, implementation specifications, and certification criteria
- Requires the HHS secretary to report on the status of interoperabilty by no later than July 1, 2017;
- Requires the HHS secretary to publish in the Federal Register the following: (1) status against interoperability goals, (2) a list of qualified EHR vendors and their compliance or non-compliance with adopted standards; and (3) actions to be taken related to non-compliant vendors;
- Requires that ONC certification include interoperabilty standards by January 1, 2018;
- Requires that as of January 1, 2018, any vendors offering qualified EHRs, must attest that they have performed the following and authorizes the HHS secretary to decertify qualified EHRs if such criteria are not met:
    - Not taken any actions to restrict or limit the exchange of information or prevent or disincentivize widespread interoperability;
    - Posted and made available pricing information associated with interfaces for interoperability;
    - Published application programming interfaces; and
    - Successfully tested and has in place implementation guidelines to support interoperability.
- Authorizes the inspector general to investigate claims associated with violations related to various provisions; and
- Authorizes the HHS secretary to offer hardship exemptions to eligible professionals and hospitals in relation to compliance with the CMS Medicare and Medicaid EHR Incentive Programs (Meaningful Use) for situations in which such providers' EHRs become decertified.

Policy Recommendations

Congress should improve the interoperability of health IT by requiring the following:

1. Require the federal government to adopt standards for health IT.
    a. Federally adopted standards should include those required for accurate identification and matching of patient data, provider identification, transport,

terminologies, clinical models, clinical data query language, security, and application interfaces.

   b. Federal adoption should encompass inclusion of standards within certified EHR technology required under the CMS Medicare and Medicaid EHR Incentives Programs, health IT systems procured by federal agencies, various electronic health data submissions required by federal agencies, and health IT systems directly funded through federal agency contracts, grants, and cooperative agreements.

2. To assure that federal agencies comply with federal standards, require each federal agency to report annually on its compliance with federally adopted standards and require the GAO to issue a report, every two years, on federal compliance with such standards.
3. Designate responsibility for identification of standards for federal adoption to the OMB Director, with support from the National Coordinator for Health IT.
4. Require that any standards for federal adoption are (1) developed by a voluntary consensus body as defined by the National Technology Transfer and Advancement Act and OMB Circular A-119, (2) tested prior to adoption, and (3) established through formal rulemaking and a collaborative, public process, to assure appropriate public input and transparency.
5. Require that standards for federal adoption be published annually and that effective dates for adoption should not occur until at least 12 months subsequent to publication.
6. Authorize the Director of OMB and the National Coordinator for Health IT to use federal advisory committees to assist with the identification of areas for which standards are needed and evaluation of standards against established criteria for federal adoption, to inform federal decision-making.
7. To promote testing and validation of standards adoption and interoperability of systems, direct NIST to develop and make publicly available methods for testing compliance with federal standards and authorize federal agencies to recognize independent testing and certification bodies that will provide assurance that software complies with federally adopted standards.

SECTION 2: INCREASING REGULATORY CLARITY

2.1 Clarify Regulatory Authority Related to Health Information Technology

Background

The promise of health information technology is currently unrealized due to uncertain regulatory authority and the resulting marketplace confusion. Health IT plays a critical role in improving the health and wellness of individuals and the quality, cost-effectiveness and patient experience of care. Building upon numerous legislative proposals with bipartisan support over the last decade, the HITECH Act of 2009 brought about new authorities, standards, and investments in health IT. As a result of federal, state, and private-sector action, the number of clinicians, hospitals, and other providers across the United States that have adopted health IT to improve the quality, safety, and efficiency of care has significantly increased.

According to the National Center for Health Statistics, the percentage of physicians who have adopted at least a basic EHR increased from 21.8 percent in 2009 to 48.1 percent in 2013.[94] A survey of hospitals published in *Health Affairs* indicates that the percentage of hospitals that have adopted at least a basic EHR increased from 12.2 percent in 2009 to 59 percent in 2013.[95] Many clinicians, hospitals, and other providers have qualified for funding under the CMS Medicare and Medicaid EHR Incentive Programs by demonstrating the meaningful use of EHR technology to improve care. As of May 31, 2015, approximately $31 billion in payments had been made through these incentive programs to nearly 5,000 hospitals and approximately 464,000 eligible professionals.[96]

Currently, there is regulatory uncertainty regarding federal agency authority associated with the oversight of EHRs and other clinical software. Section 201(h) of the Food, Drug and Cosmetic Act, as amended in 1976, provides FDA with the authority to regulate EHRs and other clinical software. At the same time, ONC has been granted authority under HITECH to provide oversight over health IT.[97]

Such regulatory uncertainty stifles innovation and creates confusion in the marketplace about what technologies may be regulated, by which agencies, and to what standards. This uncertainty creates barriers to the development of promising technologies that can help improve health and health care. To address such uncertainty, Congress called for the administration to clarify its strategy and approach for regulating health IT within FDASIA.

Following passage of FDASIA, BPC conducted research and engaged hundreds of experts and stakeholders across every sector of health care to develop a set of principles and recommendations for a health IT oversight framework that protects patient safety, is risk-

based and flexible, promotes innovation, and avoids regulatory duplication. The results of this ongoing effort are reflected in *An Oversight Framework for Assuring Patient Safety in Health IT,* released in February 2013.[98]

BPC's report makes the following conclusions, which are consistent with bipartisan legislation that has been introduced, as well the draft health IT safety plan developed by FDA, Federal Communications Commission (FCC), and ONC:[99]

1. A risk-based regulatory framework for health IT should contain three broad categories of health IT.
2. FDA regulation should continue to be focused on the category of technologies that present a high risk to patient safety.
3. Health IT that presents no risk should remain unregulated.

In addition, BPC noted in its report that health IT that presents some risk should be subject to risk-based oversight that uses consensus standards, independent certification bodies, reporting of patient safety events, and the creation of a learning environment to promote collaboration, shared responsibility, and continuous improvements in the development, implementation and use of health IT.[100] Authorities brought about by the Patient Safety and Quality Improvement Act of 2005 (Public Law 109-41) should be leveraged to support reporting and analysis of health IT-related patient safety events. Because health IT safety is a shared responsibility among those who develop, implement, and use health IT, all of those who participate in development, implementation, and use should be able to participate in patient safety activities without breaking statutory confidentiality protections for providers under the Patient Safety and Quality Improvement Act. Further clarification of the law is needed to achieve this goal.

Since the passage of FDASIA and the publication of BPC's report, there has been considerable bipartisan agreement and action within Congress to clarify regulatory authority associated with health IT, as summarized in the table below. The administration has also taken action, publishing a draft report in response to FDASIA.

Congressional and Executive Branch Action on Clarifying Regulatory Authority for Health IT

Date	Congressional or Executive Branch Action
July 2012	Passed and signed into law in July 2012, FDASIA required the HHS secretary , "acting through the Commissioner of Food and Drugs, and in consultation with the National Coordinator for Health Information Technology and the Chairman of the FCC," to post a report within 18 months that "contains a proposed strategy and recommendations on an appropriate, risk-based regulatory framework pertaining to health information technology, including mobile medical applications, that promotes innovation, protects patient safety, and avoids regulatory duplication."[101]
April 2014	In response to FDASIA, FDA, ONC, and FCC published the draft report, *FDASIA Health IT Report: Proposed Strategies and Recommendations for a Risk-Based Framework*, in April 2014.[102]
October 2013	Representatives Marsha Blackburn (R-TN), G.K. Butterfield (D-NC), Diana DeGette (D-CO), Phil Gingrey (R-GA), Gene Green (D-TX), and Greg Walden (R-OR) introduced the Sensible Oversight for Technology Which Advances Regulatory Efficiency (SOFTWARE) Act of 2013 (H.R. 3303), to provide clarity that clinical and health software should be excluded from the definition of a medical device regulated by the FDA.[103]
February 2014	Senators Deb Fischer (R-NE), Angus King (I-ME), and Marco Rubio (R-FL) introduced the Preventing Regulatory Overreach to Enhance Care Technology (PROTECT) Act of 2014, to provide clarity that clinical and health software should be excluded from the definition of a medical device and also to provide a general description of the type of oversight that should be applied to clinical software.[104]
December 2014	Senators Michael Bennet (D-CO) and Orrin Hatch (R-UT) introduced the Medical Electronic Data Technology Enhancement for Consumers' Health (MEDTECH) Act of 2014 to provide clarity that clinical and administrative software should be exempted from medical device regulation.[105]

