Senate Medical Innovation Bills: Overview and Comparison with the 21st Century Cures Act (H.R. 6)

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Summary

Both the House and the Senate are considering legislation to support medical innovation, primarily through reforms to the National Institutes of Health (NIH) and changes to the drug, biologic, and device approval pathways at the Food and Drug Administration (FDA). On February 3, 2015 Senators Lamar Alexander and Patty Murray, chairman and ranking Member of the Committee on Health, Education, Labor and Pensions, announced the start of a bipartisan initiative to "examine the process for getting safe treatments, devices and cures to patients and the roles of the [FDA] and the [NIH] in that process." This initiative culminated in a package of 19 bipartisan bills that were reported out of the Senate Health, Labor, Education, and Pensions (HELP) Committee in a series of three executive sessions held on February 9, 2016; March 9, 2016; and April 6, 2016.

The Senate's medical innovation package is that chamber's companion effort to the House's 21st Century Cures initiative, which culminated in the House passage of H.R. 6, the 21st Century Cures Act, on July 10, 2015, on a vote of 344 to 77. H.R. 6 is the result of a series of hearings and roundtable meetings hosted by the House Energy and Commerce Committee dating back to spring 2014. While consisting of many different provisions, H.R. 6 is primarily focused on efforts to increase strategic investments in medical research at NIH and change some aspects of how the FDA executes its regulatory oversight mission with regard to the review and approval of new drugs, biologics, and medical devices.

This report provides for each of the bills in the Senate medical innovation package (1) background on the issue, or issues, addressed by the bill, including a summary of relevant current law; (2) a summary of the bill's provisions; and (3) where applicable, identification of comparable provisions in H.R. 6 that address the same topic. For a summary of all the provisions in H.R. 6, as passed by the House, including an explanation of how the bill would change current law, see CRS Report R44071, *H.R. 6: The 21st Century Cures Act*.

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Introduction

Both the House and the Senate are considering legislation to support medical innovation, primarily through reforms to the National Institutes of Health (NIH) and changes to the drug, biologic and device approval pathways at the Food and Drug Administration (FDA). Both NIH and FDA are agencies within the Department of Health and Human Services (HHS). On February 3, 2015 Senators Lamar Alexander and Patty Murray, chairman and ranking Member of the Committee on Health, Education, Labor and Pensions, announced the start of a bipartisan initiative to "examine the process for getting safe treatments, devices and cures to patients and the roles of the [FDA] and the [NIH] in that process."[1] This initiative culminated in a package of 19 bipartisan bills that were reported out of the Senate Health, Labor, Education, and Pensions (HELP) Committee in a series of three executive sessions held on February 9, 2016; March 9, 2016; and April 6, 2016.

One of these 19 bills, The Adding Zika Virus to the FDA Priority Review Voucher Program Act (S. 2512), subsequently was passed by both chambers and signed into law on April 19, 2016 (P.L. 114-146). The remaining 18 bills that comprise the Senate's medical innovation legislative effort include the following:

- S. 1878, The Advancing Hope Act of 2015;
- S. 1622, The FDA Device Accountability Act of 2015;
- S. 2503, Preventing Superbugs and Protecting Patients Act;
- S. 2030, The Advancing Targeted Therapies for Rare Diseases Act of 2015;
- S. 2014, Next Generation Researchers Act;
- S. 800, The Enhancing the Stature and Visibility of Medical Rehabilitation Research at NIH Act;
- S. 849, Advancing Research for Neurological Diseases Act of 2015;
- S. 2511, Improving Health Information Technology Act;
- S. 1077, The Advancing Breakthrough Medical Devices for Patients Act of 2015;
- S. 1101, The Medical Electronic Data Technology Enhancement for Consumers Health Act;
- S. 2055, The Medical Countermeasures Innovation Act of 2015;
- S. 1767, The Combination Products Innovation Act of 2015;
- S. 1597, Patient Focused Impact Assessment Act of 2015;
- S. 185, Promise for Antibiotics and Therapeutics for Health Act;
- S. 2713, Advancing Precision Medicine Act of 2016;
- S. 2745, Advancing NIH Strategic Planning and Representation in Medical Research Act;
- S. 2742, Promoting Biomedical Research and Public Health for Patients Act; and
- S. 2700, FDA and NIH Workforce Authorities Modernization Act.

[1] Senate Health, Education, Labor, and Pensions Committee, February 3, 2015, at http://www.help.senate.gov/chair/newsroom/press/alexander-murray-announce-initiative-to-examine-drug-device-development-and-review-process.

The Senate's medical innovation package is that chamber's companion effort to the House's 21st Century Cures initiative, which culminated in the House passage of H.R. 6, the 21st Century Cures Act, on July 10, 2015, on a vote of 344 to 77. H.R. 6 is the result of a series of hearings and roundtable meetings hosted by the House Energy and Commerce Committee dating back to spring 2014. The hearings and roundtables focused on a broad range of topics, including modernizing clinical trials, incorporating patient perspectives into medical research and regulatory processes, precision/personalized medicine, digital health care, and more.

While consisting of many different provisions, H.R. 6 is primarily focused on efforts to increase strategic investments in medical research at NIH and change some aspects of how the FDA executes its regulatory oversight mission with regard to the review and approval of new drugs, biologics, and medical devices.

Report Roadmap

This report provides for each of the 18 bills in the Senate medical innovation package: (1) background on the issue, or issues, addressed by the bill including a summary of relevant current law; (2) a summary of the bill's provisions; and (3) where applicable, identification of comparable provisions in H.R. 6 that address the same topic. In some cases, the House and Senate legislation address the same topic in an entirely different way. In other cases, the House and Senate legislation address the topic in a similar way but with key substantive differences. In a few instances, the language in the House and Senate bills is substantively identical.

For a summary of all the provisions in H.R. 6, as passed by the House, including an explanation of how the bill would change current law, see CRS Report R44071, *H.R. 6: The 21st Century Cures Act*.

The FDA Device Accountability Act of 2015 (S. 1622)

Use of Nonlocal Institutional Review Boards for Review of Investigational Device Exemptions and [Humanitarian][2] Device Exemptions (§2)

Issue Background

The HHS Human Subject Regulations are a core set of federal standards for protecting human subjects in HHS-sponsored research.[3] These regulations are commonly referred to as the Common Rule because the same requirements have been adopted by many other federal departments and agencies, which apply the regulations to the research they fund. Under the Common Rule, research protocols must be approved by an Institutional Review Board (IRB) to ensure that the rights and welfare of research subjects are protected.[4]

[2] Senate provision uses the word "Human."

[3] 45 C.F.R. Part 46, Subpart A.

[4] 45 C.F.R. §46.109.

FDA has issued its own set of Human Subject Regulations, which are similar, but not identical, to the Common Rule.[5] FDA applies these regulations to all the research it regulates, including clinical trials of new drugs and medical devices, regardless of the source of funding for the research. All clinical evaluations of investigational devices (unless exempt) must have an investigational device exemption (IDE) before the clinical study is initiated.[6] An IDE allows an unapproved device (most commonly an invasive or life-sustaining device) to be used in a clinical study to collect the data required to support a premarket approval (PMA) submission.[7] The IDE permits a device to be shipped lawfully for investigation of the device without requiring that the manufacturer comply with other requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA), such as registration and listing. Devices approved by FDA via the humanitarian device exemption (HDE) are for diagnosing or treating diseases or conditions that affect fewer than 4,000 individuals in the United States each year. An HDE application is similar to a PMA, but it is exempt from the effectiveness requirements. Such devices may be used in a facility only after a local IRB has approved their use in that facility, except in certain emergency situations.[8]

Senate Legislation

The provision would amend Section 520(g) of the FFDCA, regarding IDEs, and Section 520(m) of the FFDCA, regarding HDEs, by removing the word "local" in all references to local IRBs, including in the stipulation that an approved humanitarian use device may be used in a facility only after a local IRB has approved such use, except in certain emergency situations.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The use of non-local IRBs for review of IDEs and HDEs provision in H.R. 6 (i.e., Title II, Subtitle O, Section 2262) is comparable to S. 1622. The House provision would also require the Secretary, within 12 months of enactment, to revise or issue regulations or guidance, as necessary, to carry out these amendments.

CLIA Waiver Study Design Guidance for In Vitro Diagnostics (§3)

Issue Background

The Clinical Laboratory Improvement Amendments (CLIA) of 1988 provide the Centers for Medicare & Medicaid Services (CMS) with authority to regulate clinical laboratories to ensure the accuracy of test results, given that these results drive clinical decisionmaking.[9] CLIA requires laboratories to receive certification before they are allowed to carry out clinical laboratory testing on a human sample. CLIA certification is based on the level of complexity of testing that a laboratory is performing, graded as low, moderate, or high. FDA is responsible for categorizing clinical laboratory tests according to their level of complexity.[10] Laboratories that perform only

[5] 21 C.F.R. Parts 50, 56, 312, and 812.

[6] See 21 C.F.R. §812. Devices are exempt from IDE requirements when testing is noninvasive, does not require invasive sampling, does not introduce energy into a subject, and is not stand-alone (i.e., is not used for diagnosis without confirmation by other methods or medically established procedures). See 21 C.F.R. §812.2(c)(3).

[7] FDA, *Device Advice: Investigational Device Exemption (IDE)*, July 9, 2009, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm.

[8] FFDCA §520(m)(4).

[9] PHSA §353; 42 U.S.C. §263a.

[10] See FDA, "CLIA Categorizations," http://www.fda.gov/medicaldevices/deviceregulationandguidance/

low-complexity tests (called *waived tests*) receive a certificate of waiver (COW) from CMS. Conversely, only laboratories certified to do so may perform moderate- and high-complexity tests.

FDA determines whether a test is waived (i.e., low-complexity) or not based on information submitted about the test by the manufacturer, and FDA has issued guidance to support the manufacturer's submission of this information.[11] Under current law, waived tests are those "that have been approved by FDA for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result."[12] The guidance recommends ways to demonstrate that a test is both "simple" and has "an insignificant risk of an erroneous result." Demonstrating the latter includes showing that a test's accuracy is comparable to a method whose accuracy has already been established and documented. (Section V of the guidance document addresses approaches to demonstrating accuracy.)

Senate Legislation

S. 1622 Section 3 would require the Secretary, not later than one year after enactment, to publish draft guidance that revises Section V of the current guidance, including providing clarification on the appropriate use of comparable performance between a waived and moderately complex laboratory user to demonstrate accuracy. Not later than one year after the comment period for the draft guidance closes, the Secretary would be required to publish final revised guidance.

Comparable Provisions in the 21st Century Cures Act

Section 2228 of H.R. 6 (Title I, Subtitle M) is substantively identical to the Senate legislation.

Ensuring Least Burdensome Means of Evaluating Devices (§4)

Issue Background

Section 205 of the Food and Drug Administration Modernization Act of 1997 (FDAMA, P.L. 105-115) amended Section 513 of the Federal Food, Drug, and Cosmetic Act (FFDCA), adding two provisions commonly referred to as the "Least Burdensome Provisions." The two provisions stipulate that FDA consider the "least burdensome" data or information "necessary" to demonstrate a reasonable assurance of device effectiveness in a premarket approval (PMA) application or substantial equivalence to predicate devices with differing technological characteristics in certain 510(k) notifications. The two provisions are as follows:

> **Section 513(a)(3)(D)(ii)** Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of

ivdregulatoryassistance/ucm393229.htm.

[11] FDA, "Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," Center for Devices and Radiological Health, January 30, 2008, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070890.pdf.

[12] PHSA §353(d)(3), "Requirements for Certificate of Waiver"; 42 U.S.C. §263a(d)(3).

> evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.
>
> **Section 513(i)(1)(D)** Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.

FDA published final guidance on the least burdensome provisions on October 4, 2002.[13] Under the guidance, FDA may allow the use of non-clinical data—such as laboratory and/or animal testing—in place of clinical data for the approval of PMA devices in certain circumstances, such as "devices or modifications of approved devices for which scientifically valid information is available in the public domain."[14] When clinical data are needed, FDA allows manufacturers to consider study designs to shorten the length of the study. Such study designs include the use of "surrogate endpoints and statistical methods, such as Bayesian analyses," and study designs other than the gold standard—the randomized controlled trial.[15] Although FDA allows for substitution of laboratory data in certain circumstances, the absence of problems in laboratory testing may not always predict what happens to a device over time in the human body, where forces that cannot be replicated in laboratory testing act upon the device. For example, "the malfunction of [Medtronic and St. Jude Medical] implantable cardioverter-defibrillator leads, which resulted in a widespread recall, and the hazards posed by particles shed from [DePuy] metal-on-metal hip replacements were not predictable based on engineering insights or in vitro studies."[16]

The 2002 FDA guidance states, "[r]eliance on postmarket controls (e.g., ... postmarket surveillance, and the Medical Device Reporting requirements) should be considered as a mechanism to reduce the premarket burden for 510(k)s and PMAs, while still ensuring the safety

[13] FDA, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, October 4, 2002, http://www.fda.gov/RegulatoryInformation/Guidances/ucm085994.htm.

[14] Ibid.

[15] Ibid. In a randomized controlled trial (RCT), participants are randomly assigned to two or more groups. One group receives the intervention (the new treatment), while the control group receives current therapy or a placebo. Randomization ensures that any patient characteristics that might affect the outcome will be roughly equal across each group in the study. Any difference in outcomes between the groups is then likely due to the intervention. The RCT is often called the gold standard of evidence for a clinical trial. A surrogate end point may not be a reliable predictor of actual patient benefit. It is a laboratory measurement, such as blood pressure or cholesterol level, used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives. The use of Bayesian analyses allows studies to be combined in order to reduce the sample size needed for the experimental and/or control device.

[16] Steven N. Goodman and Rita F. Redberg, "Opening the FDA Black Box," *JAMA*, vol. 311, no. 4 (January 22, 2014), pp. 361-363. The Medtronic Sprint Fidelis and the St. Jude Medical Riata leads are specific models of cardiac electrodes (thin wires) that connect an implantable cardioverter-defibrillator (ICD) directly to the heart. An ICD monitors heart rhythms and can deliver an electrical shock to restore normal rhythm if life-threatening, irregular heartbeats are detected. The ICD keeps the heart from beating too fast and is surgically implanted in patients who may be at risk of sudden cardiac arrest. Both the Medtronic Sprint Fidelis and the St Jude Medical Riata were recalled because of the potential for wire fracture, causing the ICD to deliver an unnecessary shock or to not operate at all. Deaths and serious injuries were reported in which a fractured Sprint Fidelis or Riata lead may have been a possible or likely contributing factor. As of October 4, 2007, about 268,000 Sprint Fidelis leads had been implanted worldwide, including 172,000 Sprint Fidelis leads implanted in the United States. More than 227,000 Riata leads had been distributed worldwide, and as of 2011, about 79,000 Riata leads remained implanted in U.S. patients. See FDA website at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm103022.htm and http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314930.htm.

and effectiveness of the device."[17] However, the FDA's authority to require postmarket studies of medical devices is limited. A September 2015 GAO study found that of the 392 postmarket surveillance studies ordered by FDA between May 1, 2008, and February 24, 2015, 88% were inactive, 10% were ongoing, and 2% were complete.[18] Activities related to implementing the least burdensome provision, including training for staff and advisory panels, are posted on FDA's website.[19]

Senate Legislation

S. 1622, Section 4, would amend FFDCA Section 513 by adding a new subsection (j), "Training and Oversight of Least Burdensome Requirements." The Secretary would be required to ensure that each FDA employee involved in the review of premarket submissions, including supervisors, receives training on the "meaning and implementation of the least burdensome requirements" and to periodically assess the implementation of such requirements, including employee training.

Under the Senate bill, 18 months after enactment, the FDA ombudsman responsible for device premarket review would be required to conduct an audit of the least burdensome training, including the effectiveness of the training. The audit would be required to include "interviews of persons who are representatives of the industry regarding their experience in the device premarket review process" and a list of the measurement tools used to assess the implementation of the least burdensome requirement. A summary of the audit findings would be required to be submitted to the Senate HELP Committee and the House Energy and Commerce Committee and posted on the FDA website.

Regarding PMA applications, S. 1622 would amend FFDCA Section 515(c), adding a new paragraph that would require the Secretary to "consider the least burdensome appropriate means necessary to demonstrate device safety and effectiveness." It would define the term *necessary* to mean "the minimum required information that would support a determination by the Secretary that an application provides a reasonable assurance of the safety and effectiveness of the device" and would state that the role of postmarket information must be considered in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness.

In addition, the provision would amend FFDCA Section 517A(a), adding that each substantive summary of the scientific and regulatory rationale for any decision made by FDA's Center for Devices and Radiological Health (CDRH) regarding the submission or review of a PMA, a 510(k), or an IDE must also include a brief statement on how the least burdensome requirements were considered and applied.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The provision regarding training and oversight in least burdensome appropriate means in H.R. 6 (Title II, Subtitle M, Section 2223) is comparable to S. 1622. Under the House provision, the Secretary would be required to issue draft guidance, no later than 12 months after enactment, that

[17] FDA, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, October 4, 2002, http://www.fda.gov/RegulatoryInformation/Guidances/ucm085994.htm.

[18] GAO, *Medical Devices: FDA Ordered Postmarket Studies to Better Understand Safety Issues, and Many Studies Are Ongoing*, GAO-15-815, September 2015.

[19] FDA, Medical Devices, The Least Burdensome Provisions - Activities Related to Implementation, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm#7.

would update the October 4, 2002, final guidance on the least burdensome provisions. In developing the draft guidance, the Secretary would be required to hold a meeting of stakeholders "to ensure a full record to support the publication of such document."

The House provision amending FFDCA Section 515(c) would not require that postmarket information be considered in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness.

The House provision does not amend FFDCA Section 517A(a) regarding the substantive summary of any decision made by CDRH on the least burdensome requirements.

Preventing Superbugs and Protecting Patients Act (S. 2503)

Issue Background

FFDCA Section 510(k) requires medical device manufacturers to register with the Secretary and, at least 90 days prior to introducing a device intended for human use into interstate commerce, to report to the Secretary (1) the class in which the device is classified and (2) actions taken to comply with applicable device regulatory requirements under FFDCA Sections 514 and 515. This notification requirement is part of the 510(k) premarket approval pathway, a process that is unique to medical devices and if successful results in FDA *clearance*. Under the 510(k) pathway, the manufacturer must demonstrate that a new device is substantially equivalent to a device already on the market (a predicate device). Substantial equivalence is determined by comparing the performance characteristics of a new device with those of a predicate device; clinical data demonstrating safety and effectiveness are usually not required.

Reusable medical devices are those devices that may be reprocessed and used on multiple patients. In March of 2015, FDA released final guidance on the reprocessing of reusable medical devices: *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*. This guidance states that, among other things, "(m)anufacturers seeking to bring to market certain reusable devices, such as duodenoscopes, bronchoscopes and endoscopes, should submit to the FDA for review their data validating the effectiveness of their reprocessing methods and instructions."[20]

Under Section 604 of the Food and Drug Administration Safety and Innovation Act (FDASIA), the Secretary was required to withdraw draft guidance, issued by FDA in July 2011, entitled "Guidance for Industry and FDA Staff—510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device," and leave the prior guidance issued in 1997 in effect. Although patient and consumer groups have generally supported a more rigorous 510(k) notification system, industry had voiced concerns that the 2011 guidance would slow the device regulatory process.[21] Section 604 of FDASIA also required a report to House and Senate committees on when a 510(k) notification should be submitted for a modification or change to a legally marketed device. Any new draft guidance (or proposed regulation) on 510(k) device

[20] FDA, "*Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*," March 15, 2015, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM253010.pdf.

[21] Alexander Gafney, "In a Major Victory for Industry, FDA says Existing 510(k) Guidance to Remain 'Mostly Unchanged,'" *RAPS Regulatory Focus*, February 26, 2014, at http://www.raps.org/regulatoryDetail.aspx?id=9982.

modification could not be issued before the committees received the report. Final guidance (or regulation) could not be issued until one year after the committees had received the report. This report was completed by FDA in January 2014.[22]

Senate Legislation

S. 2503 would amend FFDCA Section 510 by adding a new subsection (q), "Reusable Medical Devices," which would require the Secretary, not later than six months after enactment, to identify and publish a list of reusable device types for which reports under Section 510(k) must include (1) instructions for use and (2) validation data regarding cleaning, disinfection, and sterilization. Reports issued after the publication of this list would be required to include instructions for use and validation data, as specified by the Secretary.

S. 2503 also would require the Secretary, acting through the FDA Commissioner and not later than one year after the date on which the comment period closes for the draft guidance, to issue final guidance regarding when a notification under 510(k) would have to be submitted for a modification or change to a legally marketed device.

Comparable Provisions in the 21st Century Cures Act

There are no comparable provisions in H.R. 6.

The Advancing Breakthrough Medical Devices for Patients Act of 2016 (S. 1077)

Issue Background

Under FFDCA Section 515(d)(5), in order to provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human diseases or conditions, the Secretary shall provide review priority for devices that represent breakthrough technologies for which no approved alternatives exist, that offer significant advantages over existing approved alternatives, or whose availability is in the best interest of the patients.

On April 23, 2014, FDA issued the following draft guidance: *Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions - Draft Guidance for Industry and Food and Drug Administration Staff*. As indicated in the title, the FDA draft guidance covered only premarket approval (PMA) medical devices. FDA issued final guidance on April 13, 2015.[23]

The guidance focuses on balancing risks versus benefits for patients, drafting a Data Development Plan by the medical device sponsor, and collecting postmarket data on a medical device that has received a priority review designation. As described in the FDA guidance, the

[22] FDA, Report to Congress, *Report on FDA's Policy to be Proposed Regarding Premarket Notification Requirements for Modifications to Legally Marketed Devices*, January 7, 2014, at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM387121.pdf.

[23] See http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf. Note that the final FDA Guidance added de novo 510(k) devices. A de novo 510(k), a modified type of 510(k) review pathway, though requiring more data than a traditional 510(k), often requires less information than a PMA application. According to the final guidance, de novo devices "are not eligible for the full scope of the EAP program." For a definition of EAP, see page 9.

expedited review process for a medical device that has received a priority review designation in exchange for lower requirements in the premarket review process, such as less information in the PMA application, relies on the use of surrogate endpoints[24] and the collection of postmarket data. According to FDA, the "Expedited Access PMA" (EAP) program features "earlier and more interactive engagement with FDA staff—including the involvement of senior management and a collaboratively developed plan for collecting the scientific and clinical data to support approval—features that, taken together, should provide these patients with earlier access to safe and effective medical devices."[25]

FDA intends to withdraw approval for a device if the sponsor fails to adhere to the postmarket requirements, such as data collection, or if the postmarket data prove the device is not safe and effective:

> As part of the EAP program, FDA intends to impose postmarket requirements, including requiring post-approval studies as a condition of approval for devices subject to a PMA when applicable.[26] The extent to which FDA will accept certain data to be collected for an EAP Device in the postmarket setting, rather than premarket, is affected by the Agency's current authority to mandate completion of post-approval studies and to withdraw PMA approval for marketed devices for which FDA later determines that there is a lack of a showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, as well as by the current capabilities of FDA's medical device surveillance system.[27]

Comments on the April 2014 FDA draft guidance questioned FDA's ability to enforce postmarket study requirements and urged the agency and Congress "to evaluate whether FDA has sufficient authorities to promptly withdraw product approval if the necessary data are not promptly collected or suggest that the product benefits do not outweigh risks."[28] One media source stated that, regarding the EAP program, FDA "estimates that, at least in the early stages, on average, about six devices a year may qualify for the program, and the [agency] believes it has the resources available to handle that volume."[29] The estimated six devices would represent about

[24] The FDA guidance on pages 23-24 describes a surrogate endpoint as follows: "a surrogate endpoint is not itself a measure of clinical benefit, but is used in trials as a substitute which is reasonably likely to predict clinical benefit, based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence. The types of measurements which may be used as a surrogate endpoint are in vitro laboratory or medical imaging measurements, or physical signs (e.g., blood pressure measurements in trials of antihypertensive therapeutics, as a surrogate for clinical endpoints such as stroke, myocardial infarction, or mortality)."

[25] See http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394294.htm.

[26] 21 C.F.R. 814.82 states: "FDA may impose post-approval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval." In addition, under §522 of the FD&C Act and FDA's implementing regulations at 21 C.F.R. Part 822, FDA may order postmarket surveillance for certain Class III devices.

[27] FDA, Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions, Guidance for Industry and Food and Drug Administration Staff, April 13, 2015, pp. 8-9, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf.

Regarding de novo 510(k) devices, the final FDA Guidance on page 9 also stated the following: "FDA would not offer a greater ability to collect postmarket benefit-risk data otherwise typically collected premarket for a de novo request (as we may for a PMA device) because once a de novo request is granted, the product can serve as a predicate for a device that need only demonstrate substantial equivalence for a 510(k) clearance. This would be problematic if we granted a de novo for a device that subsequently was shown not to be safe or effective based on required postmarket data collection."

[28] See http://www.pewtrusts.org/en/about/news-room/news/2014/07/22/pew-comments-to-fda.

[29] David Filmore, "Leap ahead with EAP? FDA proposes new expedited PMA pathway," *The Gray Sheet*, vol. 40, no.

15% of FDA's total PMA applications in one year. Other comments on the FDA draft guidance questioned whether FDA has sufficient resources to dedicate to the EAP program.[30]

Senate Legislation

S. 1077 would add a new Section 515B, "Priority Review for Breakthrough Devices," to Chapter V of the FFDCA. The new section would require the Secretary to establish a program to provide priority review for devices that (1) provide more effective diagnosis or treatment of a life-threatening or irreversibly debilitating condition; and (2) represent breakthrough technologies for which no approved alternatives exist, offer significant advantages over existing alternatives, or the availability of which is in the best interest of patients. The section would allow requests for priority review from device sponsors of PMA medical devices and one other type of regulatory decision involving a medical device.[31]

The section would require the Secretary in 60 days to determine whether the request for priority review would be granted. Such requests would be evaluated by a team of experienced FDA staff and senior managers. All determinations—either approval or denial of priority review—would require a "substantive summary of the scientific and regulatory rationale" for the determination, pursuant to FFDCA Section 517A.

If the Secretary approves a priority review designation for a device, the Secretary would not be able to withdraw the designation because another "breakthrough" device was subsequently cleared or approved, thereby resulting in the specified criteria (i.e., no approved alternatives exist, offer significant advantages over existing approved or cleared alternatives, or the availability of which is in the best interest of patients) no longer being met.

Each priority review device would be assigned a team of staff, "including a team leader with appropriate subject matter expertise and experience." Senior FDA personnel would oversee each team to facilitate the efficient development and review of the device. Among other things, the Secretary would be required to "provide for interactive communication with the device sponsor during the review process," and expedite "the Secretary's review of manufacturing and quality systems compliance." The Secretary would be required to "disclose to the sponsor, not less than 5 business days in advance the topics of any consultation concerning the sponsor's device that the Secretary intends to undertake with external experts or an advisory committee and provide the sponsor an opportunity to recommend such external experts."

The Secretary would be allowed to, as appropriate, "coordinate with the sponsor regarding early agreement on a data development plan." The Secretary would also be able to ensure that clinical trial design is as efficient as practicable and would be able to facilitate "expedited and efficient development and review of the device through utilization of timely postmarket data collection" with regard to PMA applications. Agreements on clinical protocols would be considered binding, but may be subject to change under certain circumstances. The provision specifies that both the agreement and subsequent changes to the clinical protocol must be agreed to in writing.

The Secretary would be required to issue, not later than one year after enactment, guidance on the implementation of the new Section 515B of the FFDCA. In addition, the Secretary would be required to issue a report, on January 1, 2017, to the Senate Health, Education, Labor and Pensions Committee and the House Energy and Commerce Committee describing the program

17 (April 28, 2014), pp. 1, 5-6.

[30] See http://center4research.org/public-policy/testimony-briefings-statements/comments-on-expedited-access-for-premarket-approval-medical-devices/.

[31] A petition for classification under FFDCA §513(f)(2).

added under new FFDCA Section 515B, including recommendations to strengthen the program and better meet patient needs in a timely manner.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The provision in H.R. 6 regarding priority review for breakthrough devices (Title II, Subtitle L, Sections 2201) is comparable to S. 1077. Importantly, the House provision would allow priority review requests from device sponsors of both 510(k) devices and PMA medical devices, and one other type of regulatory decision involving a medical device.[32] The House provision would allow denied priority review requests to be reconsidered if reconsideration is requested within 30 days of the denial and other specified criteria are met.

The House provision does not specify the number of business days in which FDA would "disclose to the sponsor, in advance the topics of any consultation concerning the sponsor's device that [FDA] intends to undertake with external experts or an advisory committee and provide the sponsor an opportunity to recommend such external experts." The House provision adds specific details regarding efficient clinical trial design, such as "the adoption of shorter or smaller clinical trials, application of surrogate endpoints, and use of adaptive trial designs and Bayesian statistics." The House provision does not specify that the agreement on clinical protocols and any subsequent changes must be agreed to in writing. The House provision does not specify a deadline on the requirement for FDA guidance on Section 515B of the FFDCA, nor does it require a report by FDA on the program added under FFDCA Section 515B.

Advancing Hope Act of 2016 (S. 1878)

Issue Background

FDASIA (P.L. 112-144) added a new FFDCA Section 529, creating the pediatric priority review voucher program. This voucher program, funded by user fees, provides a transferable voucher, under specified conditions, to a sponsor of an approved new drug or biological product for a rare pediatric disease to be used for the priority review of another application. The term "rare pediatric disease" refers to a disease that affects (1) individuals aged from birth to 18 years, and (2) fewer than 200,000 persons in the United States, or affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from U.S. sales.

FDASIA terminated the authority to award such vouchers one year after the Secretary awards the third-priority voucher and required the GAO, beginning on the date of the third voucher award, to study and then report on the effectiveness of the voucher program in the development of products that prevent or treat rare pediatric diseases. FDA awarded the third voucher in March 2015, triggering the March 2016 sunset of this authority. This authority was extended until September 30, 2016, by the Consolidated Appropriations Act of 2016 (P.L. 114-113).

Senate Legislation

S. 1878 would amend the definition of "rare pediatric disease" in FFDCA Section 529(a) by adding the following words in italics: "The disease *is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily* affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents." This

[32] A petition for classification under FFDCA §513(f)(2).

legislation also would amend the definition of a "rare pediatric disease product application" to mean a human drug application, as specified, that is approved after the enactment of S. 1878.

S. 1878 would amend FFDCA Section 529(b)(4) by adding the requirement that the sponsor of a rare pediatric disease product application that intends to request a voucher for a rare pediatric disease product notify the Secretary of such intent upon submission of the rare pediatric disease product application. It would also extend eligibility for a rare pediatric disease priority review voucher, to a sponsor of a rare pediatric disease product application, unapproved as of the date of enactment of S. 1878, that submitted the application at least 90 days after the enactment of the Prescription Drug User Fee Amendments of 2012 and on or before the date of enactment of S. 1878.

The bill would extend the authority to award such priority review vouchers until September 30, 2022. A new drug application or a biologics license application submitted to FDA after the enactment of S. 1878 and before September 30, 2022, would remain eligible to receive a priority review voucher even if approval comes after September 30, 2022, provided the application is approved before September 30, 2027, and is designated as a drug for a rare pediatric disease. This section also would prohibit a sponsor of a rare pediatric disease product application from receiving more than one priority review voucher issued under S. 1878 for the same product application.

S. 1878 also would require that GAO study the voucher program and report to the Senate Committee on Health, Education, Labor, and Pensions and the House Committee on Energy and Commerce, by January 31, 2022, on the program's effectiveness as an incentive for developing drugs that treat or prevent rare pediatric diseases and that would not otherwise have been developed.

Comparable Provisions in the 21st Century Cures Act

H.R. 6 contains a comparable provision (Section 2152, Reauthorization of Rare Pediatric Disease Priority Review Voucher Incentive Program), which would extend the authority to award rare pediatric disease priority review vouchers until December 31, 2018. A new drug application or a biologics license application submitted to FDA after the enactment of H.R. 6 and before December 31, 2018, would remain eligible to receive a priority review voucher even if approval comes after December 31, 2018. Similar to S. 1878, the House provision also would amend the definition of "rare pediatric disease" by adding the following words in italics: "The disease *is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily* affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents." Unlike the Senate bill, the House provision would add to the list of characteristics of a pediatric rare disease product application that the product not have received a tropical disease priority review voucher.[33] Like S. 1878, the House provision also would require that GAO study the voucher program and report to the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions, by December 31, 2017, on the program's effectiveness as an incentive for developing drugs that treat or prevent rare pediatric diseases and that would not otherwise have been developed.

[33] FFDCA §524. Priority review to encourage treatments for tropical diseases.

Advancing Targeted Therapies for Rare Diseases Act of 2016 (S. 2030)

Issue Background

Precision medicine is a relatively new term for what has traditionally been called personalized medicine (or targeted medicine), the idea of providing health care to individuals based on specific patient characteristics. This approach relies on companion diagnostics to target drugs and biological products to specific subsets of patients. Rare diseases often have genetic origins, and advances in medicine have resulted in the development of new treatments that work by targeting genetic mutations that cause the disease. It is inherently difficult to develop drugs for rare diseases because of the small patient population available to conduct clinical trials, so targeted therapies are generally first developed for patients with the most frequent disease-causing mutations. However, to provide therapies for the full spectrum of certain genetic rare diseases, additional targeted therapies would need to be developed.

Targeted therapies, because they may be treating small subsets of patients, sometimes qualify as "orphan drugs." Such drugs are called orphan drugs because firms may lack the financial incentives to sponsor products to treat small patient populations. Orphan drugs receive their designation pursuant to FFDCA Section 526(a),[34] a designation that was created by the Orphan Drug Act (P.L. 97-414) to encourage firms to develop pharmaceuticals to treat rare diseases and conditions by providing an extended period of market exclusivity. Section 526(a) defines "rare disease or condition" as any disease or condition that affects fewer than 200,000 persons in the United States or affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from U.S. sales.

Senate Legislation

S. 2030, the Advancing Targeted Therapies for Rare Diseases Act of 2015, would add a new Section 529A "Targeted Drugs for Rare Diseases" to Subchapter B of chapter V of the FFDCA, with the purpose of facilitating the "development, review, and approval of genetically targeted drugs and variant protein targeted drugs to address an unmet medical need in one or more patient subgroups, including subgroups of patients with different mutations of a gene, with respect to rare diseases or conditions that are serious or life-threatening."

This legislation would authorize the Secretary to allow the sponsor of a new drug application for a genetically targeted drug or a variant protein-targeted drug to rely on data and information that has been previously developed and submitted, either by the same or a different sponsor (with permission), for a drug that incorporates or utilizes the same or similar genetically targeted technology or for a variant protein-targeted drug.[35] S. 2030 would define genetically targeted drugs, genetically targeted technology, and variant protein-targeted drugs. New Section 529A should not be construed to limit the Secretary's product approval authorities, or to entitle

[34] FFDCA §526, "Designation of Drugs for Rare Diseases or Conditions"; 21 U.S.C. §360bb.

[35] An example of a variant protein-targeted drug is Gleevec (imatinib), which is used to treat leukemia and other kinds of cancer. It targets at least one variant form of a tyrosine kinase enzyme (an enzyme is a protein) called BCR-Abl tyrosine kinase (chromosol translocation); see http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1907317/.

sponsors to obtain information in another sponsor's application without permission of the other sponsor.

Comparable Provisions in the 21st Century Cures Act

The comparable provision in the House bill (H.R. 6, Title II, Subtitle C, Section 2041, "Precision Medicine Guidance and Other Programs of Food and Drug Administration") would add a new Subchapter J, Precision Medicine, to Chapter V of the FFDCA; this subchapter would include a new Section 592, "Precision medicine regarding orphan-drug and expedited-approval programs."