April 2015	Sen. Michael Bennet (D-CO) and Sen. Orrin Hatch (R-UT) re-introduced the MEDTECH Act (S. 1101), providing clarity that clinical and administrative software should be exempted from medical device regulation.[106]
May 2015	The Energy and Commerce Committee of the U.S. House of Representatives passed the 21st Century Cures Act by unanimous vote, which included the SOFTWARE Act of 2015 (Title II, Subtitle N, Sections 2241-2243), providing clarity that health software should be excluded from the definition of a medical device. [107]
July 2015	The U.S. House of Representatives passed the 21st Century Cures Act (H.R. 6) which included the SOFTWARE Act of 2015 (Title II, Subtitle N, Sections 2241-2243), providing clarity that health software should be excluded from the definition of a medical device, unless the HHS secretary determines that it poses a significant risk to patient safety.[108]

Policy Recommendations

Congress should provide further clarity regarding regulatory authority associated with health IT and assure the implementation of a risk-based oversight framework for health IT that both promotes innovation and protects patient safety, by performing the following:

1. Clarify that health IT should not be subject to regulation as a medical device by FDA, except when determined by the HHS secretary that the product poses a significant risk to patient safety.
2. Require the HHS secretary to recognize independent bodies to develop voluntary consensus standards, evaluate and render decisions on compliance with such standards, and facilitate voluntary patient safety reporting to continually improve the development, implementation, and use of health IT.
3. Clarify that current law enables those who develop and implement health IT to participate in patient safety activities and direct the HHS secretary to extend confidentiality protections to health IT developers to permit them to report patient safety events, view patient safety organization-protected information, receive and analyze patient safety event reports, create and receive quality-improvement reports from patient safety organizations, and work with providers to develop strategies for improvement.

2.2 Clarifying Regulatory Authority Related to Laboratory-Developed Tests

Background

Regulatory authority associated with laboratory-developed tests (LDTs) is unclear, uneven, and duplicative. LDTs are in vitro diagnostic tests that are developed, validated, and used for in-house pathology and diagnostic purposes. LDTs historically were intended for use only by the laboratory entity where they are developed. The FDA defines an LDT as an in vitro diagnostic test that is manufactured by and used within a single laboratory). LDTs are also sometimes called in-house developed tests, or "home brew" tests.[109]

In order to ensure accurate and reliable test results, the CMS Clinical Laboratory Improvement Amendments (CLIA) program regulates laboratories that perform testing on patient specimens. The FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act, including diagnostic test kits, to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.[110]

CLIA requires LDTs to demonstrate analytic validity (i.e., a test must show that it accurately measures what it says it will measure) but not clinical validity (i.e., the probability of having a disorder based on a test result). By contrast, FDA requires demonstration of both analytic and clinical validity for tests that are considered to be diagnostic kits. Until recently, FDA claimed authority over LDTs but indicated that it was exercising "enforcement discretion," effectively deciding not to regulate them.

In October 2014, FDA issued a long anticipated draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests*. This followed an April 2008 report by the HHS secretary's Advisory Committee for Genetics, Health and Society that recommended enhanced oversight of LDTs due to of significant costs and quality concerns.[111]

There are two primary points of view regarding regulation of LDTs. First, manufacturers of traditional in vitro diagnostics (IVDs) who make kits have complained of an uneven playing field, particularly as some venture capital-backed laboratory companies have begun to sell tests under CLIA outside of the traditional walls of an individual hospital or a health care system. The Advanced Medical Technology Association (AdvaMed), a trade association representing traditional IVDs, argues in its

Overview of Stakeholder Views on LDTs	
American Clinical Laboratory Association	LDTs are laboratory services regulated under CLIA and are part of the practice of medicine
AdvaMed	FDA should implement a risk-based approach not based on the type of test developer

"AdvaMedDx" division that the "current two-tier regulatory system that differentiates between LDTs and traditional manufacturer-developed tests solely on the basis of the type of developer, without regard to patient risk, is fundamentally unsustainable and must be modernized to support the public health and robust development of new, safe and effective diagnostics."[112] The issue has had heightened prominence with advances in genomics as many genomic tests are LDTs. In its draft framework, the FDA said the Medical Device Amendments Act of 1976 explicitly amended the definition of a device to encompass in vitro diagnostics in section 201(h) of the Food, Drug and Cosmetic Act.[113]

On the other hand, many in the laboratory industry and academic world assert that LDTs are not IVDs but are instead "laboratory services" that fall outside the FDA's jurisdiction. For example, the American Clinical Laboratory Association (ACLA), the trade association for clinical laboratories, has stated, "FDA's assertion of authority over laboratory-developed testing services is clearly foreclosed by FDA's own authorizing statute, the FDCA. On the face of the statute, laboratory-developed tests fall outside the ambit of FDA's authority for at least three reasons: (1) they are not 'devices' under 21 U.S.C. §321(h); (2) they are not 'introduc[ed] into interstate commerce for commercial distribution' under 21 U.S.C. §360(k); and (3) they directly implicate the practice of medicine exempted under 21 U.S.C. §396."[114] ACLA further objects that under the draft framework, any modifications to an FDA-approved or -cleared device, which would turn the laboratory modifying the device into a device manufacturer and the modified device would have to meet pre-submission requirements.

Many pathologists would argue that providing laboratory services to patients in their systems is the practice of medicine and that some LDTs or modified devices perform better than their FDA counterparts. The opponents of FDA regulation of LDTs worry about the cost and administrative burden of FDA regulation. Many of the providers of LDTs are academic medical institutions and local laboratories. While they are accustomed to complying with accreditation requirements under CLIA, they find the language of FDA utterly foreign. Further, they object to IVD manufacturers' claim of an uneven playing field given the requirements of CLIA, and often assert that FDA approval or clearance of a test is not a marker of quality and that such tests must often be modified from their label to ensure optimal performance.

Finally some want to assure that LDTs are clinically validated. For example, in congressional testimony, a representative of the American Association for Cancer Research stated:

> *A test is a test—and presents the same risk for patients regardless of who makes it. Potential harms to patients and public health from tests that return incorrect results include unnecessary treatments with accompanying costs and side effects, treatment delay or failure to obtain appropriate treatment, unnecessary surgery, overuse of*

> *antibiotics, and overall worse outcomes than patients who received correct results. Without further action by FDA, the current regulatory system leaves critical gaps with respect to patient safety and public health regarding the use of LDTs.*[115]

The FDA, the IOM, and the HHS secretary's Advisory Committee on Genetics, Health, and Society have cited other examples in which insufficient clinical validation led to either harm or unacceptable risk of harm. [116,117] They note further that laboratories are not required to report adverse events. As noted above, currently CLIA regulations do not require clinical validation. Such validation is currently only conducted through FDA review processes, although some laboratory proposals suggest that existing oversight under CLIA could be augmented to include clinical validation as needed.

In its draft guidance, FDA did not address existing CLIA requirements in proposing new FDA requirements. Specifically, both FDA and CMS impose quality system requirements, and the two regulatory regimes overlap. Similarities between the requirements under FDA medical device regulation in 21 CFR Part 820 and the existing regulations under CLIA in 42 CFR Part 493 include quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventive actions and records.[118] However, in April 2015, FDA announced that HHS, FDA, and CMS were establishing an interagency task force that will focus on cross-agency collaboration on LDT oversight. According to the announcement, the goals of the interagency task force are to: identify areas of similarity between FDA quality system regulation and requirements under CLIA; work to clarify responsibilities for laboratories that fall under the purview of both agencies; and leverage joint resources to avoid duplication and maximize efficiency. [119]

Furthermore, to regulate LDTs, FDA first needs to know what tests are currently being conducted. To develop such a repository, FDA could use information and best practices from several existing registries tracking marketed genetic tests, such as NIH's Genetic Testing Registry (GTR). Since its launch in 2012, 431 laboratories worldwide (more than half of which are from the United States) have voluntarily registered information on more than 25,000 tests. Of those, only 16 GTR-listed tests have FDA approval or clearances, meaning the remaining tests are LDTs or are not marketed in the United States.[120] Indeed, the majority of genomic tests, which are the linchpin of precision medicine, are LDTs. If these are over-regulated, new test development will be stymied. On the other hand, without sufficient protections, important clinical decisions for cancer treatment or inherited diseases could be made based on unreliable test results.