For a precision drug or biological product application where the product is for the treatment of a serious or life-threatening disease or condition and has been designated as an orphan drug under FFDCA Section 526 as a drug for a rare disease or condition, the new FFDCA Section 592 would allow the Secretary to do two things. First, as with the Senate bill, the Secretary would be allowed to rely on information about a drug or biological product that has been previously submitted, either by the same or a different sponsor (with permission), in approval of an application. This may be for either a new product, or for a different indication for an existing product. Second, in contrast to the Senate bill, it would allow the Secretary to consider the application for expedited review programs, including accelerated approval. Similar to S. 2030, new Section 592 should not be construed to limit the Secretary's product approval authorities, or to entitle sponsors to obtain information in another sponsor's application without permission of the other sponsor.

Patient-Focused Impact Assessment Act of 2016 (S. 1597)

Issue Background

FDASIA (P.L. 112-144) expanded FDA's authorities and strengthened the agency's ability to safeguard and advance public health.[36] FDASIA added a new FFDCA Section 569C "Patient Participation in Medical Product Discussion," facilitating increased involvement of patients earlier in the regulatory process for medical product review. Section 569C directs the Secretary 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 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.

Senate Legislation

S. 1597 would amend FFDCA Section 569C by adding a new subsection (b), "Statement of Patient Experience," which would require the Secretary, upon approval of a new drug application, to make public any patient experience data and related information submitted and reviewed as part of the application. "Data and information" refers to patient experience data, information on

[36] FDA, *The Food and Drug Administration Safety and Innovation Act (FDASIA) Section 1137: Patient Participation in Medical Product Discussions Report on Stakeholder Views*, February 19, 2016, see http://www.fda.gov/downloads/ForPatients/About/UCM486859.pdf.

patient-focused drug development tools, and other relevant information, as determined by the Secretary.

In addition, S. 1597 would require the Secretary, acting through the FDA Commissioner, to develop a plan to issue draft and final guidance, over a period of five years, regarding the collection of patient experience data and the use of such data in drug development. This section describes the content of those required guidance documents and defines, for the purposes of this section, "patient experience data" as

> data that are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and are intended to provide information about patients' experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition.

Finally, S. 1597 would require the Secretary, acting through the FDA Commissioner, to publish, no later than June 1, 2021, 2026, and 2031, on the FDA website, a report "assessing the trends of the Food and Drug Administration with respect to the review of patient experience data and information on patient-focused drug development tools as part of approved applications."

Comparable Provisions in the 21st Century Cures Act

H.R. 6 also contains a provision related to patient experience data (Title II, Subtitle A, Section 2001, "Development and Use of Patient Experience Data to Enhance Structured Risk-Benefit Assessment Framework"). However, the House provision is quite different from the Senate bill. H.R. 6 would amend FFDCA Section 505 by deleting a clause from Section 505(d) and adding new subsections (x) and (y). The new 505(x) would restate the deleted 505(d) requirement for the Secretary to "implement a structured risk-benefit assessment framework in the new drug approval process." The new 505(y) would require the Secretary to "establish and implement processes under which" entities "seeking to develop patient experience data" could submit ideas and data to the Secretary and the Secretary could request materials from those entities, which could include the manufacturer and nonmanufacturer groups. This provision would define "patient experience data" as

> data collected by patients, parents, caregivers, patient advocacy organizations, disease research foundations, medical researchers, research sponsors, or other parties determined appropriate by the Secretary that is intended to facilitate or enhance the Secretary's risk-benefit assessments, including information about the impact of a disease or a therapy on patients' lives.

The new subsection would also require the Secretary to issue implementation guidance after holding several methodological workshops and a public meeting.

Promise for Antibiotics and Therapeutics for Health Act (S. 185)

Issue Background

According to the Centers for Disease Control and Prevention (CDC), each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics, and

at least 23,000 of them die from these infections.[37] Antibiotics are intended for short-term use, making the development of new ones potentially less attractive to drug developers. Addressing barriers to antibiotic drug approval may help counter this problem. One such proposal is the so-called Limited Population Antibacterial Drug (LPAD) approval pathway for new antibacterial drugs.[38] Such a pathway would involve smaller clinical trials in a limited population of patients that have serious or life-threatening infections and unmet medical needs due to the lack of an effective approved antibiotic. This streamlined approach would result in more uncertainty about potential risks posed by the product, and therefore a greater need for post-market scrutiny.[39]

Antibacterial Resistance Monitoring (§2)

Senate Legislation

Section 2 would amend PHSA Section 319E to require the HHS Secretary to (1) encourage and assist in reporting of antibacterial drug use, drug resistance, and antibiotic stewardship programs[40] in health care facilities of the Indian Health Service, Department of Veterans Affairs (VA), and Department of Defense (DOD); (2) report annually on antibacterial drug resistance trends, stewardship programs, and other matters; (3) provide guidance and other informational materials about antibiotic stewardship for residential and ambulatory health care facilities; (4) assist states with their antibacterial resistance prevention activities; and (5) establish a mechanism for facilities to report antibiotic stewardship activities and drug resistance, including for drugs approved under the LPAD pathway established in the Act.

Comparable Provisions in the 21st Century Cures Act

Section 2121, subsection (g) would add a new subsection 317U to the PHSA requiring the HHS Secretary to establish a monitoring system for the use of antibacterial and antifungal drugs, including products approved under the LPAD pathway, as well as changes in bacterial and fungal resistance to drugs. The Secretary would be required to make summaries of data from this system publicly available.

Limited Population Pathway for Antibacterial Drugs & Prescribing Authority (§§3-4)

Senate Legislation

Section 3 would create new FFDCA Section 506(g), "Limited population pathway for antibacterial drugs." This review pathway would allow the Secretary to approve an antibacterial

[37] Centers for Disease Control and Prevention (CDC), "Antibiotic Resistance Threats in the United States, 2013," http://www.cdc.gov/drugresistance/threat-report-2013/.

[38] Note that this is a proposed pathway and that FDA does not currently have the authority to review and approve new antibacterial drugs using the LPAD pathway. See for example Allan Coukell, "To Fight Antimicrobial Resistance, Allow FDA to Approve New Drugs for Limited Populations," *Health Affairs Blog,* April 5, 2016, http://healthaffairs.org/blog/.

[39] Ibid. See also President's Council of Advisors on Science and Technology (PCAST), Report to the President on Combating Antibiotic Resistance, "Goal 4.2. Drug approval based on clinical trials in limited patient populations," September 2014, pp. 32 ff., https://www.whitehouse.gov/administration/eop/ostp/pcast.

[40] Antibiotic stewardship refers to policies and programs of antibiotic use intended to optimize health benefits while minimizing the risk of development of drug resistance. For more information see CDC, "Core Elements of Hospital Antibiotic Stewardship Programs," http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html.

drug as an LPAD drug if certain conditions are met: (1) if the drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs; (2) the standards for new drug application approval are met; and (3) the Secretary receives a written request from the sponsor to approve the drug as an LPAD drug. This review pathway would include the following elements:

- It would require that the Secretary's determination of the safety and efficacy of a limited population antibacterial drug "reflect[s] the benefit-risk profile of the drug in the intended limited population."
- Products approved using this pathway must carry prominent labeling noting the intended use for a limited and specific population of patients.
- Sponsors must submit promotional materials to FDA for review 30 days prior to dissemination.
- Sponsors may pursue this pathway concurrently with other specified streamlined approval pathways, as applicable.

Section 3 would require the Secretary to issue within 18 months of enactment guidance "describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial drugs." It would also require the Secretary to provide advice to the sponsor regarding the approval of an LPAD drug. If an LPAD drug obtains approval for a broader indication, this legislation would allow the Secretary to remove any post-marketing conditions (e.g., labeling requirements).

Section 3 would require the Secretary to report to Congress at least every two years on the number of requests for approval and the number of approvals of LPAD drugs. It also would require GAO to report on the coordination of monitoring activities required by S. 185, and the extent to which this limited pathway has streamlined premarket approval for such antibacterial drugs for limited populations, among other things.

Section 4 states that S. 185 should not be construed to alter current prescribing or other medical practices.

Comparable Provisions in the 21st Century Cures Act

The House bill contains a comparable provision (Title II, Subtitle G, Section 2121, "Approval of Certain Drugs for Use in a Limited Population of Patients"). The House provision would add a new FFDCA subsection 505(z), "Approval of certain antimicrobial and antifungal drugs for use in a limited population of patients." This would be an expedited review pathway for certain antibacterial and antifungal drugs (including biologics) intended for use in limited, defined populations of patients that have severe, life-threatening infections for which current treatment options may be limited or absent, and for which the benefits of a product could outweigh harms that would not be acceptable in broader population use.

Some elements of the review pathway proposed in the House bill are comparable to those in the Senate bill, for example:

- The Secretary could consider limited data sets and non-clinical data as substantial evidence of safety and effectiveness, recognizing the smaller populations available for study of an LPAD drug, and the different balance of benefit versus harm in these populations.
- Products approved using this pathway must carry prominent labeling noting the intended use for a limited and specific population of patients.

- Sponsors must submit promotional materials to FDA for review 30 days prior to dissemination.
- Sponsors may pursue this pathway concurrently with other specified streamlined approval pathways, as applicable.
- FDA would be required to issue draft implementation guidance within 18 months of enactment.
- This provision should not be construed to alter current prescribing or other medical practices (such as off-label prescribing).

Other elements of the review pathway were found only in the House provision, for example:

- Upon a sponsor's request, FDA may enter into written agreement with the sponsor to define the process and data needed to review the limited population use application. The process could not proceed without such written agreement.
- The process must adhere to existing goals and procedures agreed upon by sponsors and FDA in the Prescription Drug User Fee Amendments of 2012 (P.L. 112-144, Title I).

In addition, the House provision would require the Secretary to conduct and publish an assessment of the program within 48 months of enactment, and to seek public input. It also would allow the Secretary to expand the limited population use pathway if deemed beneficial by the assessment above.

Advancing Precision Medicine Act of 2016 (S. 2713)

Issue Background

Precision medicine is a relatively new term for what has traditionally been called *personalized medicine*, the idea of providing health care to individuals based on specific patient characteristics. Currently, medical care is generally provided in a "trial and error" manner, with treatment adjusted based on real-time patient response. Precision medicine would tailor medical treatment to individual patients, thus aiming to improve health outcomes and save health care costs.

On February 25, 2016, the White House hosted a Precision Medicine Initiative (PMI) Summit to mark the one year anniversary of the initiative's launch, first announced in the 2015 State of the Union address. The mission of the PMI is "(t)o enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care."[41] In the first year, the PMI's three key agencies—National Institutes of Health (NIH), Food and Drug Administration (FDA), and the Office of the National Coordinator for Health Information Technology (ONC)—began work in this area. The FY2017 President's budget requests a total of $309 million for the PMI: $4 million to FDA, $5 million to ONC, and the remaining $300 million to NIH.

For More Information

CRS Insight IN10227, *The Precision Medicine Initiative*, by Amanda K. Sarata and Judith A. Johnson.

[41] Executive Office of the President, "The Precision Medicine Initiative," https://www.whitehouse.gov/precision-medicine.

> CRS Report R44026, *Genomic Data and Privacy: Background and Relevant Law*, coordinated by Amanda K. Sarata.

Precision medicine research efforts rely on the collection of large amounts of health data; therefore, access to this data may be a concern in the context of this type of research. The sharing of genetic and genomic data among private individuals, researchers, and the federal government has, at times, prompted concerns that the information, if collected or retained by a federal executive branch agency, could be subject to public release pursuant to the Freedom of Information Act (FOIA). FOIA, however, specifies nine categories of information that may be exempted from the rule of disclosure, allowing agencies to withhold applicable records. Exemption 3 allows agencies to withhold applicable records if the data are specifically exempted from disclosure by a statute other than FOIA, if that statute meets criteria laid out in FOIA. These types of Exemption 3 statutes are often referred to as b(3) exemptions because they are authorized in 5 U.S.C. §552(b)(3).

As a mechanism for addressing compelled disclosure of research data, NIH currently issues Certificates of Confidentiality pursuant to §301(d) of the Public Health Service Act (42 U.S.C. §241(d)) at the request of an investigator. A Certificate of Confidentiality protects investigators from being compelled to disclose information that would identify research subjects in any civil, criminal, administrative, legislative, or other proceeding. This requirement can help promote participation in research by adding an additional layer of privacy protection.

In contrast to compelled disclosure of research data by FOIA request, sharing of genomic data generated by NIH-funded research is a priority of NIH. The agency has established a comprehensive policy for the sharing of genomic data that "applies to all NIH-funded research that generates large-scale human or non-human genomic data as well as the use of these data for subsequent research."[42] This policy requires investigators to outline their data-sharing plans as part of their funding applications; if investigators fail to submit the required data, NIH may withhold funding.

Precision medicine research will often be considered to be highly innovative, risky, and potentially high-reward, and will also often require close partnerships with private industry. The NIH Common Fund, within the Office of the NIH Director, supports the High-Risk, High-Reward Research Program. This program has "four unique funding opportunities for exceptionally creative scientists who propose highly innovative approaches to major challenges in biomedical research."[43] These awards are intended "to encourage creative, outside-the-box thinkers to pursue exciting and innovative ideas about biomedical research."

Other transaction (OT) authority is a special vehicle used by certain federal agencies for obtaining or advancing research and development (R&D). An OT is not a contract, grant, or cooperative agreement, and there is no statutory or regulatory definition of "other transaction." Only those agencies that have been provided OT authority may engage in other transactions. Generally, OT authority is created because the government needs to obtain leading-edge R&D from commercial sources, but some companies (and other entities) are unwilling or unable to comply with the government's procurement regulations.

[42] National Institutes of Health, "National Institutes of Health Genomic Data Sharing Policy," http://gds.nih.gov/PDF/NIH_GDS_Policy.pdf, p. 1.

[43] NIH, Office of Strategic Coordination, The Common Fund, High-Risk Research, at https://commonfund.nih.gov/highrisk/index.

Senate Legislation

S. 2713, the Advancing Precision Medicine Act of 2016, has five provisions that together would support precision medicine by (1) codifying the PMI; (2) requiring issuance of Certificates of Confidentiality to investigators of federally funded research; (3) protecting identifiable, sensitive information from release under FOIA; (4) requiring the sharing of NIH-supported research data in certain circumstances; and (5) supporting high-risk, high-reward research. Specifically, the provisions would support precision medicine in the following ways:

- Codify the President's Precision Medicine Initiative (PMI) by encouraging the Secretary to establish and carry out the PMI, and by allowing specified components and authorities in the carrying out of the PMI as well as identifying requirements of the initiative (§2).
- Amend PHSA Section 301(d) to require the Secretary to issue a Certificate of Confidentiality to research investigators of federally funded research in which sensitive, identifiable information is collected to protect the privacy of research participants. The provision would prohibit the individual with the certificate from disclosing sensitive information about the research participants, with certain exceptions, as specified, and would make this type of information immune from the legal process (§3).
- Amend PHSA Section 301 to allow the Secretary to exempt from disclosure under FOIA exemption (b)(3) specified biomedical information that identifies an individual or that has an associated risk that the information may be reidentified. The Secretary would be required to make each such exemption available in writing and to the public, upon request (§4).
- Amend PHSA Section 402(b) to allow the Secretary to require recipients of NIH grants or agreements to share data generated from such NIH grants or agreements in a manner consistent with all applicable federal law (§5).
- Add a new PHSA Section 402(m) to allow the NIH Director to approve requests by institute and center directors to engage in transactions other than a contract, grant, or agreement with respect to projects for high-impact, cutting-edge research, as specified. This provision would require the Secretary to submit a report to Congress evaluating the activities under this new subsection by September 30, 2020 (§6).

Comparable Provisions in the 21st Century Cures Act

Title II, Subtitle C, Section 2041, of H.R. 6 addresses precision medicine but is not comparable to S. 2713 in its approach. This section would require the Secretary, not later than 18 months after enactment, to issue and periodically update guidance to help sponsors develop a precision drug or biological product. It would also, for a precision drug or biological product application where the product is for the treatment of a serious or life-threatening disease or condition and has been designated as an orphan drug, allow the Secretary to consider the application for expedited review programs and to rely on previously submitted information about the drug or biological product (for more information, see S. 2030, the Advancing Targeted Therapies for Rare Diseases Act of 2015).

In addition, Section 1028 of H.R. 6 (Title I, Subtitle B) addresses high-risk, high-reward research, and has a similar focus as the Senate bill provision; however, it would not establish OT authority, nor would it require a report to Congress. This section would require the NIH institute directors to

establish programs to conduct or support projects that pursue innovative approaches to major contemporary challenges in biomedical research and to set aside a specific percentage of funding for such projects. The Senate bill would not require the allocation of a certain percentage of funding for this research.

The Combination Products Innovation Act of 2016 (S. 1767)

Issue Background

FDA regulatory authority over medical product safety and effectiveness covers drugs, biological products, and medical devices. The agency generally divides responsibilities for the review of marketing applications in its product-centered offices. The Center for Drug Evaluation and Research (CDER) reviews new drug applications for approval, the Center for Biologics Evaluation and Research reviews biologics license applications for licensure, and the Center for Devices and Radiological Health (CDRH) reviews premarket approval applications for approval and 510(k) notifications for clearance.

In 2002, Congress directed FDA to establish an Office of Combination Products (OCP) to facilitate the timely review and regulation of drug-device, drug-biologic, and device-biologic combination products, pursuant to the requirements in FFDCA Section 503. Both drugs and devices are defined in the FFDCA as products intended to diagnose, prevent, or treat disease, or otherwise affect the structure or any function of the body. Unlike a drug, however, a device "does not achieve its primary intended purposes through chemical action within or on the body ... and is not dependent upon being metabolized for the achievement of its primary intended purposes." OCP is required to determine the primary mode of action of a combination product and regulate it based on that determination. Generally, OCP treats a drug-device combination product as a drug unless the manufacturer can prove that it satisfies the device exclusionary clause; i.e., the product does not rely on chemical action to achieve its primary intended purpose.

A manufacturer whose product is assigned to CDER will have a higher standard of evidence, a potentially higher requirement for supporting data, a higher user fee, and probably a longer premarket review time period than a manufacturer whose product is assigned to CDRH.

Senate Bill

S. 1767 would amend Section 503(g) of the FFDCA to require the Secretary to assign a primary center for the regulation of combination products and to conduct premarket review of these products under a single application whenever appropriate, among other things. The bill would require the Secretary to determine the primary mode of action for a combination product—defined as the single mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the product—in order to determine how best to review the product. The Secretary would not be permitted to determine that the primary mode of action is that of a drug or biologic solely because the combination product has any chemical action within or on the body.

If the sponsor of a combination product disagreed with the Secretary's determination and requested an explanation, the Secretary would be required to provide a substantive scientific rationale for the determination. In addition, the sponsor would be able to propose and, subject to

an agreement with the Secretary, conduct additional studies to establish the relevance of any chemical action in the product's primary mode of action.

At any time following the Secretary's determination of the product's primary mode of action, the sponsor would be permitted to submit a proposed combination product review plan, as specified. The Secretary would be required to provide a written response to the sponsor indicating whether the plan was accepted, accepted in part, or denied. The bill would allow the sponsor, if the plan were to be denied, to request a meeting with the Secretary to discuss the information and requirements necessary to make the plan acceptable. A denied plan would be allowed to be resubmitted.

With respect to an accepted plan, in whole or part, the Secretary would be required to accept the plan if the Secretary determines the data to be collected are appropriate for premarket approval; in addition, a plan, in whole or in part, that has been accepted would be required to remain in effect except with written agreement of the Secretary and the sponsor or pursuant to a decision by the reviewing primary agency center director that a relevant scientific issue had been identified since acceptance of the plan. If such a decision were to be issued, the Secretary would be required to provide written notice to the sponsor as well as an opportunity for a meeting.

For premarket review of a combination product that includes an approved constituent component (e.g., a drug or device), the Secretary would be allowed to require that a sponsor submit only that information that is necessary to determine the safety of the combination product, including any incremental risks or benefits posed by the product, taking into account any prior findings for the approved constituent parts.

For premarket review of a combination product that contains an approved drug constituent, the applicant would be permitted to rely upon investigational studies not conducted by the applicant and for which the applicant has not obtained a right of reference.[44] In relying upon these studies, the applicant would be required to certify any patents that claim the approved drug or claim use of the approved drug.[45] The applicant would also be required to give notice to the holder of the approved application and patent owner that the patent is invalid or will not be infringed upon. The approval of an application containing such certification would be required to be made effective as specified in FFDCA Section 503(c)(3), among other requirements. Notwithstanding any other provision of Section 503(g)(5), an application for a combination product that contains an approved drug constituent would be considered a 505(b)(2) application.[46] The bill would not prohibit a sponsor from submitting separate applications for the constituent parts of a combination product, unless the Secretary determines that a single application is necessary.

The bill would further require OCP to help coordinate timely review of combination products across relevant agency centers and to ensure that persons are designated in each primary agency center as points of contact for the sponsors of combination products. The bill would specify additional duties for OCP related to communication; facilitating meetings between the agency and the sponsors; and dispute resolution. The bill would require the Secretary, not later than four years after enactment, to issue final guidance on the combination product review process, as specified,

[44] Right of reference means "the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary." 21 C.F.R. 314.3.

[45] Such patent information is generally published in the Orange Book when the application is approved.

[46] A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." FFDCA §505(b)(2)).

and would add reporting requirements to the annual report to Congress on the activities of OCP as specified.

The bill would amend FFDCA Section 520(h)(4) to prohibit the use of information contained in an application for premarket approval of a class III device from being used in an application for premarket approval of a combination product that contains an approved drug constituent, unless the applicant provides a patent certification and notifies the holder of the approved application and patent owner that the patent is invalid or will not be infringed upon.

The bill would also require the Secretary to identify, not later than 18 months after enactment, types of combination products that the Secretary proposes may adopt different good manufacturing practices. This list would be required to be published in the Federal Register and updated as needed.

Comparable Provisions in the 21st Century Cures Act

Section 2181 of H.R. 6 addresses the issue of combination products, but would take a different approach than the Senate legislation. The H.R. 6 section would amend FFDCA Section 503(g)(4)(C) to require that the Secretary "issue final guidance that describes the responsibilities of each agency center regarding its review of combination products."

Health Software: The Medical Electronic Data Technology Enhancement for Consumers' Health Act (S. 1101)

Issue Background

Increasingly, health care facilities are using computer systems for routine administrative and financial transactions (e.g., patient scheduling, claims processing) and for capturing and exchanging clinical information (e.g., electronic health records). One area that is undergoing especially rapid growth and innovation is mobile health. This term refers to the use of portable devices, such as smartphones and tablets, for medical purposes. Users interface with mobile devices through the use of software applications ("apps").

The number of health-related mobile apps being developed, downloaded, and used is increasing at an almost exponential rate. Some apps simply access stored medical information, while others capture and input patient data into an electronic health record (EHR). Many apps now provide clinical decision support (CDS) using algorithms that use clinical information to generate customized (i.e., patient-specific) diagnosis and treatment recommendations.

Regulators are particularly interested in mobile apps that could pose a risk to patients if they malfunction. These include apps used to display and transfer data from a patient monitor; apps that control an existing device; and apps that transform a mobile platform into a medical device (e.g., an app that allows patients to use their smartphone to record electrocardiograms using a lead that connects to the phone).

Under the FFDCA, the FDA has regulatory authority over software that meets the statutory definition of a medical device and is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease."[47]

FDA released a nonbinding guidance document on mobile medical apps in September 2013, in which it stated its intention to focus on the functionality of the mobile health product, not the mobile platform itself.[48] Thus, the agency does not plan to regulate smartphone or tablet manufacturers. FDA further stated its intention to adopt a risk-based approach by applying its regulatory oversight to "only those mobile apps that are medical devices and whose functionality could pose a risk to patient safety if the mobile app were to not function as intended."

In February 2015, FDA released updated guidance on its risk-based approach to regulating mobile medical apps.[49] The agency provided examples of mobile apps that do not meet the statutory definition of a medical device and so are not subject to its regulatory authority. They include apps used to automate general office operations in health care settings. The agency then gave examples of mobile apps that may meet the definition of a medical device but for which the agency intends to exercise enforcement discretion—meaning that it does not intend to apply regulatory oversight—because the apps pose minimal risk to the public. This category includes mobile apps that help asthmatics track inhaler usage and asthma episodes; apps that give patients a portal into their own EHR; and apps intended for individuals to log, track, or make decisions related to general wellness (e.g., Fitbit).

Finally, FDA provided examples of mobile apps that are the focus of the agency's regulatory oversight. These apps meet the definition of a medical device, and they pose a significant risk to patient safety if they do not function as intended. Examples include apps that connect to an existing device for the purpose of controlling its operation, function, or energy source; apps that are used in active patient monitoring or analyzing patient-specific medical device data from a connected device; and apps that transform a mobile platform into a regulated medical device.

The updated guidance did not address regulation of CDS software. That topic remains under consideration.

Senate Legislation

S. 1101, the Medical Electronic Data Technology Enhancement for Consumers' Health (MEDTECH) Act, would exclude certain types of health software from the FFDCA definition of medical device, including products that provide a variety of administrative and health management functions; electronic health record technology that creates, stores, transfers, and displays patient information; and software that interprets and analyzes patient data to help make clinical diagnosis or treatment decisions (including CDS tools). In general, this would preclude FDA from regulating these products as medical devices.

However, S. 1101 creates an exception allowing FDA to exercise regulatory authority if the agency determines that the use of the software "would be reasonably likely to have serious adverse health consequences" based on four specified criteria. One of the criteria is the likelihood and severity of patient harm if the software were not to perform as intended. The exception would

[47] FFDCA §201(h), 21 U.S.C. §321(h).

[48] Food and Drug Administration, *Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff*, September 25, 2013.

[49] Food and Drug Administration, *Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff*, February 9, 2015, http://www.fda.gov/downloads/MedicalDevices/UCM263366.pdf.

apply to EHR systems (and other software that simply creates, stores, transfers, and displays data), as well as CDS and other analytic tools.

This risk-based approach broadly reflects the agency's current guidance on regulating mobile medical apps.

Comparable Provisions in the 21st Century Cures Act

The health software provisions in H.R. 6, Sections 2241-2243, are similar to those in S. 1101. Like the Senate bill, H.R. 6 would exclude various types of software applications from FDA's regulatory oversight. Excluded applications include products that provide administrative and health management functions; software that creates, stores, transfers, and displays patient information; and analytic tools that provide both general health information and patient-specific information (i.e., CDS). The House bill also would establish a risk-based exception allowing FDA to exert regulatory authority. However, H.R. 6 would create a narrower exception for CDS software that the agency determines "poses a significant risk to patient safety" based on the same four criteria specified in S. 1101.

Interoperability: Improving Health Information Technology Act (S. 2511)

Issue Background

The Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 authorized Medicare and Medicaid incentive payments to acute-care hospitals and physicians who attest to being meaningful users of certified electronic health record (EHR) technology.[50] The law instructed the Secretary to make the measures of meaningful use more stringent over time, which CMS has done in stages.

Stage 1 of meaningful use requires eligible hospitals and physicians to use EHR technology to meet a series of meaningful use objectives that generally involve capturing and storing structured patient data (e.g., vital signs, medications, lab test results). Providers must use EHR technology that has been tested and certified as having the capability to perform these functions. Testing and certification entities are authorized by the HHS Office of the National Coordinator for Health Information Technology (ONC).

Stage 2 of meaningful use requires eligible hospitals and physicians to use their EHR technology to perform more advanced functions, such as giving patients access to their electronic health information and exchanging patient data during transitions of care (e.g., a hospital discharge to a rehabilitation facility, or a physician referral).

Beginning in 2015, hospitals and physicians that are not meaningful EHR users are subject to a Medicare payment adjustment (i.e., penalty) unless they qualify for a hardship exception.

CMS published a final rule in October 2015 modifying the meaningful use Stage 2 objectives and establishing the objectives for Stage 3, which hospitals and physicians must meet by 2018.[51] The agency made significant changes to the meaningful use program in response to the concerns of

[50] P.L. 111-5, Division B, Title IV; 123 Stat. 467.

[51] Centers for Medicare & Medicaid Services, "Medicare and Medicaid Programs; Electronic Health Record Incentive Program - Stage 3 and Modifications to Meaningful Use in 2015 Through 2017; Final Rule," 80 *Federal Register* 62761, October 16, 2015.

health care providers about the challenges and burdens they face in making EHR technology work. For example, CMS eliminated several clinical documentation objectives, and instead focused on a few objectives that capture more advanced uses of the technology (e.g., CDS, health information exchange).

CMS also published an accompanying final rule (the 2015 Edition final rule) that expands the certification program.[52] In addition to certifying the next generation of EHR technology that hospitals and physicians need to achieve meaningful use Stage 3, the program will be able to certify health information technology (HIT) products with a different combination of capabilities and functionalities that meet the needs of other types of health care providers and settings that are not eligible to participate in the EHR incentive program.

The 2015 Edition final rule for the certification program established new transparency requirements for HIT developers. It also seeks to improve interoperability, for example, by requiring certified HIT products to adopt new and updated vocabulary and content standards for structured health information, including a common clinical data set composed of standardized data elements, and by improving the testing of the ability of HIT systems to transmit, receive, and use standardized clinical documents.

ONC released a national interoperability roadmap in October 2015—developed over an 18-month period with input from numerous stakeholders—to coordinate efforts around achieving HIT interoperability.[53] ONC expects the roadmap to evolve in partnership with the public and private sectors as technology and policy dictate. The roadmap establishes interoperability goals for the next 10 years, with 2017 set as the deadline for individuals and health care providers along the care continuum to be able to send, receive, find, and use core clinical data.

The roadmap discusses the payment and regulatory drivers for promoting interoperability, as well as the central policy and technical components of a fully interoperable nationwide health information infrastructure. A key challenge is overcoming legal and governance barriers to trusted information exchange by getting stakeholders to agree to and follow a common set of standards, services, policies, and practices that facilitate exchange and use of electronic health information without limiting competition.

Medicare Access and CHIP Reauthorization Act of 2015 (MACRA)[54]

MACRA declared it a national objective to achieve widespread interoperability of certified EHR technology by the end of 2018. The law defines interoperability as the ability of health information systems to not only exchange clinical information but to also use the information based on common standards in order to improve care and patient outcomes.

In addition, MACRA instructed the Secretary, within one year of enactment, to submit a report to Congress on ways to help health care providers compare and select certified EHR technology, such as through surveying EHR users and vendors and making such information publicly available.

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[52] Office of the National Coordinator for Health Information Technology, "2015 Edition Health Information Technology (Health IT) Certification Criteria, 2015 Edition Base Electronic Health Record (EHR) Definition, and ONC Health IT Certification Program Modifications; Final Rule," 80 *Federal Register* 62601, October 16, 2015.

[53] Office of the National Coordinator for Health Information Technology, *Connecting Health and Care for the Nation: A Shared Nationwide Interoperability Roadmap*, Final Version 1.0, October 2015, https://www.healthit.gov/sites/default/files/hie-interoperability/nationwide-interoperability-roadmap-final-version-1.0.pdf.

[54] P.L. 114-10, §106(b), 129 Stat. 138.

Finally, MACRA required the Secretary, in consultation with stakeholders, to establish interoperability metrics to measure progress toward achieving the national objective of widespread interoperability of certified EHR technology by July 1, 2016. If that objective is not met by December 31, 2018, the Secretary will have until December 31, 2019, to submit a report to Congress identifying the barriers to widespread interoperability and providing recommendations for achieving it.

Information Blocking

ONC released a report to Congress on health information blocking in April 2015.[55] The report defined information blocking as knowingly and unreasonably interfering with the exchange or use of electronic health information, and examined the nature and extent of the practice based on available evidence. It also detailed the actions that ONC is taking, in coordination with other federal agencies, to address information blocking. Finally, the report identified gaps in authority that limit the ability of ONC and other federal agencies to effectively target, deter, and remedy such conduct.

MACRA requires eligible hospitals and physicians, beginning April 2016, to indicate through meaningful use attestation (or some other process specified by the Secretary) that they have not knowingly and willfully taken any action to limit or restrict the interoperability of their certified EHR technology.

Patient Access

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule gives individuals the right of access to inspect, obtain a copy of, and transmit to a third party a copy of their health information.[56]

One of the meaningful use objectives that must be met by hospitals and physicians using certified EHR technology is to provide individuals with the ability to view, download, and transmit (VDT) their electronic health information. As part of meeting that objective, the 2015 Edition final rule for the certification program requires EHR developers to publish programming instructions to enable other software application developers to produce apps giving individuals access to their clinical data.

Patient Matching

ONC released a report on patient identification and matching (i.e., linking patient records with the correct individual) in February 2014. It recommended standardizing patient attributes for the purpose of information exchange, coordinating activities among organizations, and introducing EHR certification criteria for capturing patient identification standards.

Patient matching was addressed in the 2015 Edition final rule for the HIT certification program. Certified EHR systems must be able to create a summary-of-care document that includes the following standardized patient data: first name; last name; previous name; middle name (including middle initial); suffix; date of birth (year, month, and day are required fields; hours and minutes are optional); address; phone numbers (home, business, cell); and sex.

[55] Office of the National Coordinator for Health Information Technology, *Report on Information Blocking*, Report to Congress, April 2015, https://www.healthit.gov/sites/default/files/reports/info_blocking_040915.pdf.

[56] 45 C.F.R. §164.524.

Senate Legislation

The Improving Health Information Technology Act (S. 2511) includes multiple provisions to promote HIT interoperability, penalize information blocking, reduce the administrative and other burdens of using EHR technology, and increase patient access to electronic health information. In broad terms:

- S. 2511 would require ONC to reduce the regulatory and administrative burdens of using EHR technology and relieve physicians of EHR documentation requirements specified in HHS regulations. ONC also would be required to encourage the certification of HIT for use in medical specialties and sites of service, and to adopt certification criteria for HIT used by pediatricians. (§2)
- S. 2511 would establish a program and methodology for calculating and awarding a star rating to each certified HIT product—based on criteria such as the product's security, user-centered design, interoperability, and conformance to certification testing—to help health care providers choose HIT products. HIT developers would be required to report on these criteria for each of their certified products. The rating program's methodology and criteria would be posted online, as would each HIT product's star rating (the rating system must use at least three stars). Each developer of an HIT product that received a one-star rating would have to develop and implement a plan to improve the rating, or risk having the product decertified. Hospitals and physicians would be exempted from the Medicare EHR payment adjustment if their EHR technology was decertified. (§3)
- S. 2511 would give the HHS Office of Inspector General the authority to investigate and penalize information-blocking practices by HIT developers, health information exchanges and networks, and health care providers. Developers, exchanges, and networks found to have engaged in information blocking would be subject to civil monetary penalties. Health care providers found to have engaged in information blocking would be subject to incentives and disincentives to change their behavior. ONC would be authorized to refer instances of information blocking to the Office for Civil Rights if a HIPAA privacy consultation would resolve the matter. (§4)
- S. 2511 would require ONC to convene stakeholders to develop a trusted exchange framework and a common agreement among existing networks to exchange electronic health information (i.e., a "network of networks"). The Secretary would be required to establish a digital contact directory for health care professionals, practices, and facilities. (§5)
- S. 2511 would require certified HIT to be capable of transmitting data to, and receiving data from, clinician-led (and other) registries. And it would extend federal privilege and confidentiality protections to HIT developers who report and analyze patient safety information related to HIT use. (§6)
- S. 2511 would facilitate patients' access to their electronic health information by requiring ONC to (1) encourage partnerships between health information networks, health care providers, and other stakeholders to offer access through secure, user-friendly software; (2) educate providers on using exchanges to provide patient access; and (3) issue guidance to exchanges on providing patient access. ONC and OCR would be required to develop policies that support dynamic technology solutions for promoting patient access, and would have to

help educate individuals and providers on patients' rights under HIPAA. Finally, ONC would have to ensure that HIT standards and certification support patients' access to their electronic health information. (§7)

- S. 2511 would require GAO to conduct a review of the methods used for secure patient matching and report its findings to Congress within two years. (§8)

Comparable Provisions in the 21st Century Cures Act

Section 3001 of the 21st Century Cures Act ("Ensuring Interoperability of Health Information Technology") includes a series of HIT interoperability provisions. While a few of these provisions are comparable—though by no means identical—to the language in S. 2511, other provisions in H.R. 6 have no counterpart in the Senate bill. Similarly, several of the topics addressed in S. 2511 are not covered in the House bill.