Nonetheless, questions have been raised about the FDA's capacity to take on the regulation of LDTs.[121] FDA officials have said that in order to build that capacity the agency would consider reclassifying traditional IVDs.[122] IVD makers have complained that the FDA's risk classification scheme for diagnostics does not take into account the unique nature of diagnostics and instead conflates it with the risks of therapeutic devices. Safety and effectiveness are essential to therapeutic devices. For laboratory tests—whether they are IVDs or LDTs—the key issues are whether the provider and patient receives analytically valid and clinically valid information on which they can base appropriate care decisions.[123]

The FDA's regulation of the majority of LDTs would also create a challenging problem for pathologists as physicians who lead laboratories. If LDTs are IVDs, then pathologists would be test-manufacturers and prohibited from discussing off-label use of the tests they produce. However, the use of a test off-label is considered the routine practice of medicine. Tests approved or cleared for one use (or in the case of an LDT, made for a particular indication) are often used for other indications.[124]

Policy Recommendations

Congress should clarify regulatory authority related to laboratory-developed tests by performing the following:

1. Require that 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 including but not limited to those of the Diagnostic Test Working Group and the College of American Pathologists, when developing the risk classification scheme.
3. Notwithstanding the FDA's October 3, 2014 draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests*, 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 which 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 (i.e., 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 (e.g., 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 FDA and CMS through its Clinical Laboratory Improvement Amendments (CLIA) authorities.

4. Require FDA to examine its current risk classification scheme for traditional IVDs to ensure that it aligns with the unique nature of risk associated with diagnostic tests. 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.

2.3 Advance a Regulatory Framework for Precision Medicine

Background

Precision medicine is an emerging field with the potential to transform our response to disease.[125] In January 2015, President Obama announced a $215 billion initiative that seeks to leverage advances in genomics, emerging methods for managing and analyzing large data sets while protecting privacy, and health IT to accelerate biomedical discoveries. While still in its early days, precision medicine has already led to significant new discoveries and treatments customized to address patients' specific genetic makeup or the genetic profile of a specific tumor—leading to a transformation of how diseases such as cancer are treated. Today patients with breast, lung, and colorectal cancers, as well as melanomas and leukemia, routinely undergo molecular testing as part of their care, enabling physicians to select treatments that improve their chances of survival and reduce exposure to adverse effects.[126]

But expanding both the scope and scale of precision medicine and translating its early successes into significantly more robust scientific and clinical breakthroughs will require a coordinated and sustained national effort.

Given the rapid evolution of this emerging approach to understanding and treating disease, regulatory authorities have understandably struggled to keep up. While in certain select specialties—most notably oncology—FDA has begun to adopt precision-medicine approaches to regulation,[127] greater urgency is needed to ensure that any forthcoming regulatory policies hasten, not hinder, the growth in this emerging field. At the core of the issue is the regulatory status of Next-Generation Sequencing (NGS), which refers to technologies that perform DNA sequencing in parallel, allowing for the production of thousands or millions of sequences concurrently.[128] In 2013, FDA cleared an NGS instrument for the first time, as well as two NGS tests for cystic fibrosis.[129] In a subsequent discussion paper on the topic, FDA noted that a similar approach could be applied to establish clinical significance for other NGS tests and indications.[130]

Precision medicine experts believe the progress made so far is bringing the industry to the cusp of a critical inflection point: the ability to radically alter, or perhaps abandon altogether, the half-century-long drug development paradigm that many say costs too much, takes too long, and delivers too little. Combining the use of NGS tools with a significantly enhanced understanding of the molecular basis of disease ushers in an era of N-of-1 or single subject clinical trials. In contrast to the current drug development paradigm, which requires billions of dollars, thousands of subjects, and eight to 12 years, the N-of-1 paradigm requires a single patient who is the sole unit of observation in a study designed to investigate the efficacy and/or side-effect profile of different interventions. The ultimate goal of an N-of-1 trial is to determine the optimal or best intervention for an individual patient using objective data-driven criteria.[131]

Equally promising are so-called basket trials, a new and evolving form of clinical trial design that has generated significant interest. Basket trials use a hypothesis-driven strategy incorporating precision medicine into clinical trials even for mutations that are rare or difficult to study solely within a disease-specific context.[132] They are based on the hypothesis that the presence of a molecular marker predicts response to a targeted therapy independent of tumor histology. The intention of basket designs is to conduct several independent and parallel phase II trials. The success of a basket trial depends in large part on the strength of the data linking the target and targeted therapy. For this trial design to work, two key conditions must be met: the tumor must depend on the target pathway, and the targeted therapy must reliably inhibit

the target. In this sense, a basket trial that is completely independent of tumor histology may be more effective in truly addressing the efficacy of targeting a specific genetic aberration.

Section 2041 of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, requires the FDA to issue guidance on the development of precision medicine products.[133] In addition, the NIH and Cures Innovation Fund authorized in the bill explicitly includes precision medicine as one of four strategic focus areas for dedicated funding.

Policy Recommendations

1. Congress should improve regulatory clarity associated with precision medicine by establishing a working group that includes the FDA, the NIH, NIST, and ONC, to develop and submit a report to Congress. The report should characterize the rapidly evolving precision medicine landscape and develop a risk-based regulatory framework for precision medicine that protects patient safety, promotes innovation, and is flexible enough to accommodate rapid changes in science. The working group should leverage and build upon existing efforts of federal agencies, as well as the President's Precision Medicine Initiative.

2.4 Improve Regulatory Clarity Associated with Combination Products

Background

For historical reasons, the FDA regulates drugs in its Center for Drug Evaluation and Research (CDER), devices in its Center for Devices and Radiological Health (CDRH), and biologics in its Center for Biologics and Research (CBER). Some of the most innovative products are hybrids—neither pure devices, 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.

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 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. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval

modifications.[134] The problem is that different sets of current good manufacturing practices (CGMPs) cover different types of products. The manufacture of pharmaceutical and biological products is regulated under 21 CFR 210-11 and 600-680, while medical devices are manufactured under Quality Systems Regulation (QSR) regulations (21 CFR 820) and blood- and tissue-based products are regulated under 21 CFR 1271. There is no special type of marketing application for combination products.

However, Congress has long recognized the issues associated with hybrid products, and the Medical Device User Fee and Modernization Act (MDUFMA) of 2002 created an Office of Combination Products (OCP) to address it. OCP determines "the primary mode of action" of the combination product—drug, device, or biologic—and wherever the primary mode falls, that center takes the regulatory lead with consultations from the other involved center. The primary mode of action designation also determines which center (CDRH, CBER or CDER) receives user fees, with the non-primary center receiving nothing. According to the latest FDA data available, from 2008 to 2012, there was an annual average of 23 applications for combination products.[135] Furthermore, although one Center will lead the premarket review, consultation is frequently required with another FDA center.[136]

MDUFMA's combination product provision amended Section 503(g) of the FDCA (21 U.S.C. 353(g)) to state that OCP "(4)(C)(i) in carrying out this subsection, the Office shall ensure timely and effective premarket reviews by overseeing the timeliness of and coordinating reviews involving more than one agency center." However, whether this MDUFMA goal for OCP is being met is unclear. "The concern of legislators—and some regulatory professionals—has been that combination product reviews involving multiple centers (CDER, CBER, and/or CDRH) get overly complicated when a sponsor is hearing back different things from different review groups at FDA. For example, CDER might be reviewing the drug component of a drug-device combo, while CDRH reviews the device portion of the product."[137]

There is a lack of inter-center delineation of the roles and responsibilities of CDER, CBER and CDRH, resulting in conflicting feedback to sponsors, duplicative testing on patients and time and money spent with questionable return on the part of the agency and the innovators. Further, industry has also complained that there is little consistency and predictability in the decisions OCP makes regarding which center is in the lead (e.g., what the primary mode of action is for the product.) Since the non-lead center receives no user fees and the centers' performances are usually judged at least in part on an ability to review products subject to user-fee agreements, there is little incentive for timely review of products by the non-lead center. These challenges may unnecessarily depress investment in the development of promising combination products.

FDA has offered guidance on combination products in the past, including the CGMP Requirements for Combination Products, dated January 27, 2015 and the Final Rule-CGMP Requirements for Combination Products, dated January 22, 2013.[138,139]

Providing greater regulatory clarity associated with combination products will require action. Steps could include improving inter-center coordination among CDER, CBER and CDRH; establishing a lead center with a single point of contact to harmonize communications with sponsors; having non-lead FDA center representatives attend milestone meetings and assure center compliance with agreed-upon decisions; consistently publishing lists of primary mode of action decisions; and deferring to precedent for new similar combination products.

Section 2181 of the of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, would require FDA to issue a final guidance document within 18 months that describe the role of each agency center when reviewing a combination product.[140]

Policy Recommendations

Congress should improve the consistency of combination product reviews and address delays associated with development and evaluation of combination products through the following actions:

1. Amend the Food, Drug, and Cosmetic Act to provide greater clarity regarding designation of combination products.
2. Require FDA to take actions to address the lack of coordination and agreement among collaborative centers regarding requirements, the timeliness of response, and the lack of clarity regarding data requirements.
3. Require FDA to publish a timely list of decisions to requests for designation (i.e., which FDA center has primary jurisdiction) and encourage FDA to abide by precedent when faced with a similar combination product, unless the FDA can present a rationale for making a different decision.
4. Require FDA to track and issue reports that demonstrate that milestone meetings involving sponsors and FDA are meaningfully attended by the non-lead FDA center(s), and that reviewers in non-lead centers have completed their reviews within timelines consistent with user fee performance goals of the coordinating center, e.g., the new molecular entity review model expectations and the principles outlined in the Good Review Management Principles and Practices.

2.5 Improve Regulatory Clarity for Regenerative Medicine

Background

Regenerative medicines have the unique ability to repair, replace, and regenerate tissues and organs, which have been affected through aging, disease, or injury, returning them to healthy function. The concept of using one's own cells and tissues to treat diseases is not new – it has been going on for decades through skin grafts, as well as bone-marrow and organ transplants.[141] The future of regenerative medicine, however, lies in stem cells and other forms of cell-based therapy.

It has become clear that stem cells exist in many niches within the human body. One relatively new method extracts and concentrates stem cells from an individual's adipose (fat) tissue, before re-injecting them back into the same individual ("autologous") either intravenously or at a site of injury. This new procedure is far less intrusive, and less painful than bone marrow transplants, with a significantly higher success rate. This is in part due to the nature of the cells being used, and the fact that cells are not shared between individuals. As such, these procedures have gained tremendous attention in the medical field.

In the United States, cellular therapeutics are regulated by the FDA, which has clear authority to regulate stem-cell transfers between different donors and recipients. Whether transplantation of a patient's own cells should be regulated as a drug, device, or treated as the "practice of medicine" is currently the subject of much debate. Surgically transplanting an organ or piece of tissue from one part of the body to another is defined as "practice of medicine" and does not fall under FDA regulation. For instance, coronary artery bypass graft surgery typically removes the saphenous vein from the patient's leg with the purpose of using that vein to re-route coronary circulation to bypass an occluded artery. Spinal surgery often uses bone from a patient's pelvis or rib to fuse vertebrae. Withdrawing adult stem cells from adipose tissue (body fat) is far less invasive than either of these or many other procedures relying on the patient's own tissue.[142] However, isolated stem cells, even if transplanted back into the same patient (i.e. autologous stem cells), are regulated as drugs, even though many people have argued the reinjection of autologous stem cells is no more invasive than other surgical practices that do not fall under FDA jurisdiction. [143, 144]

Despite profound differences between inanimate chemicals and living human cells, a new regulatory process has never been developed for this class of treatment. Under existing legislation, the FDA regulates cell-based therapies with rules derived from those developed for chemical drugs, vaccines, and biologics, which has forced cellular therapies into the existing regulatory regime. Moreover, the FDA regulatory requirements, designed for products

manufactured and sold on a mass scale, cannot be readily satisfied when it comes to treatments that are more akin to practicing medicine and personalized to individual patients.

In 2001, the FDA codified a three-tiered regulatory structure for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) with regulatory oversight increasing as product risk potential increases. This is set forth in 21 C.F.R. Part 1271, based upon the agency's statutory authority to prevent the spread of communicable disease according to Section 361 of the Public Health Service Act.

Specifically:

- The lowest risk category is not subject to FDA oversight, and includes human organs for transplantation, whole blood and blood-derived products, and extracted human products such as collagen and bone marrow.
- The mid-level risk category applies to "any human tissue derived from a human body and intended for transplantation into another human…that meets the following criteria: minimally manipulated, intended for homologous use, not combined with another agent (with a few exceptions), and either does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or if it has such an effect, is intended for autologous use or allogeneic use in close relatives. [145] These are known as 361 HCT/Ps and are eligible for regulation solely under Part 1271 (communicable diseases). This designation exempts the products from the pre-market FDA approval process. These products are required only to meet requirements regarding: (1) registration and listing; (2) donor screening and testing; (3) Current Good Tissue Practices; (4) labeling; (5) adverse-event reporting; and (6) inspection and enforcement.[146]
- The third tier comprises what the FDA considers the riskiest HCT/Ps, which are regulated under both Part 1271 and FDA's traditional pre-market and post-market regulation of medical devices and drugs under the FDCA and biological products under section 351 of the PHS Act. Tissue and cells are considered 351 HCT/Ps if they fail to meet the 361 exemptions.

Because the 2001 guidance described 361 HCT/Ps as being transferred into "another human,"[147] this excluded autologous stem cells. However, in an effort to expand its reach, the FDA revised the guidance in 2006 without a formal rulemaking and comment period, changing the phrase from "another human" to "a human." This expanded its jurisdiction to autologous stem cells, which the FDA acted on by reprimanding Regenerative Sciences LLC in 2008, arguing its procedures did more than minimally manipulate tissue.[148] The net effect of these

current regulations, therefore, has been to cause confusion for companies, researchers and physicians, hinder innovation and curtail investment, and ultimately delay the benefits of potential groundbreaking therapies to patients.

Although legislation has been introduced to support regenerative medicine (below), to date such legislation has focused predominantly on funding, high-level governance, and support for research collaboration.

Legislation	Description
H.R. 4494 Regenerative Medicine Promotion Act of 2014	▪ Sponsored by Representative Diana DeGette (D-CO); Co-sponsors include Representatives Erik Paulsen (R-MN), Chris Van Hollen (D-MD), Chaka Fattah (D-PA), and Rick Nolan (D-MN) ▪ Authorizes FDA Commissioner to (1) conduct, support, or collaborate in regulatory research to assist the FDA in performing its functions with respect to regenerative medicine and (2) make grants to fund regulatory research for such purpose. ▪ Authorizes NIH grants for regenerative medicine ▪ Establishes a Regenerative Medicine Coordinating Council-national strategy, identifying funding sources, and making recommendations regarding federal policies to support regenerative medicine products ▪ Requires report from Comptroller General on all federal programs regarding regenerative medicine
S. 2126 Regenerative Medicine Promotion Act of 2014	▪ Sponsored by Senator Barbara Boxer (D-CA; Co-sponsors include Senators Mark Kirk (R-IL), Mary Landrieu (D-LA), Tammy Baldwin (D-WI), Cory Booker (D-NJ), and Bob Casey (D-PA) ▪ Establishes a Regenerative Medicine Coordinating Council-national strategy, identifying funding sources, and making recommendations regarding federal policies to support regenerative medicine products ▪ Requires report from Comptroller General on all federal

	programs regarding regenerative medicine

Regenerative medicine holds great promise for future cures, but more regulatory clarity is required if the field is to reach its full medical potential, particularly regarding autologous stem cells.

Policy Recommendations

Congress should improve the regulatory framework for regenerative medicine by performing the following:

1. Require FDA to provide additional clarity regarding its regulation of regenerative medicine, specifically addressing adult autologous stem cell therapy.
2. Encourage FDA's recognition of the unique nature of stem cell therapeutics, in particular autologous or similar therapies, and the fact that they require a different regulatory approach than that applied to traditional drugs or biologics. Explore the creation of a new regulatory category separate from HCT/P 351 or 361.