Like S. 2511, the House bill would give the HHS Office of Inspector General new enforcement authority to investigate claims of HIT developers engaged in information blocking. However, in place of the Senate bill's star rating program for certified HIT products, which H.R. 6 does not include, the House bill would require HIT developers to attest to a series of requirements as a condition of product certification. They include not taking any action (including business, technical, or organizations practices) that constitutes information blocking.

In other areas of comparability between the two bills, H.R. 6 also would extend federal privilege and confidentiality protections to HIT developers who report and analyze patient safety information related to HIT use. And it would require ONC to publish guidance on the HIPAA privacy rule and its relationship to information blocking.

H.R. 6 addresses a number of areas not covered by the Senate bill. For example, the House bill includes extensive language on the development of new interoperability standards. It would eliminate the HIT Standards Committee and require the Secretary to contract directly with standards development organizations. In addition, beginning in 2020, hospitals and physicians demonstrating EHR meaningful use would have to attest that they are not engaged in information blocking. Importantly, H.R. 6 would repeal the interoperability provisions in MACRA.

Unlike the Senate bill, H.R. 6 would not establish a star rating program for certified HIT products, nor would it address patient access to electronic health information, patient record matching, the regulatory and administrative burdens of using EHR technology, or the development of trusted relationships between existing HIT networks.[57]

[57] For a detailed comparison of the interoperability provisions in H.R. 6 and S. 2511, see CRS congressional distribution memorandum, "Side-by-Side Comparison of the HIT Interoperability provisions in H.R. 6 (21st Century Cures Act), as Passed by the House, and S. 2511 (Improving Health Information Technology Act), Reported by the Senate HELP Committee," February 12, 2016. The memorandum is available upon request to congressional staff.

The Medical Countermeasures Innovation Act of 2015 (S. 2055)

Medical Countermeasures (§§2-6)

Issue Background

Following the terrorist attacks of 2001, the federal government determined that it needed additional medical countermeasures (such as diagnostic tests, drugs, vaccines, and other treatments) to respond to an attack using chemical, biological, radiological, or nuclear (CBRN) agents. The Project BioShield Act (P.L. 108-276), the Pandemic and All-Hazards Preparedness Act (PAHPA, P.L. 109-417), and Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA, P.L. 113-5) established new authorities and programs in the Department of Health and Human Services (HHS) to support the development and procurement of new CBRN medical countermeasures.

Implementation of the federal countermeasure strategy requires coordinated activities by several separate agencies. An interagency working group, the Public Health and Emergency Medical Countermeasure Enterprise (PHEMCE), is responsible for coordinating these activities to ensure federal countermeasure needs are addressed efficiently. The PHEMCE is headed by the HHS Assistant Secretary for Preparedness and Response (ASPR) and includes representatives from the Food and Drug Administration, Centers for Disease Control and Prevention, National Institutes of Health, Department of Defense, Department of Homeland Security, Department of Agriculture, and Department of Veterans Affairs. In addition, the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (P.L. 113-5) requires the ASPR to develop an annual "coordinated 5-year budget plan" for countermeasure basic and advanced research, development, and procurement activities.

The Pandemic and All-Hazards Preparedness Act (P.L. 109-417) established the Biomedical Advanced Research and Development Authority (BARDA) to develop and procure medical countermeasures against CBRN agents, pandemic influenza, and emerging infectious diseases. BARDA contracts with companies to develop and commercialize potential countermeasures. These contracts specify development activities for the company to perform and may extend multiple years. The Project BioShield Act (P.L. 108-276) established a special process and funding mechanism through which the HHS Secretary may obligate funds to procure countermeasures that still need up to 10 more years of development. Up to half of the total amount of the Project BioShield contract may be paid out for the company meeting specified developmental milestones. The remaining amount of the contract is payable on delivery of the countermeasure to the Strategic National Stockpile. Thus, HHS has two separate mechanisms to support CBRN countermeasure advanced development and commercialization: (1) countermeasure advanced development contracts and (2) Project BioShield acquisition contracts with developmental milestone payments.

Senate Legislation

S. 2055, The Medical Countermeasures Innovation Act of 2016, as reported, has several provisions that would change the manner in which the federal government supports the development and procurement of medical countermeasures against CBRN agents.

Section 2 of S. 2055 would require the HHS Secretary to provide "timely and accurate recommended" guidelines for using the medical countermeasures in the Strategic National Stockpile. Under current law, the HHS Secretary must report to "appropriate committees of Congress" within "30 days" when the amount available for Project BioShield procurements (the "special reserve fund") falls below $1.5 billion. This bill would change that requirement to specify the recipients of the report as the Senate Committee on Health, Education, Labor, and Pensions, the Senate Committee on Appropriations, the House Committee on Energy and Commerce, and the House Committee on Appropriations. This report would be required by "March 1 of each year in which" the amount available drops below $1.5 billion.

Section 3 would move contracting authority for Project BioShield and BARDA advanced development from ASPR to BARDA. Such a move was recommended by the Blue Ribbon Panel on Biodefense to "reduce unnecessary bureaucratic delays, improve efficiency and decision making, and enhance BARDA program effectiveness and accountability."[58]

Section 4 would require ASPR to provide additional information in its "coordinated 5-year budget plan" and require that it be made publically available in "a manner that does not compromise national security." The budget plan would also need to consider the development of countermeasures and products for emerging infectious diseases that may present "a threat to the nation."

Section 5 would allow the HHS Secretary to partner with "an independent, non-profit entity" to "foster and accelerate the development of medical countermeasures; ... promote the development of new and promising [countermeasure] technologies; ... [and] address unmet public health needs ... such as novel antimicrobials for multidrug resistant organisms and multiuse platform technologies for diagnostics, prophylaxis, vaccines, and therapeutics." This partner could provide business advice and use venture capital practices to invest in companies developing medical countermeasures. The U.S. intelligence community has successfully used a similar strategic investor model to address its unmet technology needs through In-Q-Tel.[59] This bill would establish certain criteria for the partner, including prior experience in technology innovation and successful partnering with the federal government. The HHS Secretary acting through the BARDA Director would provide the entity with the government needs and requirements and a description of the work to be done under the agreement. The entity would be required to provide regular reports on the spending of funds provided by HHS and on progress meeting the identified needs. The bill would require the Government Accountability Office to evaluate this partnership four years after enactment. This authority would sunset on September 30, 2022.

Section 6 would remove the current need for the President to approve use of the Project BioShield special reserve fund.[60] The Blue Ribbon Study Panel on Biodefense recommended this change to streamline the Project BioShield contracting process.[61] This section would also specify the congressional committees that HHS must notify of a decision to use Project BioShield funds as the Senate Committee on Health, Education, Labor, and Pensions, the House Committee on Energy and Commerce, and the appropriation committees in each chamber.

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[58] Blue Ribbon Study Panel on Biodefense, *A National Blueprint for Biodefense: Leadership and Major Reform Needed to Optimize Efforts*, Washington, DC, October 2015, p. 57, http://www.biodefensestudy.org/.

[59] See https://www.iqt.org.

[60] The President delegated this authority to the Office of Management and Budget.

[61] Blue Ribbon Study Panel on Biodefense, *A National Blueprint for Biodefense: Leadership and Major Reform Needed to Optimize Efforts*, Washington, DC, October 2015, p. 57.

Comparable Provisions in the 21st Century Cures Act

Other than the provisions relating to Food and Drug Administration priority review (discussed elsewhere in this report), the 21st Century Cures Act contains no comparable provisions to S. 2055 as reported.

Priority Review to Encourage Treatments for Agents that Present National Security Threats (§§7-8)

Issue Background

Under the Prescription Drug User Fee Act of 1992 (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times: Standard Review and Priority Review. Compared with the amount of time standard review generally takes (approximately 10 months), a Priority Review designation means FDA's goal is to take action on an application within 6 months.[62] Currently, FDA has two authorized priority review voucher programs (the rare pediatric disease priority review program, and the tropical disease priority review program), funded by user fees, which provide a transferable voucher, under specified conditions, to a sponsor of an approved new drug or biological product to be used for the priority review of another application. The purpose of the priority review drug voucher programs is to incentivize development of new treatment for diseases that may otherwise not attract development interest from companies due to either cost or lack of market opportunities.

Senate Legislation

Section 7 of this bill would add a new FFDCA section 565A, "Priority Review to Encourage Treatments for Agents that Present National Security Threats." This section would establish a new priority review voucher program, funded by user fees, to provide a transferable voucher, under specified conditions, to a sponsor of an approved new human drug product application for a material threat medical countermeasure to be used for the priority review of another application. This section defines a "material threat medical countermeasure application" as, among other things, a human drug application "to prevent or treat harm from a biological, chemical, radiological, or nuclear agent identified as a material threat" under the Public Health Service Act,[63] or "to mitigate, prevent, or treat harm from a condition that may result in adverse health consequences or death and may be caused by administering a drug, or biological product against such agent."

Section 8 of this bill would require GAO to report on the effectiveness of the priority review voucher program.

Comparable Provisions in the 21st Century Cures Act

There is no comparable provision in the House bill.

[62] FDA, Priority Review, http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm.

[63] PHSA §319F-2(c)(2)(A)(ii)

Next Generation Researchers Act (S. 2014)

Issue Background

Congress has had a long-standing interest in developing the future biomedical research workforce. Recent concerns have focused on ways to reduce the time between when young investigators complete their training and when they receive their first independent NIH research grant (i.e., achieve research independence). The NIH has created a number of initiatives that strive to shorten this time, in part, to attempt to better retain young investigators in biomedical research.[64] The Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2016 (P.L. 114-113, Division H), instructed the NIH Director to enter into a contract with the National Academy of Sciences (NAS) to conduct a comprehensive study of the policies affecting the next generation of researchers in the United States.

NIH funds seven loan repayment programs for researchers.[65] Three of these are intramural programs that provide educational loan repayment benefits to researchers in exchange for undertaking research while employed by NIH. Intramural loan repayment programs support researchers from disadvantaged backgrounds, those who are investigating AIDS, and those undertaking general research (including general research by physicians during their fellowship training). NIH also funds four programs to assist in the repayment of extramural researchers' educational loans. These funds are awarded competitively to researchers who are employed by a qualifying educational institution. Specific programs are available to extramural researchers investigating health disparities, undertaking contraception and infertility research, engaging in clinical research, and examining pediatric-related topics. Researchers may receive up to $35,000 per year in loan repayment benefits under each of these programs. The regulations that govern the National Health Service Corps Loan Repayment program regarding participant eligibility, application procedures, selection criteria, loan repayment contract terms, tax liability for payments received, service obligation, and penalties for breach of contract apply to the NIH loan repayment programs (where not inconsistent with the specific program).[66] Under current law, appropriations for loan repayments remain available until the end of the second fiscal year after they are appropriated.

Senate Legislation

S. 2014, the Next Generation of Researchers Act, includes two provisions that would create programs designed to develop and retain the biomedical workforce funded or employed by the NIH.

Section 2 of S. 2014 would amend Part A of Title IV of the PHSA by adding a new Section 404M to establish within the office of the NIH Director the Next Generation of Researchers Initiative (the Initiative). Through the Initiative, the NIH Director would be required to coordinate all NIH policies and programs focused on promoting and providing opportunities for new researchers.

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[64] See discussion in "NIH Initiatives to Assist Young Investigator" in CRS Report R41705, *The National Institutes of Health (NIH): Background and Congressional Issues*.

[65] For description of these programs, see Appendix A of CRS Report R43571, *Federal Student Loan Forgiveness and Loan Repayment Programs*.

[66] For program description, see CRS Report R43920, *National Health Service Corps: Background and Trends in Funding and Recruitment*. For program guidance, see U.S. Department of Health and Human Services, Health Resources and Services Administration, "National Health Service Corps: Loan Repayment Program," available at http://nhsc.hrsa.gov/loanrepayment/lrpapplicationguidance.pdf.

Among other things, the NIH Director would have to coordinate with relevant agencies, professional associations, and academic institutions to improve and update information on the biomedical workforce in order to inform training, recruitment, and retention programs of biomedical researchers. In establishing the Initiative, the NIH Director would have to take into consideration recommendations made by NAS in its study on the next generation of researchers. Not later than two years after completion of the NAS study, the NIH Director would be required to submit a report to specified congressional committees regarding any actions taken by NIH with respect to the NAS recommendations.

(Note that S. 2745 Section 5(a) also would add a new PHSA Section 404M, "Research Related to Sexual and Gender Minority Populations.")

Section 3 of S. 2014 would amend PHSA Section 487A to consolidate existing NIH intramural and extramural loan repayment programs. Regarding intramural loan repayment programs, Section 3 would (1) transfer the authority to administer these program from the HHS Secretary to the NIH Director; (2) increase annual loan repayment amounts from a maximum of $35,000 to a maximum of $50,000; and (3) provide loan repayment benefits for individuals who conduct research in areas of emerging scientific or workforce needs, in addition to individuals who conduct research on AIDS, and clinical researchers from disadvantaged backgrounds. Under the provision, the NIH Director would be authorized to amend the categories eligible for intramural loan repayment as scientific and workforce priorities change. Finally, the provision would prohibit the NIH Director from entering into a loan repayment contract with individuals unless they have substantial amounts of educational loans relative to income as determined by the NIH Director and would permit amounts appropriated for new loan repayment contracts to remain available until the end of the second fiscal year after they are appropriated.

Section 3 of S. 2014 would similarly amend the NIH's extramural loan repayment program. Specifically, it would increase loan repayment amounts to a maximum of $50,000 per year, prohibit the NIH Director from entering into a loan repayment contract with individuals unless they have substantial amounts of educational loans relative to income as determined by the NIH Director, and allow amounts appropriated for new loan repayment contracts to remain available until the end of the second fiscal year after they are appropriated. The provision would also retain authorization for current topics eligible for extramural loan repayment (contraception and infertility, pediatric research, minority health disparities, clinical research, and clinical research conducted by individuals from disadvantaged backgrounds), and make eligible for loan repayment benefits extramural researchers who are conducting research in an area of emerging scientific or workforce need, and authorize the NIH Director to amend the categories eligible for extramural loan repayment as scientific and workforce priorities change.

Finally, this provision would repeal existing authorizations for NIH loan repayment programs in PHSA Sections 464z, 487C, 487E, and 487F and would require a GAO report, not later than 18 months after enactment, that would (1) report on NIH efforts to attract, retain, and develop emerging scientists, including underrepresented individuals in the sciences; (2) report on the research areas where individuals are receiving increased loan repayment amounts; and (3) analyze the impact of changes included in this act on addressing workforce shortages.

Comparable Provisions in the 21st Century Cures Act

Subtitle C of H.R. 6 titled "Supporting Young Emerging Scientists" included two provisions that are similar, but less comprehensive, than those included in S. 2014. The first, Section 1042 of H.R. 6, would require the NIH Director to submit to Congress a report, not later than 18 months

following enactment, on NIH efforts "to attract, retain and develop emerging scientists, including underrepresented individuals in the sciences, such as women and other minorities."[67]

The second provision in H.R. 6, Section 1041, focuses on NIH's loan repayment programs; however, rather than consolidating programs like the Senate bill would do, it would authorize a new extramural NIH loan repayment program that would provide not more than $50,000 of loan repayment benefits annually to extramural researchers investigating areas identified as NIH scientific or workforce needs, which is similar to the new category of intramural and extramural loan repayment that the Senate bill would create. H.R. 6 would also increase the amounts that could be repaid under existing loan repayment programs from $35,000 to $50,000 and would, unlike the Senate bill, authorize the HHS Secretary to adjust these amounts annually for inflation beginning in FY2017.

Advancing NIH Strategic Planning and Representation in Medical Research Act (S. 2745)

NIH Strategic Plan (§2)

Issue Background

Section 402(b)(5) of the PHSA specifies that the NIH Director "shall ensure that scientifically based strategic planning is implemented in support of research priorities as determined by the agencies of the National Institutes of Health." NIH provides access to many of its strategic plans on the agency's website.[68]

The focus of NIH research, and to some extent its organizational structure, have been criticized by some in the academic literature.[69] A point often made is that the United States spends more on health care than any of the other 30 countries that make up the Organization for Economic Cooperation and Development (OECD)—in fact, U.S. health care spending is more than 2.5 times the OECD average—and yet, the health of the U.S. populace, as measured by life expectancy, is ranked 24th of the 30 countries.[70] "Despite its name, NIH's mission has not generally been current health, per se, but rather research for tomorrow's health.... An agency devoted to current health would do well to focus on tobacco control, exercise, nutrition, sanitation, and more cost-effective delivery of health care—prevention and efficiency, rather than research on diseases currently not treatable."[71] Questioning or making changes to the focus of NIH research (whether basic, clinical, prevention, health care delivery, or patient-centered outcomes research) is perhaps "especially pertinent in light of the nation's continually mediocre public health outcomes, and their stark contrast to the sophistication and productivity of the biomedical research enterprise."[72]

[67] Amendment 4 (Castro), agreed to by voice vote during floor debate on H.R. 6, added the language ensuring that underrepresented individuals in the sciences (women and minorities) would be included as a focus topic in the NIH report to Congress.