2.6 Improving Use of Guidances

Background

FDA issues much of its current regulatory thinking through guidance documents. In fiscal year 2014, the FDA's Center for Drug Evaluation and Research alone issued 51 draft guidances and 13 final guidances.[149] Developing guidance documents is resource intensive for FDA staff. Given the breadth and continuously growing responsibilities of FDA staff, contributing to a regulatory activity such as the development of a guidance document often becomes secondary to their primary job, particularly given constrained agency resources.[150] On the one hand, it can be easier for an agency to produce and release guidance than rulemaking. On the other, guidances are generally considered "interpretations," and are not enforceable by the courts in the same ways as rules.

The FDA's standards and interpretations—whether they are released via guidances or other means—should be transparent and predictable for all stakeholders. The problem with the use of guidances is that they can often stay in draft form for many years, creating uncertainty for stakeholders—including the FDA's own employees. Indeed, in a recent congressional hearing, it was revealed that the FDA currently has 172 outstanding draft guidance documents, one of which goes back to 1988.[151] Further, while guidances can be helpful in communicating the agency's thinking to the regulated community and patients and physicians, they can also be

very time-consuming to develop, which may take resources away from other high priority activities, such as product reviews.

Some also question FDA's reliance on guidance documents and believe that rulemaking should be used in some instances in lieu of guidance documents. In the fight over whether or not the FDA has the authority to regulate laboratory developed tests, many who oppose such regulation have argued that such a significant change should be made through rulemaking and not through guidance.

Most of the FDA user fee acts have required the Agency to promulgate a number of guidance documents.

The 21st Century Cures Act mandates the issuances of guidances on a number of issues. Four Republican Senators on the Senate HELP Committee have sent inquiries to the FDA on the number of FDA guidance documents and their status.[152] In its response, the FDA reported that CBER took 743 days on average between 1999 and 2014 to finalize a draft guidance. In that same time period, CDER took 710 days. In one extreme case, a guidance (on monoclonal antibodies) took 15 years to finalize.[153]

In its 2012 report, PCAST urged reorganization of FDA's internal processes for issuing guidance documents and clearing up guidance backlogs. In particular, the agency could seek public input on the highest priority topics for guidance and seek third party expertise to develop recommendations for guidance. The FDA should speed up finalization by partnering with outside scientific experts. The FDA should also reserve the use of guidance documents for truly scientific issues and ensure compliance with the Administrative Procedures Act by issuing regulations for other issues.

Policy Recommendations

To improve FDA's process for creating guidances and regulations, Congress should perform the following:

1. Require FDA to seek public input on a guidance prioritization scheme.
2. Clarify that FDA should use formal rulemaking processes when making substantive policy changes.
3. Authorize and encourage FDA to use public-private partnerships to develop and draft guidance documents requiring significant scientific input, while leaving final approval authority with FDA.
4. Explore and address administrative barriers to finalizing guidances.

SECTION 3: STRENGTHENING THE FDA'S ABILITY TO CARRY OUT ITS MISSION

3.1 Assuring Adequate Scientific Expertise and Capacity at FDA

Background

In 2007, FDA's Science Advisory Board concluded the agency lacked sufficient internal scientific expertise to keep pace with rapidly emerging scientific and technological advances. Questions remain about the pace of progress to address this challenge over the last eight years despite significant increases in FDA funding.[154] The FDA's budget has grown 63 percent over the last five years; in 2006, the FDA's annual budget was about $2.7 billion and in FY 2014 it was $4.4 billion.[155] Much of this increase, however, can be linked to the passage of the Tobacco Control Act and FDA's increasing the review of drugs, biologics and devices.[156]

A little more than half (8,769) of FDA's 15,700 worldwide employees are exclusively dedicated to biologics, drugs and devices.[157] (Some employees in FDA headquarters and field inspectors work across multiple programs.) The agency's responsibilities are increasing at a rate far faster than its budget for drug, biologics and device reviews.

Key issues arise in two areas: (1) the capacity of the agency to do all the things it has been asked to do, and (2) agency management challenges.

Agency Capacity

The FDA faces barriers in hiring scientists who are up-to-date on the latest advances. Part of this challenge is attributable to what the Partnership for Public Service found to be FDA's poor reputation among private industry and policymakers. As a result, the Partnership concludes, FDA's efforts to recruit highly skilled, talented scientists are especially challenging.[158]

FDA lacks targeted recruitment programs and talent pipelines for high-priority scientific and medical disciplines including those that are most novel. It experiences difficulty with recruiting executives from outside the FDA to bring fresh perspectives to the organization. This is in part because of the agency's strict conflict of interest policy. The FDA acknowledges: "[A]s science becomes more specialized, it becomes more difficult for general scientists to keep up with the scientific advances in the many areas that FDA regulates. To a large extent, the critical science base exists at the major research institutions in the private sector."[159] Leading experts typically have a financial stake in their work, preventing them from serving in an Advisory Committee role or working directly for the FDA unless they are willing to fully divest. A desire to contribute to public service can be outweighed by requiring liquidation of nest egg investments. Alternatives to divestiture should be considered. FDA's hiring processes are also in need of improvement. Subject matter experts have limited opportunities to become

meaningfully involved in assessing job applicants for critical scientific and medical positions. The FDA also faces challenges not only in recruiting employees, but also in retaining them, although in recent years its retention in the device area has improved, while the drug review offices continue to face challenges. [160,161] Employee turnover can affect the timeliness of product reviews. Furthermore, the FDA is limited in its ability to be proactive in developing relationships with universities and the private sector to recruit scientific talent.[162]

A 2012 PCAST report found that "the FDA staff is stretched thin addressing formal PDUFA milestones due to insufficient total funding from Federal appropriations and PDUFA." Further, PCAST faulted FDA for failing to task a "single high-level individual …with responsibility for providing clear, consistent ongoing advice to the sponsor. As a drug progresses from the pre-investigational stage (pre-IND) to final consideration for approval (NDA), many staff across divisions and offices are involved in the review. There are also significant imbalances in workload across divisions, which have a variable and unpredictable impact on clinical review holds, review timelines, and ultimately total time to approval."[163]

Agency Management Challenges

It is clear that not all of the FDA's challenges have been resolved. At the beginning of every Congress, GAO issues a report cataloguing those parts of the federal government that are "most high risk due to their vulnerabilities to fraud, waste, abuse, and mismanagement, or are most in need of transformation."[164] The most recent report found weakness in FDA's ability to ensure the quality of medical products manufactured overseas; a lack of "clear and effective processes for making decisions about, and providing management oversight of post-market safety issues"; failure of FDA to keep pace in its oversight of promotional communications for prescription drugs as well as weaknesses in FDA's oversight of clinical trials. However, the GAO noted that FDA has recently announced plans that may help to ameliorate some of these problems. Specifically, the agency intends to embark on a multi-year hiring initiative and to invest in information technology.[165]

Furthermore, there are widespread performance inconsistencies across FDA. For example, a recent study found wide variation in drug division performance. In fact, the most productive divisions (oncology and antivirals) approve new drugs roughly twice as fast as the CDER average and three times faster than the least efficient divisions—without the benefit of greater resources, reduced complexity of task, or reduction in safety.[166] Another study asserted similar variability in the timeliness of device reviews across the CDRH.[167] At a March 10, 2015 Senate HELP Committee hearing, outgoing FDA Commissioner Hamburg acknowledged the variances in Agency performance across divisions, and attributed these differences to management and resources.[168]

PCAST also faulted the FDA's management practices. It found that "FDA leadership lacks mechanisms to evaluate management issues and improve the consistency of processes. The agency also requires greater flexibility to test new ways of improving the management of the review process, and to identify the best approaches and scale up and ensure their consistent implementation" as well as to judge the consistency of practices in different parts of the agency. Part of the FDA's management challenges may be due to the inadequate IT systems, as PCAST also found.[169]

PCAST's 2012 *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation* includes a recommendation for reforming management practices at FDA. Specifically, it states that FDA should implement a range of reforms, including the use of pre-market review leaders to oversee each drug candidate application from its investigational stage through final marketing decision. Other reforms included establishing a regulatory innovation program, overhauling the IT systems, and establishing a Commissioner's Advisory Board for Medical Products to improve management and ensure consistent implementation of reforms.[170]

Subtitle P of Title II of the of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015 includes multiple provisions to improve scientific expertise and capacity at the FDA, including: [171]

- Section 2281 removes the limit of 500 staff within the Silvio O. Conte Senior Biomedical Research and Biomedical Product Assessment Service, giving FDA the ability to hire more expert staff through this program.
- Section 2282 expresses the sense of Congress that participation in scientific conferences is essential to the mission of FDA.
- Section 2283 provides administrative reforms to the Reagan-Udall Foundation to support FDA.
- Section 2284 exempts FDA from the OMB Paperwork Reduction Act with respect to surveys and questionnaires, which will improve the agency's ability to collect voluntary patient data.
- Section 2285 enables FDA to hire more efficiently by giving the agency broad and flexible new authority to recruit and retain the staff. It also gives the agency the ability to offer salaries competitive with those in the private sector and in academia.