[68] See for example http://report.nih.gov/strategicplans/#tab2.

[69] See for example Michael M. Crow, "Time to rethink NIH," *Nature*, vol. 471 (March 31, 2011), pp. 569-571; and Robert Cook-Deegan, "Has NIH lost its halo?" *Issues in Science and Technology*, Winter 2015, pp. 37-47.

[70] Michael M. Crow, "Time to rethink NIH," *Nature*, vol. 471 (March 31, 2011), p. 570.

[71] Robert Cook-Deegan, "Has NIH lost its halo?" *Issues in Science and Technology*, Winter 2015, p. 43.

[72] Ibid.

Senate Legislation

The Senate bill would amend Section 402 of the PHS Act by adding a new subsection (m), which describes a strategic plan for NIH. Within two years of enactment, and once every six years thereafter, the NIH Director, in consultation with the Institute and Center (IC) Directors, would develop and submit to the appropriate committees of Congress, and post on the NIH website, a six-year NIH Strategic Plan. The NIH Strategic Plan would provide direction to the biomedical research investments made by NIH, facilitate IC collaboration, leverage scientific opportunity, and advance biomedicine.

The NIH Strategic Plan would identify research priorities, such as advancement of treatment, cure and prevention of health conditions, emerging scientific opportunities, and rising public health challenges. The research strategy would address the disease burden in the United States, including rare diseases, and the many factors that contribute to health disparities. Other elements to be included in the NIH Strategic Plan would be coordination of research among the ICs, priorities for funding research through the Common Fund, training the biomedical workforce, and collaboration with other agencies and departments. The individual IC strategic plans would be required to be prepared regularly and informed by the NIH Strategic Plan.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The NIH Research Strategic Plan provision in H.R. 6 Section 1021 is comparable to S. 2745.

The House provision would add a new subsection (m) to Section 402 of the PHSA, which describes a Research Strategic Plan for NIH. Every five years, beginning in 2016, the NIH Director, along with the IC Directors, researchers, patient advocacy groups, and industry leaders, would be required to develop a biomedical research strategic plan. The strategic plan would be used to identify research opportunities and develop individual strategic plans for each IC's research activities. The IC plans would have a common template and identify strategic focus areas. The IC plans would consider and identify the return on investment to the U.S. public of such biomedical research and identify contributions to improving U.S. public health through biomedical research. Mission Priority Focus Areas would be identified that best serve the goals of preventing or eliminating the burden of a disease and scientifically merit focused research over the next five years. Rare and pediatric diseases would remain a priority. In developing the strategic plan, the NIH Director would be required to ensure that maintaining the biomedical workforce, including the participation of scientists from traditionally underrepresented groups, would remain a priority. The initial strategic plan would be completed not later than 270 days after enactment. The NIH Director, in consultation with the IC Directors, would be required to conduct annual progress reviews for each strategic focus area in the IC plans. The plans would be reviewed and updated every five years.

Inclusion of Women and Minorities in Research (§§3-9)

Issue Background

Minorities traditionally have been underrepresented in clinical trials. For example, according to a 2011 report from an FDA-sponsored conference, "African Americans represent 12% of the U.S. population but only 5% of clinical trial participants and Hispanics make up 16% of the population

but only 1% of clinical trial participants."[73] There can be biological differences in how people process or respond to medical products, based on, for example, genetic differences. This could make a treatment less effective or perhaps more toxic for individuals with specific genotypes. Therefore, it is important to study in clinical trials the safety and effectiveness of medical products in a broadly representative sample of people who will likely use the products following FDA approval.

Section 492B of the PHSA requires the Director of NIH to include women and minorities in NIH-funded clinical research and to conduct or support outreach to recruit minorities and women into clinical research. Section 492B(d) requires the Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, to develop guidelines regarding the requirements under Section 492B.

Senate Legislation

Sections 3 through 9 of S. 2745 address aspects of NIH research related to inclusion of women and minority populations in clinical research.

Section 3 would amend Section 402(b) of the PHSA. The NIH Director, in assessing research priorities, would be required to assemble accurate data on study populations in clinical research that specifies the inclusion of women, members of minority groups, relevant age categories, and other demographic variables. The data would have to be disaggregated by research area, condition, and disease categories and made publically available on the NIH website. The NIH Director also would be required to foster collaboration between the ICs that conduct research on human subjects, allow for an increase in the number of subjects studied, and utilize a diverse study population with special consideration of the determinants that contribute to health disparities.

Section 4 would amend Section 492B of the PHSA, adding that the IC Directors must consult at least once annually with the Director of the National Institute on Minority Health and Health Disparities and the Director of the Office of Research on Women's Health regarding IC objectives to ensure that the objectives take into account women and minorities and focus on reducing health disparities. The IC strategic plans would have to include details of such objectives. The NIH Director would be required to consider whether applicable grant award recipients have complied with the reporting requirements of ClinicalTrials.gov when awarding any future grants to such an entity. Reporting requirements for IC advisory councils under Section 492B of the PHS Act would change from biennial to triennial. Each such triennial report would have to include specified data on the number of women and members of minority groups included in clinical research projects conducted during the reporting period.

Section 5 would amend Part A of Title IV of the PHSA, adding a new Section 404M, "Research Related to Sexual and Gender Minority Populations." It would require the NIH Director to encourage efforts to improve research related to the health of sexual and gender minority populations through the increased participation of such groups in clinical research. The Secretary, in collaboration with the NIH Director and taking into account the recommendations of the National Academy of Sciences, would have to continue to support research for the development of appropriate measures related to reporting health information of sexual and gender minority populations. Within two years of enactment, the Secretary would have to disseminate and make public such measures.

[73] FDA, For Consumers, Clinical Trials Shed Light on Minority Health, at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm349063.htm.

Section 6 would amend Section 464z-3 of the PHSA, adding that the Director of the National Institute on Minority Health and Health Disparities may foster partnerships between the ICs and may encourage the funding of collaborative research to achieve the goals of the NIH related to minority health and health disparities.

Section 7 would require the Secretary, acting through the Director of NIH, to convene a working group to make recommendations for a formal policy to enhance the rigor and reproducibility of scientific research funded by the NIH. It would require the working group to consider various specified factors, including, for example, preclinical and clinical experiment design, and methods of statistical analysis. It also would require the Director of NIH, not later than 18 months after enactment, to consider the recommendations and develop or update policies as appropriate. Finally, the section would require the Director of NIH to issue a report to the Secretary and Congress, not later than two years after enactment, regarding the recommendations and any subsequent policy changes.

Section 8 would require the Secretary, not later than 90 days after enactment, to establish a Task Force on Research Specific to Pregnant and Lactating Women. It specifies the duties, membership, meeting schedule, and reporting requirements of the task force, which would be terminated two years after its establishment, with an option for a two-year extension. The section would require the Secretary, not later than two years after enactment, to update regulations and guidance, as appropriate, regarding the inclusion of pregnant women and lactating women in research.

Section 9 would require the Director of NIH, within two years of enactment and taking into consideration the findings of the working group established under Section 7 of this bill, to develop policies for basic research to assess relevant biological variables, including sex, and how differences between male and female cells, tissues, or animals may be studied. It also would require the Director of NIH to consult with outside groups and conduct outreach in developing (and updating) the policies, among other requirements. With respect to clinical research involving women and minorities, the section would require the Director of NIH to update the guidelines established under PHSA Section 492B(d) to reflect the science regarding sex differences and improve adherence to the requirements of Section 492B of the PHSA, among other things.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

Section 1029 of H.R. 6, "The Sense of Congress on Increased Inclusion of Underrepresented Communities in Clinical Trials," is broadly comparable to Sections 3 through 6 of S. 2745. The House provision would express the sense of Congress that the NIH National Institute on Minority Health and Health Disparities "should include within its strategic plan ways to increase representation of underrepresented communities in clinical trials."

Promoting Biomedical Research and Public Health for Patients Act (S. 2742)

Reducing and Streamlining Administrative Burden at NIH (§2, 3, 5, and 10)

S. 2742 contains several provisions aimed at streamlining and improving administrative matters at NIH. These include Sections 2, 3, 5, and 10.

Issue Background

Title IV of the PHSA establishes numerous reporting requirements for the NIH Director related to the activities of the agency. Specifically, Section 403(a) of the PHSA requires the NIH Director to submit to Congress biennially a report on NIH activities. Among other things, the report must include an assessment of the state of biomedical and behavioral research, and details of all the research activities conducted or supported by the ICs of NIH.

The Federal Demonstration Partnership (FDP) is "a cooperative initiative among 10 federal agencies and 119 institutional recipients of federal funds, sponsored by the National Academies, with a purpose of reducing the administrative burdens associated with federal research grants and contracts."[74] In 2005 and 2012, FDP conducted surveys of principal investigators of federally funded projects to determine the impact of federal regulations and requirements on the research process. In both surveys, researchers reported spending 57% of their time engaged in research and 43% of their time in completing pre- and post-award requirements. "The most commonly experienced administrative responsibilities included those related to federal project finances, personnel, and effort reporting. These were also among the most time-consuming responsibilities. For researchers engaged in projects that required human or animal subjects, the related Institutional Review Board (IRB) and Institutional Animal Care and Use Committee (IACUC) requirements were by far the most time-consuming. Other areas viewed as particularly time-consuming were those involving clinical trials, subcontracts, and cross-agency differences."[75]

Section 405 of the PHSA specifies that the Director of the National Cancer Institute is appointed by the President and the Directors of the other NIH Institutes are appointed by the Secretary. Each NIH Institute Director reports directly to the NIH Director.

Section 202 of the Labor/HHS/ED Appropriations Act, 1993 (P.L. 102-394), states at the end of the section that the payment of compensation to consultants or individual scientists appointed for limited periods of time is "not to exceed the per diem rate equivalent to the maximum rate payable for senior-level positions," which is "not less than 120% of the minimum rate of basic pay payable for GS–15 of the General Schedule; and ... not greater than the rate of basic pay payable for level III of the Executive Schedule."[76]

Senate Legislation

Section 2 of S. 2742 would amend Section 403(a) of the PHSA to replace the biennial reporting requirement of the NIH Director with a triennial requirement. The section would add new, and clarify existing, reporting requirements, including a description of intra-NIH activities and funding made available for conducting and supporting research that involves collaboration between an IC and one or more other ICs.

Section 3 of S. 2742 includes a series of requirements that would address the administrative burden on researchers funded by NIH and other federal agencies. First, the bill would direct the Secretary, within two years of enactment, to lead a review by research funding agencies of all financial conflict-of-interest regulations and policies and make revisions to harmonize the policies and reduce the administrative burden on researchers, as appropriate. Second, it would require the NIH Director to implement measures to reduce the administrative burdens

[74] Sandra L. Schneider et al., *Federal Demonstration Partnership (FDP) 2012 Faculty Workload Survey: Executive Summary*, April 2014.

[75] http://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_087823.pdf; http://sites.nationalacademies.org/PGA/fdp/PGA_055749.

[76] P.L. 102-394 and 5 U.S.C. §5376.

experienced by primary NIH grant awardees related to monitoring grant sub-recipients. Third, the Secretary, in consultation with the NIH Director, would be required to evaluate financial expenditure reporting procedures and requirements for NIH funding recipients and take appropriate action to avoid duplication of effort and minimize burden to funding recipients.

Fourth, within two years of enactment, the Secretary, in consultation with the NIH Director, the Secretary of Agriculture, and the FDA Commissioner, would have to complete a review of regulations and policies for the care and use of laboratory animals and make appropriate revisions to reduce administrative burden on investigators. Fifth, the Secretary would be required to clarify the applicability of OMB Uniform Guidance requirements regarding documentation of personnel expenses for entities receiving HHS grants.

Finally, within one year of enactment, the OMB Director would be required to establish a Research Policy Board, consisting of up to10 federal and 9 to 12 non-federal members, as specified, to provide the NIH Director and other members of the federal government with information on the effects of regulations related to federal research requirements. The board would have to make recommendations on harmonizing regulations and policies to minimize administrative burden across federal research agencies. Within two years of enactment, and once thereafter, the board would have to submit a report to specified offices in OMB, the heads of relevant federal departments and agencies, and specified House and Senate committees. The report would provide recommendations on scientific research policy, including regulatory benefits and burdens. The board would sunset on September 30, 2020. Within four years of enactment, GAO would be required to conduct an evaluation of board activities regarding its purpose and responsibilities and submit a report to Congress.

Section 5 would modify or eliminate a number of different NIH reporting requirements. Within two years of enactment, it would require the heads of each IC to submit to the NIH Director a report on the amount of funding made available for conducting or supporting research that involves collaboration between a given IC and at least one other IC. This information would be included in the triennial report required by Section 403(a), as amended by Section 2 of S. 2742.

Section 5 also would (1) eliminate an annual reporting requirement regarding the number of experts and consultants whose services are used by NIH; (2) make a minor modification to the doctoral degree reporting requirement; (3) make a technical correction to a vaccine reporting requirement; (4) change the NCATS annual report to a biennial report; (5) eliminate the report on Centers of Excellence; (6) eliminate the periodic reports on rapid HIV testing; and (7) eliminate the National Institute on Nursing Research biennial report.

Section 10 of S. 2742 would amend Section 405 of the PHSA. It would require that Directors of ICs be appointed by the NIH Director, with the exception of the Director of the National Cancer Institute (who would continue to be appointed by the President). It would add a new requirement that the term of office for the director of an IC be five years and would permit the director of an IC to be reappointed at the end of a five-year term, with no limit to the number of terms served. It would require that, if the office of a director of an IC becomes vacant before the end of a five-year term, the director appointed to fill the vacancy begin a new five-year term (as opposed to finishing the five-year term of the previous director). Each current IC Director would be deemed to be appointed for a five-year term as of the date of enactment, and the NIH Director would be able to terminate the appointment of an IC Director prior to the end of a five-year term.

The compensation limitations in Section 202 of the Labor/HHS/ED Appropriations Act, 1993, related to time-limited appointments of consultants and individual scientists, would not apply to directors appointed under this new authority.[77]

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The Reducing Administrative Burdens of Researchers provision in H.R. 6 Section 1023 is comparable to Section 3 of S. 2742. The House provision would require the NIH Director to implement measures to reduce the administrative burden on NIH-funded researchers, taking into account the recommendations of the NIH Scientific Management Review Board, the National Academy of Sciences, the Faculty Burden Survey conducted by the Federal Demonstration Partnership, and the Research Business Models Working Group. Not later than two years following enactment, the NIH Director would be required to submit a report to Congress on the measures that have been implemented to reduce the administrative burden on NIH-funded researchers.

The Increasing Accountability at the National Institute of Health provision in H.R. 6 Section 1022 is comparable to Section 10 of S. 2742. Although they use slightly different language, they achieve the same goals. The House provision would remove compensation limitations for consultants and individual scientists (not just NIH IC Directors) as stipulated by Section 202 of the Labor/HHS/ED Appropriations Act, 1993.

Reimbursement for Research Substances and Living Organisms (§4)

Issue Background

Section 301(a) of the PHSA establishes the general research authorities of the Public Health Service through the Secretary of Health and Human Services. Specifically, it requires the Secretary to "conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man." As part of these authorities, the Secretary is authorized to make available substances and living organisms for biomedical and behavioral research.

Senate Legislation

Section 4 would amend Section 301(a) of the PHSA to allow the Secretary, where research substances and living organisms are made available to researchers through contractors, to direct the contractors to collect payments for the costs incurred to make available these substances and organisms. These amounts would be credited to the appropriations accounts that incurred the costs of making the substances and organisms available.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

There are no comparable provisions in H.R. 6.

[77] Ibid.

National Vaccine Injury Compensation Program (§6)

Issue Background

In 1986, in order to stabilize the pediatric vaccine market, Congress waived the liability of manufacturers (in most cases) and established the National Vaccine Injury Compensation Program (VICP) to compensate persons injured by certain vaccines.[78] Initially, the list of covered vaccine types and associated compensable injuries and time frames (called the "Injury Table") was provided in law (PHSA Title XXI, Subtitle 2). The Secretary may, through rulemaking, create or modify listed compensable injuries and time frames for vaccines on the Injury Table, but the Secretary may not add additional vaccine types. An exception is made under current law for new vaccines that are routinely recommended by CDC for use in children, which are automatically included in the Injury Table. In 2013, the Advisory Commission on Childhood Vaccines (ACCV), which advises on the VICP, informed the Secretary that current VICP authority may discourage the growing use of vaccines for pregnant women, as the law does not allow for addition of such vaccines to the Injury Table if they are not also recommended for children, and does not clearly cover injury to an infant born to a woman who was vaccinated during pregnancy.[79]

Senate Legislation

Section 6 of S. 2742 would require the Secretary to incorporate into the list of covered vaccines any vaccine recommended by CDC for routine use in pregnant women, using the rulemaking process to establish covered injuries and related matters. It also would clarify that both the woman and a child or children in utero when the vaccine was administered would be eligible for compensation.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

There is no comparable provision in H.R. 6.

Vaccine Meetings; Report on Vaccine Innovation (§7)

Issue Background

A vaccine may be both a commercial product and a public good, and Congress has established several federal payment mechanisms and health insurance coverage requirements to support the production and use of vaccines in the United States. Some of these incentives are tied to recommendations of CDC and/or its Advisory Committee on Immunization Practices (ACIP).[80] In contrast to FDA, which licenses vaccines when they are shown to be safe and effective for individuals, ACIP and CDC also consider epidemiology and vaccine availability, and may recommend routine use of a vaccine for only a subset of the population for whom FDA has

[78] Health Resources and Services Administration (HRSA), "National Vaccine Injury Compensation Program," http://www.hrsa.gov/vaccinecompensation/.

[79] See letters to the HHS Secretary from the ACCV regarding compensability of in utero injuries from vaccines, HRSA, "Reports and Recommendations," 2013, http://www.hrsa.gov/advisorycommittees/childhoodvaccines/reportsrecommendations.html.