Policy Recommendations

Congress should assure adequate capacity and scientific expertise at the FDA by performing the following:

1. Require FDA to conduct an organizational review process to identify gaps in scientific expertise, capacity to carry out various aspects of its mission, and opportunities for streamlining and using existing resources more efficiently.
2. Require FDA, working with HHS and the Office of Personnel Management, to modernize human resources practices and systems to address gaps in scientific expertise and capacity, by performing the following and reporting to Congress on progress, within 12 months:
    a. Reviewing and improving recruiting, hiring, and retention strategies;
    b. Implementing direct hiring authority;
    c. Allowing use of qualified blind trusts or other appropriate mechanisms to address conflict-of-interest concerns;
    d. Exploring and improving personnel policies that support appropriate turnover; and
    e. Implement additional exemptions from standard federal agency hiring policies (including increasing the number of employees that can exceed federal salary compensation caps).
3. Eliminate barriers that prevent FDA staff from attending scientific conferences and meetings, which are crucial to helping FDA staff keep up with the latest scientific development.
4. Encourage FDA to expand its partnerships with academic institutions to raise awareness of the opportunities at FDA and build a pipeline of talented graduates who can establish a career at the agency.
5. Encourage FDA to improve its IT infrastructure to support knowledge management and sharing, workflow management, and more effective communications across reviewers and centers, as well as with sponsors.
6. Create for FDA a waiver of the OMB Paperwork Reduction Act to further FDA's ability to more readily collect information from industry, academia, patient groups, and other experts and stakeholders through voluntary surveys and questionnaires, to rapidly expand knowledge and insights.

3.2 Encouraging Effective Use of Public-Private Partnerships

Background

Public-private partnerships and advisory committees, when used appropriately, can expand the resources available to FDA and address gaps in scientific expertise and capacity issues.

Public-Private Partnerships

On its own and under congressional direction, the FDA has set up multiple public-private partnerships, including the Critical Path Institute, the Reagan-Udall Foundation, the Biomarker Consortium, and others. Public-private partnerships bring together pharmaceutical companies, academic institutions, science and regulatory agencies, biotechnology firms, patient-advocacy associations, and sometimes other industries dedicated to medical devices, telecommunications, and information technology. Other stakeholders in the health care ecosystem may also be included such as representatives of private and public payers. However, it is unclear whether the FDA has the resources to maximize these relationships.

The Critical Path Institute (C-Path) is a nonprofit, public-private partnership with the FDA created under the auspices of the FDA's Critical Path Initiative program in 2005. C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.[172]

In 2006, the Foundation for NIH, the NIH, FDA, and the Pharmaceutical Research and Manufacturers of America founded the Biomarkers Consortium. Among the goals of the consortium is to generate useful information to inform regulatory decision-making.[173]

In 2007, Congress created the Reagan-Udall Foundation as an independent nonprofit in response to the FDA's own *FDA Science and Mission at Risk* report prepared by the FDA's Science Board. The foundation's goal is to advance regulatory science and bring an array of resources and perspectives to bear on high priority FDA regulatory science projects.[174,175]

As of February 2014, the CDER alone is involved in 22 science-driven, public-private partnerships that promote development of research tools, platforms, clinical databases and predictive models to advance knowledge of disease and safety profiles of drugs—some of which were funded under legislation authorized in FDASIA 2012.[176]

The FDA's partnerships extend beyond drugs. The Medical Device Innovation Consortium (MDIC) is the only device industry-focused FDA partnership. It aims to advance regulatory science in the medical device industry by coordinating the development of methods, tools, and resources used in managing the total product life cycle of a medical device to improve patient

access to cutting-edge medical technology.[177] Outgoing Commissioner Hamburg recently cited the MDIC as an example of what the FDA "can and should be doing."[178]

There is a paucity of data regarding the impact that FDA's current partnerships—either as a whole or individually—are having on the timeliness of the FDA's approval decisions for drugs and devices for both final products and IND and IDEs (investigational drugs and devices).

Advisory Committees

FDA benefits from the ability to apply the recommendations of its myriad advisory committees in making product approval or clearance decisions. However, there has been much conflict in recent years on how strict FDA's conflict-of-interest policies should be for its advisers. Clearly, the agency should not receive advice biased by self-interest. On the other hand, especially for cutting-edge and novel therapies, many of the individuals most qualified to share their unique expertise with the agency have conflicts. FDASIA modified the law to remove a previously enacted cap on the number of advisory committee members who could have a financial conflict.[179] From FY 2008 to FY 2013, FDA reduced advisory committee vacancies from 40 percent to 14 percent.[180]

Rationale for Expansion and Accountability in the Use of Public-Private Partnerships

As noted throughout this document, FDA lacks the internal scientific expertise and capacity to carry out several aspects of its mission, including critical goals associated with accelerating the development and evaluation of medical products. FDA also struggles with providing clear guidance to promote predictability and transparency of expectations associated with review and approval of medical products. Expanded reliance on outside experts, including through the use of public-private partnerships, can help to address gaps in scientific expertise and capacity. Currently, policy proposals addressing public-private partnerships are limited.

PCAST's 2012 *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation* includes recommendations for catalyzing the creation of a broad-based partnership to accelerate therapeutics.[181]

Section 1141 of the of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015 would create the Council for 21st Century Cures, a public-private partnership in the United States to accelerate the discovery, development, and delivery of medical products.[182] The Council would include the director of the NIH, the commissioner of the FDA, the administrator of CMS, and five other federal agency heads determined by the HHS secretary as well as 17 appointed stakeholder members.

In addition, Section 2226 of H.R. 6 would improve the medical-device advisory committee review process at FDA to ensure adequate expertise among classification panel members to assess the device and allow for presentation by the device sponsor.[183]

Policy Recommendations

Congress should encourage the effective use of public-private partnerships at the FDA by performing the following:

1. Reconfirm and encourage FDA to use its existing authority to use partners and trusted intermediaries to augment FDA's internal resources, particularly for novel or complex technologies that may be outside of the FDA's normal expertise.
2. Require FDA to monitor, evaluate, and report on the outcomes and effectiveness of existing public private partnerships to determine whether additional investment in these programs and/or further coordination and accountability associated with such programs is warranted, as well as whether outdated or ineffective public-private partnerships should be phased out.
3. Support the launch of a study to both assess current conflict of interest policies associated with advisory groups and develop recommendations that both effectively address conflict of interest concerns and enable FDA to gain input from a broad and representative set of individuals representing patients and academia.

3.3 Improving FDA Internal Review Processes

Background

In 2014, FDA approved 51 novel drugs and biologics (41 by CDER and ten by CBER), the most in almost 20 years. Seventeen of these approvals are "first in class" therapies, which represent new approaches in the treatment of disease (see Figure 2).[184] But it remains an open question whether 2014 represents an aberration from a previous decade of limited progress with respect to product approvals or a

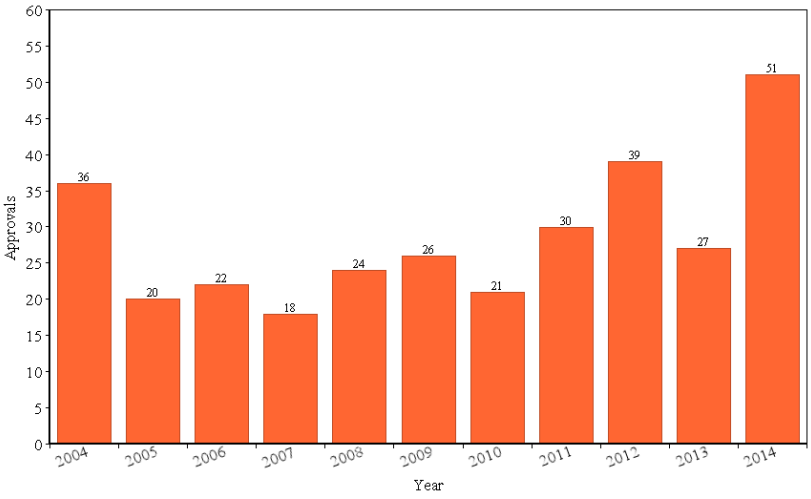

Figure 2: Number of New Drug Approvals and Biologics License Applications

critical inflection point signaling the commencement of a new era in drug, biologic, device, and diagnostic approvals.

Trends in the medical-device arena have been more mixed.[185,186] Preliminary data suggest that the Premarket Approval (PMA) (i.e., FDA's process of scientific and regulatory review to evaluate the safety and effectiveness of novel Class III medical devices) in 2011 and 2012 was the best overall review-time performance of the device user fee era; and 2013 has yielded further improvement. [187]

But while PMA approval times have declined, the same cannot be said for the clearance of 510(k) products (i.e., follow-on devices that must demonstrate equivalence to a device already placed in one of three classifications categories).[188] This is significant because 510(k) products represent the vast majority of devices (more than 3,000 annually) reviewed by the FDA.[189]

Regulatory challenges have contributed to sub-optimal outcomes for drug, biologic, and device development and approval. With respect to the FDA, few deny that prudence is warranted when deciding whether to approve a novel drug, biologic, device, or diagnostic for commercial use. Where differences arise is over the degree and appropriateness of that prudence—especially when assessing novel products targeting areas of unmet medical need. Just as an ambulance speeding to the site of a car wreck is afforded a degree of latitude with respect to traffic ordinances, an increasing number of researchers, patient advocates, legislators, and regulators acknowledge that similar latitude is warranted when assessing innovative drugs, biologics, or devices targeting diseases for which there remain neither effective nor sufficient treatments. The need to protect public health requires not only preventing unsafe products from reaching the market but also ensuring that potentially life-saving and life-enhancing biomedical products—especially those for unmet medical needs—are reviewed efficiently and expeditiously.[190,191]

Wide variation exists across different review divisions with respect to performance. The most productive divisions (oncology and antivirals) approve new drugs roughly twice as fast as CDER and three times faster than the least efficient divisions—without the benefit of greater resources or reduction in safety (see Figure 3).[192] Similar variability exists in the timeliness of device reviews across CDRH).[193]

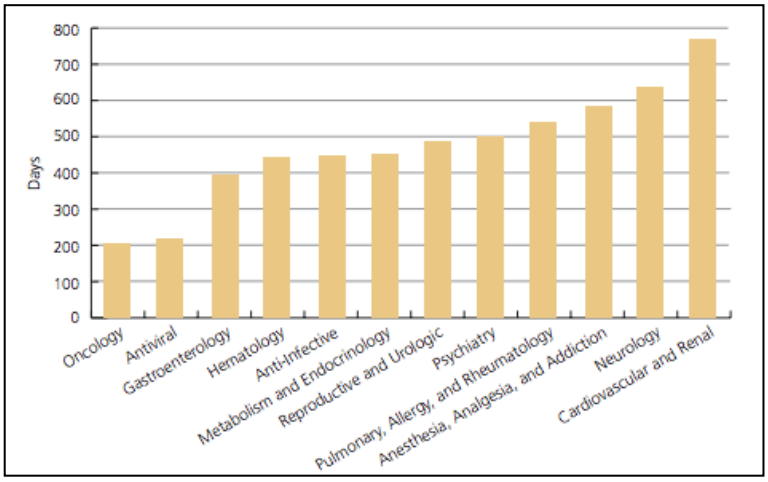

Figure 3: Mean Approval Time by CDER Division

CDRH has recently reformed its review practices for medical devices and received favorable reviews.[194] Center and review division attitudes toward risk tolerance may reflect past practices and underlying cultural constraints rather than evolving understandings of how best to determine benefit/risk of innovative biomedical products.

FDA should consider applying the best practices from the oncology and virology divisions to other review divisions when appropriate.

Ensuring the implementation of best practices (where applicable) across the respective CDER, CBER, and CDRH review divisions would contribute to reducing the cost and time to discover, develop, and approve drugs, biologics, devices, and diagnostics, enabling more timely access to drugs and biologics, while simultaneously safeguarding the safety of medical products.

Policy Recommendations

Congress should improve the FDA's internal review processes by performing the following:

1. Direct FDA to both conduct and implement strategies in response to an organizational study of its review and approval processes. This study should evaluate review times, identify root causes of delays, identify best practices, and recommend measurable goals and actions to support faster turnaround times. As part of this effort, FDA should conduct a best-practices study of review divisions to identify best practices that can be applied across divisions.
2. Direct FDA to develop an inter-agency education and training program to implement best practices across centers and divisions.
3. Direct FDA to establish a monitoring system to track and report progress against implementation goals and impact on drug and device review times.

SECTION 4: INCREASING INVESTMENT IN MEDICAL PRODUCTS TO ADDRESS UNMET AND PUBLIC HEALTH NEEDS

4.1 Accelerating the Development and Approval of New Antibiotics

Background

One of the most urgent public health needs in the United States is new treatments for antibiotic resistant infections. The CDC reports that at least two million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.[195] Despite this growing threat, only ten new antibiotics have been approved by the FDA since 2000. The FDA, sponsors, and patients would benefit from new flexible pathways that encourage the development of new antibacterial drugs. Antibiotic-resistant bacteria is also a significant concern to U.S. troops, affecting more than a third of returning Iraq and Afghanistan veterans, according to the Department of Defense.[196]

In response to this public health challenge, in 2012 PCAST recommended the creation of a new pathway for initial approval of drugs shown to be safe and effective in a specific subgroup of patients, specifically calling out antibiotic resistance as a key target for this pathway. [197] PCAST suggested that "this would be an optional pathway under which sponsors could propose early in the development process to study a drug for a narrow population. Such drugs would be approved under a designation of Special Medical Use, signaling strongly to payors and prescribers the limited population that should be prescribed a drug."[198]

Led by the Infectious Diseases Society of America and building on the PCAST recommendation, a new mechanism was suggested for "limited population antibacterial drugs (LPAD)." IDSA reports "it is not feasible for antibacterial drugs that treat serious infections due to highly resistant bacterial pathogens to be developed using traditional, large scale clinical trials due to the limited numbers of patients in which such serious infections occur. Instead, under the LPAD mechanism, a drug's safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials—much as the Orphan Drug Program permits for other rare diseases. LPAD products then would be narrowly indicated for use in small, well-defined populations of patients for whom the drugs' benefits have been shown to outweigh their risks."[199]

The FDA to a large extent has concurred with the need for new approval mechanisms that complement their existing authority to grant approvals based on subpopulations of patients. Janet Woodcock, director of the Center for Drug Evaluation and Research at the FDA testified in 2014 that "[g]iven the public health threat posed by antimicrobial resistance, the FDA believes it is necessary to consider new mechanisms for encouraging the development of new

antibacterial drugs to address unmet medical needs in the treatment of serious and life-threatening bacterial infections."[200]

To ensure that these new drugs are only used in the appropriate population, Woodcock agreed that the LPAD would need "a clear branding mechanism to convey accurately to physicians prescribing the product the limitations of the data supporting approval, including the uncertainty and the unique benefit-risk profile associated with the drug. Such labeling is particularly important in the context of antibiotic drugs, where historical overuse has led to increased antimicrobial resistance."[201]

In January 2015, Senators Orrin Hatch (R-UT) and Michael Bennet (D-CO) introduced legislation that built on the recommendations of PCAST to create a new limited pathway for antibiotics. Their bill, the *Promise for Antibiotics and Therapeutics for Health (PATH) Act* addressed some of the significant regulatory obstacles facing antibiotic development and hindering patient and veteran access. The PATH Act permits the FDA to accelerate an antibacterial drug's approval for an identifiable, limited patient population upon determining that the drug treats a serious or life-threatening condition and addresses an unmet need. In addition, the Act requires a drug's label to include special designation from the FDA indicating its intended use in limited, high-risk populations approved under the pathway. The Act also calls for further guidance and potential expansion to other appropriate therapeutic areas.[202]

FDA would benefit from the flexibility to work with sponsors in any therapeutic area of high need to undertake similar programs that will result in accelerated access. Use of Special Medical Use approvals for appropriate products and indications could allow accelerated approval of medicines that might ultimately have broader use with restricted distribution. An analysis should be considered to assess whether FDA has sufficient statutory authority to allow this flexibility.[203] FDA could also consider supporting new approaches that combine more reasonably sized clinical trials with robust post-market surveillance.