[80] For more information, see "Subtitle H—Vaccine Access, Certainty, and Innovation" in CRS Report R44071, *H.R. 6: The 21st Century Cures Act*.

licensed its use. Vaccine manufacturers have an interest in understanding the factors considered by ACIP and CDC, as well as FDA, in making vaccine use and licensing decisions.

Senate Legislation

Section 7 of S. 2742 does not explicitly require that CDC personnel meet with vaccine developers. It does, however, require the CDC Director to ensure that CDC centers and offices coordinate their vaccine program and policy efforts, including consultations with stakeholders.

The provision also would require HHS to report to Congress on ways to promote innovation in the development of vaccines against infectious diseases, including the processes to determine priority needs, and obstacles (and proposed remedies) to vaccine innovation. The Secretary may consult with specified stakeholders, including vaccine developers, in producing this report.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

Section 2143 would require CDC personnel to meet with vaccine developers regarding their vaccine products that are either licensed by FDA or for which a developer intends to seek licensure. The stated purpose is for CDC to share with developers information about epidemiology and related matters that could inform the sponsor's vaccine research and development plan. The section specifies types of information that may be shared, deadlines, representation at meetings, and other administrative matters.

Section 2142 would require the CDC Director to review ACIP processes, evaluation criteria, and consistency in issuing recommendations, and to publish a report on such review not later than 18 months after enactment, including recommendations to improve the consistency of ACIP's processes.

H.R. 6 also includes a provision (Section 2141) that would expedite ACIP's consideration of certain vaccines. There is no comparable provision in S. 2742.

Clinical Trials Database (§§8-9)

Issue Background

Sponsors of clinical trials for drugs, biologics, and devices regulated by the FDA are required to submit registration and summary results information to ClinicalTrials.gov, the clinical trial registry and results data bank operated by NIH's National Library of Medicine (NLM) pursuant to Sections 402(i)-(j) of the PHSA. Subparagraph 402(j)(2)(B) requires the NIH Director to ensure that the public may, in addition to keyword searching, search the entries in the data bank by various specified criteria, including the disease or condition being studied, the name of the drug or device under investigation, and the location of the clinical trial. The NIH Director is instructed to add search categories as deemed necessary and to ensure that the data bank is easy to use, and that its entries are easily compared.

Under Section 402(j) of the PHS Act, those responsible for specified clinical trials of FDA-regulated products have been required to submit registration information to ClinicalTrials.gov since December 2007, submit summary results information for clinical trials of approved products since September 2008, and submit adverse events information since September 2009. The Secretary is required, by rulemaking, to expand the requirements for submission of summary results information, and authorized to use rulemaking to make other changes in the requirements for submission of registration and results information. In November 2014, HHS published a

proposed rule to clarify and expand requirements for the submission of clinical trial registration and results information to ClinicalTrials.gov.

Senate Legislation

Section 8 of S. 2742 would amend Section 402(j)(2)(D) of the PHSA, regarding posting of data, by adding new language requiring the NIH Director to inform responsible parties of the option to request that information for a medical device clinical trial be publically posted prior to the date of clearance or approval. A clinical trial for a combination product would be considered a drug clinical trial, if the Secretary determines that the primary mode of action of the product is that of a drug or biological product, or a device clinical trial, if the Secretary determines that the primary mode of action of the product is that of a device.

Section 9 of S. 2742 would require the Secretary, acting through the NIH Director and not later than two years after enactment, to submit to Congress a report that "describes education and outreach, guidance, enforcement, and other activities undertaken to encourage compliance with Section 402(j) of the PHSA."

This section also would require the Secretary, acting through the NIH Director and in collaboration with the FDA Commissioner, to submit to Congress a report on registered clinical trials, as specified, including activities undertaken by the Secretary to educate responsible persons about compliance with the requirements in Section 402(j). The Secretary would be required to submit an initial report not later than two years after the compliance date of the final rule implementing Section 402(j) of the PHSA. Two follow-up reports would be required, which include information on actions taken to enforce compliance with the ClinicalTrials.gov reporting requirements.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

Section 1101 and Section 1121 of H.R. 6 are comparable to S. 2742. However, while S. 2742 focuses on compliance with the reporting requirements, the House provisions address public access to, and research on, the information in ClinicalTrials.gov.

Section 1101 of H.R. 6 would add new language to Section 402(j) of the PHS Act ("Expanded Clinical Trial Registry Data Bank") requiring the NIH Director to ensure that (1) the registry and results data bank is easily used by the public; (2) the registry and results data bank entries are easily compared; (3) information is submitted to the registry and results data bank in a standardized format, including certain specified data; and (4) standard terminologies and code sets are used, to the extent possible, to facilitate electronic data matching. The House provision would strike subparagraph 402(j)(2)(B).

Within 90 days of enactment, the Secretary would be required to seek the advice of relevant stakeholders and experts on enhancements to the clinical trial registry data bank that are necessary to implement the provision. The Secretary would be required to begin implementation of the provision within 18 months of enactment.

Section 1121 of H.R. 6 would instruct the Secretary to enter into a seven-year cooperative agreement, contract, or grant—the Clinical Trial Data System Agreement—with one or more eligible entities (i.e., tax-exempt academic institutions) to implement a pilot program to enable registered users to conduct further research on reported clinical trial data. Eligible entities seeking funding would have to submit an application that contains certain specified information, including, among other things, (1) information demonstrating that the eligible entity can compile clinical trial data in standardized formats; (2) a description of the system the eligible entity will

use to store and maintain such data; (3) a certification that the eligible entity will allow only registered users to access and use de-identified clinical trial data; (4) evidence demonstrating the ability of the eligible entity to ensure that registered users disseminate the results of their research; and (5) evidence demonstrating that the eligible entity has a proven track record of protecting confidential data.

National Center for Advancing Translational Sciences (§11)

Issue Background

Prior to FDA approval, medical products are tested in a clinical trial using human volunteers to see how the products compare to standard treatments or to no treatment. FDA uses the data from clinical trials to determine whether to approve a manufacturer's application for marketing a medical product. Clinical trials are conducted in three phases.

> **Phase I** trials try to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects. Usually, a small number of healthy volunteers (between 20 and 80) are used in Phase I trials.
>
> **Phase II** trials include more participants (about 100-300) who have the disease or condition that the product potentially could treat. In Phase II trials, researchers seek to gather further safety data and preliminary evidence of the drug's beneficial effects (efficacy), and they develop and refine research methods for future trials with this drug. Sometimes Phase II clinical trials are divided into Phase IIA (to assess dosing requirements) and Phase IIB (to study efficacy). If the Phase II trials indicate that the drug may be effective—and the risks are considered acceptable, given the observed efficacy and the severity of the disease—the drug moves to Phase III.
>
> In **Phase III** trials, the drug is studied in a larger number of participants with the disease (approximately 1,000-3,000). This phase further tests the product's effectiveness, monitors side effects and, in some cases, compares the product's effects to a standard treatment, if one is already available. As more and more participants are tested over longer periods of time, the less common side effects are more likely to be revealed.[81]

Under current law, although the National Center for Advancing Translational Sciences (NCATS) may develop and provide infrastructure and resources for all phases of clinical trials research, it may support clinical trial activities only through the end of Phase IIA, with specific exceptions. NCATS may support clinical trial activities through the end of Phase IIB for a treatment for a rare disease or condition if (1) it gives public notice for a period of at least 120 days of NCATS's intention to support the clinical trial activities in Phase IIB; (2) no public or private organization provides credible written intent to NCATS that the organization has timely plans to further the clinical trial activities or conduct clinical trials of a similar nature beyond Phase IIA; and (3) NCATS ensures that support of the clinical trial activities in Phase IIB will not increase the federal government's liability beyond the award value of the center's support.

Senate Legislation

Section 11 of S. 2742 would extend NCATS's authority to support clinical trial activities through the end of Phase IIB (instead of Phase IIA) and would extend the exception for treatment of a rare disease or condition through the end of Phase III (instead of Phase IIB).

[81] FDA, Inside Clinical Trials: Testing Medical Products in People, What Happens in a Clinical Trial? http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm.

The Senate bill would add material to the NCATS annual/biennial report regarding methods and tools developed since the last report and if such methods and tools are being used by the FDA to support medical product reviews. The next NCATS report, following enactment, would include a complete list of all such methods and tools developed by research supported by NCATS.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The NDCATS Phase IIB Restriction provision in H.R. 6 Section 1027 is comparable to S. 2742.

The House provision would extend NCATS's authority to support clinical trial activities through the end of Phase IIB (instead of Phase IIA) and would extend the exception for treatment of a rare disease or condition through the end of Phase III (instead of Phase IIB).

Enhancing the Stature and Visibility of Medical Rehabilitation Research at the NIH Act (S. 800)

Issue Background

Section 452 of the PHSA established the National Center for Medical Rehabilitation Research (the Center) within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (the Institute) at NIH to conduct and support research, and disseminate information, on the rehabilitation of individuals with physical disabilities. It also required the NIH Director to create a Medical Rehabilitation Coordinating Committee and a National Advisory Board on Medical Rehabilitation Research.

The Director of the Institute—in collaboration with the Director of the Center, the Coordinating Committee, and the Advisory Board—is required to develop, and periodically revise and update, a comprehensive plan for medical rehabilitation research.

Senate Legislation

S. 800 would amend Section 452 of the PHSA instructing the Director of the Center—in collaboration with the Director of the Institute, the coordinating committee, and the advisory board—to develop and, not less than every five years, revise and update a comprehensive plan for medical rehabilitation research. The research plan would have to include goals and objectives for such research.

Prior to revising and updating the research plan, the Director of the Center would have to report to the coordinating committee and the advisory board on the progress made toward achieving the research goals and objectives, and provide recommendations for revising and updating the plan. Within 30 days of revising and updating the plan, the Director of the Center would be required to transmit the plan to the President, the Senate Committee on Health, Education, Labor, and Pensions, and the House Committee on Energy and Commerce.

In addition, S. 800 would require the Secretary, with the other federal agencies, to review their medical rehabilitation research programs and take action to avoid duplication among those programs through actions such as entering into interagency agreements. Finally, the bill would define medical rehabilitation research as "the science of mechanisms and interventions that prevent, improve, restore, or replace lost, underdeveloped, or deteriorating function."

Comparable Provisions in the 21st Century Cures Act

There are no comparable provisions in H.R. 6.

Advancing Research for Neurological Diseases Act of 2016 (S. 849)

Issue Background

The PHSA does not explicitly authorize or require surveillance of neurological diseases in general, although the Secretary may conduct such activities under general authorities in PHSA Title III. Surveillance is explicitly authorized for certain specified neurological disorders (e.g., amyotrophic lateral sclerosis[82] and autism spectrum disorder).[83]

Senate Legislation

S. 849 would add a new PHSA Section 399S-1, "Advancing Research for Neurological Diseases." It would authorize the HHS Secretary to improve the collection of data on neurological diseases by leveraging existing surveillance activities and registries. The Secretary would be explicitly authorized to establish a new registry, using existing data sources. In doing so, the Secretary would be required, among other things, to focus on up to five of the most prevalent or burdensome diseases (as determined by the Secretary), to collect and manage information in order to facilitate research, and to consult with specified experts. The Secretary would be required to include information on demographics, relevant risk factors, and diagnostic and progression markers.[84] Optional data elements would include information about the epidemiology, natural history, prevention, detection, management, and treatment approaches for the diseases; the development of outcomes measures; and any additional matters identified by stakeholders.

The bill also would authorize the Secretary to furnish grants, contracts, or cooperative agreements with public or private nonprofit entities to implement this provision. The Secretary would be required to make information and analysis obtained from the system available to other federal health agencies and state and local agencies, and, subject to applicable laws, to make data available to researchers. The Secretary would be required to report to Congress within one year of the establishment of any registry under this section, and biennially thereafter, and would be required to report to Congress on all activities under this section not later than four years after enactment. The bill does not include an authorization of appropriations.

Comparable Provisions in the 21st Century Cures Act

Section 1122 would add a new PHSA Section 399V-6, "Surveillance of Neurological Diseases," which is similar to the Senate bill. Among the differences, rather than providing authority as in the Senate bill, it would require the Secretary—acting through the CDC Director and in collaboration with specified stakeholders and other federal agencies—to establish a National

[82] PHSA §399S; 42 U.S.C. §280g-7.

[83] PHSA §399AA; 42 U.S.C. §280i.

[84] A *disease marker* is a substance or other measurable parameter that can be used to identify the presence or severity of a health condition. A *progression marker* is one that could indicate worsening or improvement in the condition over time.

Neurological Diseases Surveillance System to track the epidemiology of neurological diseases, including multiple sclerosis and Parkinson's disease. Required and optional data elements are the same as in the Senate bill.

The Secretary would be required to make information and analysis in the surveillance system available, subject to HIPAA privacy and security protections, to the public, including researchers. The Secretary would be required to report to Congress regarding the system within four years of enactment. The provision would authorize the appropriation of $5 million for each of fiscal years 2016 through 2020.

FDA and NIH Workforce Authorities Modernization Act (S. 2700)

Silvio O. Conte Senior Biomedical Research Service (§2)

Issue Background

The Silvio O. Conte Senior Biomedical Research Service (SBRS), established in PHSA Section 228, is a special hiring mechanism used by the HHS Secretary to attract and retain accomplished scientists to work in Public Health Service (PHS) agencies. It is not subject to civil service requirements under Title 5 of the *U.S. Code*, and it is distinct from other PHS hiring mechanisms, such as the PHS Commissioned Corps. SBRS requirements are as prescribed in law and regulation (42 C.F.R. Part 24). Currently, SBRS is limited to 500 members, who are accomplished doctoral-level scientists in biomedical research or clinical research evaluation. The rate of pay may not exceed that for Level I of the Executive Schedule (currently about $206,000 per year) unless approved by the President. The Secretary may contribute up to 10% of a Service member's pay to that person's already established retirement system at the institution of higher education at which the member had been employed.

Senate Legislation

The provision would rename the SBRS as the Silvio O. Conte Senior Biomedical Research and Biomedical Product Assessment Service (the Service). It would increase the number of authorized members to 2,000, and would add "biomedical product assessment" as a desired field of expertise. It would clarify that the Secretary is not required to reduce the number of employees serving in other HHS employment systems to offset the number of new employees in the Service.

The provision would require the Secretary to appoint experts to agencies within HHS, "taking into account the need for the expertise of such expert." It also would authorize the appointment of persons who hold "a master's level degree in engineering, bioinformatics, or a related or emerging field," broadening the current requirement for doctoral-level members. It would increase the upper pay rate limit to that of the President (currently $400,000 per year) but would eliminate the authority to contribute to a member's preexisting retirement system. Finally, the provision would require GAO to study the changes to the Service and their effects on HHS departments and agencies.

Comparable Provisions in the 21st Century Cures Act

The House bill contains a similar provision (Section 2281) that would also rename the SBRS the Silvio O. Conte Senior Biomedical Research and Biomedical Product Assessment Service, with a

similar stated purpose as the Senate bill. Unlike the Senate bill, the House bill would eliminate the mention of a specific number of authorized Servicemembers. Like the Senate bill, the House bill would clarify that the Secretary is not required to reduce the number of employees serving in other HHS employment systems to offset the number of employees in the Service.

The House bill would require the Secretary to report on the HHS website regarding the changes to the Service and whether they "have improved the ability of the [FDA] to hire and retain qualified experts to fulfill obligations specified under user fee agreements."

Hiring Authority for Scientific, Technical, and Professional Personnel (§3)

Issue Background

Title 5 of the *U.S. Code* provides the broad framework of requirements under which many federal employees are hired; however, some subsets of employees are hired under alternative government-wide or agency-specific authorities. Numerous hiring authorities target scientists and other technical workers, for whom federal agencies such as FDA compete with the private sector and nonfederal public employers.[85] For example, FFDCA Section 714 authorizes the Secretary to appoint employees to positions in FDA to perform, administer, or support activities related to review of medical device applications and human generic drugs "without regard to the provisions of title 5, United States Code, governing appointments in the competitive service."

Senate Legislation

The provision would add a new FFDCA Section 714A, "Hiring Authority for Scientific, Technical, and Professional Personnel," which would authorize the Secretary to "appoint outstanding and qualified candidates to scientific, technical, or professional positions that support the development, review, and regulation of medical products" within the competitive service "without regard to the provisions of title 5, United States Code, governing appointments in the competitive service." The FDA Commissioner would be allowed to determine pay (not to exceed the annual rate of pay of the President) for the purposes of retaining qualified employees, notwithstanding certain General Schedule pay rate requirements. This provision would require the Secretary to submit a report to Congress on workforce planning and certain specified elements with regard to the FDA workforce. This provision also would require GAO to conduct a study of FDA's ability "to hire, train, and retain qualified scientific, technical, and professional staff ... necessary to fulfill the mission of the Food and Drug Administration to protect and promote public health," among other specified contents with regard to the FDA workforce.

Comparable Provisions in the 21st Century Cures Act

The House bill contains a comparable provision (H.R. 6, Title II, Subtitle P, Section 2285, "Hiring Authority for Scientific, Technical, and Professional Personnel), which would add a new FFDCA Section 714A, Additional Hiring Authority. Like the Senate bill, the House provision would allow the Secretary to "appoint qualified candidates to scientific, technical, or professional positions" in the competitive service "without regard to the provisions of title 5, United States Code, governing appointments in the competitive service." Unlike the Senate bill, the House provision specifies

[85] CRS Report R40604, *Hiring and Pay Authorities for Federal Scientific and Technical (S&T) Personnel*.

that these positions would be within FDA's Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health.

Like the Senate bill, the House provision would allow the HHS Secretary to determine pay (not to exceed the annual rate of pay of the President) for the purposes of retaining qualified employees, notwithstanding certain General Schedule pay rate requirements. Like the Senate bill, the House provision would require the Secretary to submit a report to Congress on workforce planning and certain specified elements with regard to the FDA. Unlike the Senate bill, the House provision would not require a GAO study with regard to the FDA workforce.