Section 2121 of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, contains provisions similar to the PATH Act, including the following[204]

- Establishes a program to expedite the approval of certain antibacterial and antifungal drugs for use in limited populations of patients at the request of the sponsor;
- Requires prominent labeling of the limited population antibacterial and antifungal drugs that indicates it is for a limited and specific population and requires the sponsor to submit promotional materials to the FDA for approval;

- Allows the FDA to remove labeling and promotion restrictions if the drug is approved for broader use; and
- Requires the HHS secretary to publish guidance describing criteria, process, and other general considerations for demonstrating the safety and effectiveness of antibacterial and antifungal drugs approved for use in limited populations.
- Requires the HHS secretary to publish an assessment of the program, hold a public meeting, and consider expansion of the limited use pathway and program beyond antibacterial and antifungal drugs.

Policy Recommendations

Congress should accelerate the development and approval of antibiotics by performing the following:

1. Require FDA to establish a program to expedite the approval of certain antibacterial and antifungal drugs for use in limited populations of patients at the request of the sponsor, which includes the following:
    a. Requires prominent labeling of the limited population antibacterial and antifungal drugs that indicates it is for a limited and specific population and requires the sponsor to submit promotional materials to FDA for approval; and
    b. Allows FDA to remove labeling and promotion restrictions if the drug is approved for broader use.
2. Require FDA to publish guidance describing criteria, process, and other considerations for demonstrating the safety and effectiveness of antibacterial and antifungal drugs approved for use in limited populations.
3. Require FDA to publish an assessment of the program, hold a public meeting, and consider expansion of the limited use pathway and program beyond antibacterial and antifungal drugs.

4.2 Expanding Early Patient Access to Medical Products

Background

Creating targeted pathways that give patients faster access to appropriate, beneficial treatments has been a long-standing goal of all stakeholders in drug development. The FDA now has at its disposal expedited pathways including accelerated approval, breakthrough therapy designation, fast track designation, and priority review.

Despite these tools, which speed up the existing pathway through FDA, many patients lack effective options to treat their serious and potentially life-threatening conditions. For those patients with the most pressing unmet needs, the FDA has a process for expanded access, also called "compassionate use," that provides a pathway for patients to gain access to unapproved investigational drugs, biologics, and medical devices for serious diseases or conditions.[205] With oversight of this process from FDA, patients are able to access experimental treatments.

The expanded-access process currently includes burdens for both physicians and sponsors that act as roadblocks. Physicians currently must spend about eight hours to prepare an individual patient request for expanded access.[206] New policies and procedures are needed to reduce this task. Greater transparency between sponsors and physicians is also necessary because regulations require the physician to determine that the risks of the disease outweigh the risks of the drug, but there is usually little published literature relating to the drugs at issue.[207]

For patients to receive expanded access to a drug, the sponsor must agree to allow early access to its products. In April 2014, 32,304 studies were listed at ClinicalTrials.gov as enrolling new participants. Only 86 were available for expanded access.[208] Opening up studies for expanded access requires sponsors to accept significant administrative and manufacturing burdens. In addition, the sponsor must also consider the impact of expanded access to ongoing development and regulatory approval efforts.[209]

Expanded access policies need to recognize sponsor concerns that adverse events could negatively impact the regulatory review of the product, and the FDA should clarify how it will interpret adverse events under expanded access in their review.

To improve the existing expanded access program, FDA needs to work with sponsors to improve transparency and increase appropriate access. At the same time, FDA must create assurances that the possibility for adverse events will not hinder the product's review at the FDA.

Subtitle E of Title II (Sections 2081-2083) of the 21st Century Cures Act (H.R. 6) passed by the U.S. House of Representatives on July 10, 2015, contains provisions to improve the processes for early patient access to medical products:[210]

- Requires sponsors to make their policies on expanded access during clinical trials publicly available, including procedures for requests and qualification criteria.
- Requires FDA to finalize guidance regarding how it interprets and uses adverse drug event data resulting from drug use under expanded access programs.

Policy Recommendations

Congress should improve processes for early patient access to medical products by performing the following:

1. Require sponsors to make their policies on expanded access during clinical trials publicly available, including procedures for requests, qualification criteria, and a single point of contact.
2. Require FDA to finalize guidance regarding how it interprets and uses adverse drug event data resulting from drug use under expanded access programs.

4.3 Creating Incentives for Development of Medical Products for Unmet Medical Needs

Background

Only two out of every ten medicines will recoup the money spent on their development.[211] To continue searching for the next generation of treatments, drug-makers need sufficient protections for marketed drugs to recover their investments in drug discovery, including the large majority of compounds that fail to make it through the research and clinical-trial phases. Currently, drug-makers can receive five years of data exclusivity for a new prescription medicine and 12 years for a biologic. In addition, drug compounds are protected through patents granted early in the drug development process and last for 20 years. However, the "patent clock"—the time before the patent expires—runs out regardless of whether or not the compound is ever successfully approved by the FDA and marketed.

This incentive structure may make it financially untenable for companies to commit the necessary resources to bring a drug to market based on scientifically promising compounds that lack patent protection.

Data has shown that exclusivity periods are very effective incentives for drug development. The Orphan Drug Act of 1983 is widely cited as a model of success. The Act gave the FDA the authority to create a market exclusivity period of seven years (two years longer than the standard exclusivity period) for drugs and biologics with "orphan status." Drugs and biologics with orphan status are those intended for rare diseases that affect fewer than 200,000 people in the United States.

The Act has had demonstrable impact. Prior to passage of the Orphan Drug Act, there were only 38 approvals of drugs meeting the orphan status definition.[212] After the passage of the Act, there were 511 approvals during the period 1983 through 2014, with 49 in 2014 alone.[213]

More recently, the Generating Antibiotic Incentives Now (GAIN) provisions of FDA's 2012 Safety and Innovation Act granted five years of added exclusivity for antibiotics that treat serious or life-threatening infections.[214] Since the start of the program, 39 newly developed antibiotics have been qualified for this new designation and six have been approved.[215,216] However, since all of the products qualified under GAIN were already in early stages of development prior to the provisions being signed into law, it is too early to determine what impact, if any, the added exclusivity period is having on incentivizing investment.

While GAIN and the Orphan Drug Act demonstrate success in addressing market failures in important but limited areas of drug discovery, millions of patients still lack effective treatments for their conditions. In the case of many scientifically promising compounds for unmet needs, the lack of certainty of patent protections makes their development cost-prohibitive.

Senators Orrin Hatch (R-UT) and Michael Bennet (D-CO) introduced the Dormant Therapies Act of 2014 to establish a new class of pharmaceuticals known as dormant therapies. Dormant therapies are defined as a new drug or biological product that has insufficient patent protection and meets the FDA definition of therapies targeted at unmet medical needs.[217] Further, dormant therapies must not contain active ingredients that have been previously approved by the FDA, preventing drug sponsors from seeking patent extensions on previously available medicines.[218] The FDA defines an unmet medical need as a condition whose treatment or diagnosis is not addressed adequately by available therapy.[219] Dormant therapies would be eligible for 15 years of data protection.[220]

The Dormant Therapies Act also requires waiver of patent provisions to create predictable timelines for generic or biosimilar competition. This gives patients and providers realistic expectations about when these lower-cost alternatives will be available.[221]

Many patient groups, including the National Health Council, support the dormant therapy provisions, believing that they fix current legal and market failures for a category of products

that could address unmet medical needs, but have insufficient patent protection to justify investment in development.[222]

Policy Recommendations

Congress should increase incentives for the development of medical products with unmet medical needs by creating a new regulatory pathway for dormant therapies at the FDA, by performing the following:

1. Give FDA the authority to designate a new treatment as a dormant therapy if intended to treat an unmet medical need. A dormant therapy must not contain active ingredients that have been previously approved by the FDA.
2. Determine a fixed period of protection from generic and biosimilar competition for dormant therapies.
3. Require sponsors of approved dormant therapies to waive certain rights to patents of the approved dormant therapy at the end of the protection period.

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