Establishment of Food and Drug Administration Intercenter Institutes (§4)

Issue Background

FDA regulatory authority over medical product safety and effectiveness covers drugs, biological products, and medical devices. The agency generally divides responsibilities for the review of marketing applications in its product-centered offices. The Center for Drug Evaluation and Research reviews new drug applications for approval, the Center for Biologics Evaluation and Research reviews biologics license applications for licensure, and the Center for Devices and Radiological Health reviews premarket approval applications for approval and 510(k) notifications for clearance.

As part of the Vice President's Cancer Moonshot Initiative, the Obama Administration has proposed an Oncology Center of Excellence to streamline collaboration across FDA's Human Drugs, Biologics, and Devices and Radiological Health programs. According to the FY2017 Congressional Justification, "With the continued development of companion diagnostic tests and the use of combinations of drugs and biologics to treat cancer using methods developed through the science of precision medicine, to most benefit those affected, FDA needs to take an integrated approach in its evaluation of products for the prevention, screening, diagnosis, and treatment of cancer."[86] Although the Administration's proposed center of excellence is specific to cancer, there has arguably also been an increase in the number and complexity of diagnostics and therapeutics for other diseases as well, and some groups have suggested that such pilots could also be done in other areas (e.g., cardiology, neurology, and infectious disease).[87]

Senate Legislation

This provision would add a new FFDCA Section 1014, "Food and Drug Administration Intercenter Institutes." This provision would require the Secretary to establish one or more "Intercenter Institutes" for a major disease area(s). Such institutes would be responsible for coordinating activities applicable to specific disease area(s) between the Center for Drug Evaluation Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health; for example, coordinating staff from the three centers with diverse product expertise relevant to a major disease area, and streamlining the review of medical products related to that major disease area. This provision would require the Secretary to establish at least one institute within one year of enactment of H.R. 2700, and would require the Secretary to provide a public comment period while each institute is being implemented. This provision

[86] FY2017 Justification of Estimates for Appropriations Committees, FDA, p. 12.

[87] M. McCaughan and K Rawson, "FDA 'Intercenter Institute' Legislation Headed for Senate Mark-Up," *FDA Pink Sheet*, vol. 78, no. 13, March 28, 2016.

also would allow the Secretary to terminate any such institute if the Secretary determines that it is no longer benefitting the public health.

Comparable Provisions in the 21st Century Cures Act

No comparable provision in H.R. 6.

Scientific Meetings (§5)

Issue Background

Following allegations of misspent funds during a 2010 General Services Administration meeting held in Las Vegas, the Office of Management and Budget (OMB) imposed restrictions on conference travel for federal employees in memorandum M-12-12.[88] The memorandum directed agencies, beginning in FY2013, to spend at least 30% less than what was spent in FY2010 on travel expenses, and stated that agencies "must maintain this reduced level of spending each year through FY 2016." Senior-level agency approval is required for all conferences sponsored by an agency where the conference expenses to the agency exceed $100,000. Agencies are prohibited from spending more than $500,000 on a single conference. However, this restriction may be waived if the agency head "determines that exceptional circumstances exist whereby spending in excess of $500,000 on a single conference is the most cost-effective option to achieve a compelling purpose."[89]

Senate Legislation

Under the Senate provision, if attendance at a scientific meeting is directly related to the professional duties of scientific or medical professionals of the Department of Health and Human Services (HHS), then the meetings would not be considered to be conferences for the purposes of (1) federal reporting requirements in annual appropriations acts, and (2) a restriction in OMB memorandum M-12-12 or any other regulation restricting such travel. Each HHS operating division would be required to post on their website an annual report on scientific meeting attendance and related travel spending for each fiscal year, including details as specified.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The NIH travel (Title I, Subtitle B, Section 1025) and the enabling FDA scientific engagement (Title II, Subtitle P, Section 2282) provisions in H.R. 6 are comparable to S. 2700. Both provisions in H.R. 6 express the sense of Congress that participation in or sponsorship of scientific conferences and meetings is essential to the mission of NIH and FDA.

[88] OMB, Promoting Efficient Spending to Support Agency Operations, May 11, 2012, http://www.whitehouse.gov/sites/default/files/omb/memoranda/2012/m-12-12.pdf.

[89] Ibid.

Reagan-Udall Foundation for the Food and Drug Administration (§6)

Issue Background

FFDCA Section 770, as added by the Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85), created the Reagan-Udall Foundation for the Food and Drug Administration, a nonprofit organization "to advance the mission" of FDA. Its duties cover activities such as identifying and then prioritizing unmet needs; awarding grants or entering into other agreements with scientists, academic consortia, public-private partnerships, nonprofit organizations, and industry; holding meetings and publishing information and data for use by FDA and others; and taking action to obtain patents and licensing of inventions, among others. It is led by a Board of Directors, four of whom are ex officio members, nine from candidates provided by the National Academy of Sciences, and five from candidates provided by "patient and consumer advocacy groups, professional scientific and medical societies, and trade organizations." Section 770 specifies the number of members to be appointed representing each type of group and requires that the ex officio members ensure specific expertise among the members.

Senate Legislation

The provision would amend FFDCA Section 770 to change the membership of the Board of Directors to allow the voting members of the board to increase the size of the board and appoint new members by majority vote, without regard to the balance of expertise and affiliation required by current law. It would limit to 30% of the membership "representatives of the general pharmaceutical, device, food, cosmetic, and biotechnology industries." The obligation to ensure specific expertise among the members would be broadened to rest with all members of the board, not only ex officio appointees. That broader group would also decide other administrative matters. As with the current law, each board member's term of office would last for four years, and initially appointed board members' terms would expire on a staggered basis, as determined by the ex officio members. This provision would add that for the additional board members appointed pursuant to S. 2700, Section 6, the terms of office for the initially appointed persons can expire on a staggered basis, as determined by the members of the board.

The provision would remove the salary cap of the foundation's Executive Director, which is now set at the compensation of the Commissioner. Also amended would be the language regarding separation of funds. The current requirement is that funds received from the Treasury be held in separate accounts from funds received from other sources, including private entities. The provision would change the requirement, so that funds received from the Treasury would be "managed as individual programmatic funds, according to best accounting practices."

Comparable Provisions in the 21st Century Cures Act

The House bill provision (H.R. 6, Title II, Subtitle P, Section 2283, "Reagan-Udall Foundation for the Food and Drug Administration") is the same as the Senate bill.

NIH Research Information Collection Exempted from Paperwork Reduction Act (§7)

Issue Background

The Paperwork Reduction Act (PRA, 44 U.S.C. Chapter 35), enacted in 1980 and amended in 1995, established the Office of Information and Regulatory Affairs (OIRA) in the Office of Management and Budget (OMB). Congress required that agencies seek OIRA permission before collecting information from the public. The first of 11 stated purposes was to "minimize the paperwork burden for individuals ... and other persons resulting from the collection of information by and for the Federal Government."[90] The PRA requires that federal agencies receive clearance from OIRA before requesting most types of information from the public.[91] PRA clearance is required when standardized information is collected from 10 or more respondents within a 12-month period.[92] PRA does not apply to certain types of scientific research, including collections that are neither sponsored nor conducted by the agency and those that are subject to a clinical exception.[93]

Senate Legislation

The provision would amend Section 301 of the PHS Act by adding a subsection stating that the PRA would not apply to the collection of information during the conduct of NIH research.

Comparable Provisions in the 21st Century Cures Act (H.R. 6)

The Exemption for the National Institutes of Health from the Paperwork Reduction Act Requirements provision (Title I, Subtitle B, Section 1024) is comparable to S. 2700. It would amend 44 U.S.C. Chapter 35 to exempt NIH research from the requirements of the PRA.

Studies (§8)

Issue Background

Through various amendments to the FFDCA, Congress has required the Secretary (sometimes through the delegation of authority to FDA) to submit specified reports to Congress or to contract with other entities (e.g., the Institute of Medicine [IOM]),[94] to conduct specified studies. For example, the Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85) required FDA to take several actions regarding how it informs the public, expert committees, and others about agency actions and plans, as well as information the agency has developed or

[90] 44 U.S.C. §3501.

[91] For further information about the PRA, see CRS Report RL30590, *Paperwork Reduction Act Reauthorization and Government Information Management Issues* (out of print; available from author to congressional clients upon request), and CRS Report RL32397, *Federal Rulemaking: The Role of the Office of Information and Regulatory Affairs*.

[92] See NIH, Office of Science Policy, Genetics, Health and Society, *What is the Paperwork Reduction Act?*, at http://osp.od.nih.gov/faq/what-paperwork-reduction-act; and HHS, *Frequently Asked Questions About PRA / Information Collection*, at http://www.hhs.gov/ocio/policy/collection/infocollectfaq.html.

[93] Cass R. Sunstein, *Facilitating Scientific Research by Streamlining the Paperwork Reduction Act Process*, Executive Office of the President, Office of Management and Budget, December 9, 2010, https://www.whitehouse.gov/sites/default/files/omb/memoranda/2011/m11-07.pdf.

[94] As of March 15, 2016, the IOM has been renamed to the Health and Medicine Division. See http://www.nationalacademies.org/hmd/About-HMD/Division-Name.aspx.

gathered about drug safety and effectiveness. Other amendments to the FFDCA have imposed additional requirements upon the Secretary or the FDA.

Senate Legislation

This provision would remove from the FFDCA the following:

- Section 505(k)(5), which required the Secretary to report to Congress not later than two years after the enactment of the FDAAA in 2007 on certain FDA procedures addressing post market safety issues.
- Section 505A(p), which required the Secretary to contract with the IOM, not later than three years after the enactment of the Best Pharmaceuticals for Children Act of 2007, to conduct a study, which was further specified in this section.
- Section 505B(l), which required the Secretary, within three years of the enactment of the Pediatric Research Equity Act of 2007, to contract with the IOM to "conduct a study and report to Congress regarding the pediatric studies conducted pursuant to this section or precursor regulations."
- Section 523(d), which required the Secretary, not later than January 10, 2007, to conduct a study related to devices, as specified, and to submit the findings of this study in a report to Congress.

Comparable Provisions in the 21st Century Cures Act

There is no comparable provision in H.R. 6.

Summary Level Review (§9)

Issue Background

FFDCA Section 505 and accompanying regulations provide the framework for FDA's approval of sponsors' drug marketing applications. For a drug whose active ingredient has never been FDA-approved, the law requires the sponsor to submit a new drug application that includes data to provide evidence of the drug's safety and effectiveness for its intended use, information about the manufacturing process, and the drug labeling. Once a product has an approved new drug application (NDA), FDA requires that the manufacturer submit a supplemental NDA each time the manufacturer wants to change the labeling, the manufacturing process, or the dosing, or when it wants to add a new indication (a new intended use) of the drug. Regulations at 21 C.F.R. Sections 314.50 and 314.54 describe the required contents of those applications. Regarding clinical data, the regulations direct the applicant to submit, in addition to descriptions and analysis of controlled and uncontrolled clinical studies,

> (iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers. (21 C.F.R. 314.50(d)(5)(iv))

The clinical data submission must also include an "integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications."[95]

Senate Legislation

This provision would amend FFDCA Section 505(c) to permit the Secretary, in reviewing a supplemental NDA submitted by the sponsor of an approved drug when seeking to add to the approval a new indication that is "qualified," to rely upon "qualified data summaries" to support the approval of the supplemental NDA. This provision adds that such supplemental application is eligible only if data demonstrating the safety of the drug are available and acceptable to the Secretary, and all data used to develop the qualified data summaries are submitted as part of the supplemental drug application. This section defines qualified data summary as a "summary of clinical data that demonstrates the safety and effectiveness of a drug with respect to a qualified indication."

Comparable Provisions in the 21st Century Cures Act

H.R. 6 contains a comparable provision (Title II, Subtitle D, Section 2063, "Streamlined Data Review Program"). The House provision would add a new Section 505H to the FFDCA, which, like the Senate bill, would address the data requirements in a supplemental NDA that a sponsor of an approved drug would submit when seeking to add to the approval a new indication that is "qualified" (defined in this section as treating cancer or other indications as determined by the Secretary). Note that the Senate provision does not include treating cancer in its definition of "qualified indication."

The approach for authorizing the Secretary to rely upon qualified data summaries is a bit different in the House bill. New FFDCA Section 505H would require the Secretary to "establish a streamlined data review program" through which a sponsor could submit a "qualified data summary" when "there is an existing database acceptable to the Secretary regarding the safety of the drug developed for one or more indications" of the approved drug. The definition of "qualified data summary" in the House provision is similar to the Senate bill: "a summary of clinical data intended to demonstrate safety and effectiveness with respect to a qualified indication for use of a drug." Also similar to the Senate bill, the House provision would require the sponsor to submit the full data sets used to develop the qualified data summaries, but the House provision adds the exception "unless the Secretary determines that the full data sets are not required."

Unlike the Senate bill, the House provision would state a sense of Congress that the new streamlined data review program "should enable the Food and Drug Administration to make approval decisions for certain supplemental applications based on qualified data summaries (as defined in such Section 505H)." Also unlike the Senate bill, the House provision would require that the FDA Commissioner issue implementation guidance for the streamlined data review program and would allow the Commissioner to issue regulations for implementation.

[95] 21 C.F.R. §314.50(d)(5)(v).

Drug Surveillance (§10)

Issue Background

The Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85) required FDA to take several actions regarding how it informs the public, expert committees, and others about agency actions and plans and information the agency has developed or gathered about drug safety and effectiveness. Among other things, the law required biweekly screening of the FDA Adverse Event Reporting System (FAERS) database and quarterly reporting on the FAERS website regarding new safety information or potential signals of a serious risk.[96] The FDAAA also required the development and maintenance of a website with extensive drug safety information, and required the Secretary to "prepare, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in an unusual number."[97]

The FDAAA also named the risk-management process "risk evaluation and mitigation strategies" (REMS) and expanded the risk-management authority of FDA.[98] A REMS may include "an elements to assure safe use" (ETASU), which is a restriction on distribution or use that is intended to (1) allow access to those who could benefit from the drug while minimizing their risk of adverse events and (2) block access to those for whom the potential harm would outweigh potential benefit.[99]

Senate Legislation

This provision would amend FFDCA Section 505(k)(5) to require the Secretary to conduct regular screenings of the FAERS database instead of the bi-weekly screenings required by current law. This provision also would require the Secretary to post guidelines on the FDA website, with input from experts, that detail best practices for drug safety surveillance using FAERS and criteria for public posting of adverse event signals. This provision would also amend FFDCA Section 505(r)(2)(D) to remove the requirement that the Secretary prepare a summary analysis of the adverse drug reaction reports received for a drug "by 18 months after approval" and instead require that the Secretary make publicly available on the FDA website "best practices for drug safety surveillance activities for drugs newly approved under this section or section 351 of the Public Health Service Act."

This provision also would amend FFDCA Section 505-1(f)(5)(A), which would expand the authority to evaluate the ETASU for a drug to include "or other advisory committee," compared with current law, which designates this responsibility to the Secretary "through the Drug Safety and Risk Management Advisory Committee (or successor committee)" of the FDA. This provision would also amend FFDCA Section 505-1(f)(5)(B), which would change the requirement that the committee evaluate the ETASU for one or more drugs from "annually" to "periodically."

[96] FFDCA §505(k)(5).

[97] FFDCA §505(r)(2)(D).

[98] The REMS authority is in FFDCA §505-1 [21 U.S.C. §355-1]. REMS are discussed in CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*.

[99] CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*.

Comparable Provisions in the 21st Century Cures Act

There is no comparable provision in H.R. 6.

Biological Product Innovation (§11)

Issue Background

Biological products must be licensed by FDA, pursuant to PHSA Section 351, before they can be marketed in the United States. FFDCA Section 351(j) specifies that a biological product licensed under this authority does not also need to have an approved new drug application (NDA) under FFDCA Section 505. The U.S. Pharmacopeia Convention (USP) is a "scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide."[100] USP standards "play a role in the adulteration and misbranding provisions of the FFDCA (which apply as well to biologics, a subset of drugs, under the PHS Act)."[101] USP develops and publishes standards for drug substances, drug products, and excipients in the United States Pharmacopeia–National Formulary (USP–NF); the FFDCA defines *official compendium* as "the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them."[102] Under the FFDCA, "a drug will be deemed misbranded unless its label bears to the exclusion of any other nonproprietary name the 'established' name, which ordinarily is the compendial name.... Drugs also must comply with compendial standards for strength, quality, and purity (tests for assay and impurities)."[103]

Senate Legislation

The Senate bill would amend Section 351(j) of the PHS Act by adding that the provisions of the FFDCA that refer to an "official compendium" as developed and published by the United States Pharmacopeia would not apply to biological products regulated under PHS Act Section 351.

Comparable Provisions in 21st Century Cures Act (H.R. 6)

There is no comparable provision in H.R. 6.

Expanded Access Policy (§12)

Issue Background

FDA regulates the U.S. sale of drugs and biological products, basing approval or licensure on evidence of the safety and effectiveness for a product's intended uses. Without that approval or licensure, a manufacturer may not distribute the product except for use in the clinical trials that will provide evidence to determine that product's safety and effectiveness. Under certain circumstances, however, FDA may permit the sponsor to provide an unapproved or unlicensed

[100] U.S. Pharmacopeial Convention website at http://www.usp.org/about-usp.

[101] U.S. Pharmacopeial Convention website at http://www.usp.org/about-usp/legal-recognition/usp-us-law.

[102] FFDCA §201(j).

[103] U.S. Pharmacopeial Convention website at http://www.usp.org/about-usp/legal-recognition/usp-us-law.

product to patients outside that standard regulatory framework. One such mechanism is expanded access to investigational drugs, commonly referred to as "compassionate use."[104]

If excluded from a clinical trial because of its enrollment limitations, a person, acting through a physician, may request access to an investigational new drug outside of the trial. FDA may grant expanded access to a patient with a serious disease or condition for which there is no comparable or satisfactory alternative therapy, if, among other requirements, probable risk to the patient from the drug is less than the probable risk from the disease; if there is sufficient evidence of safety and effectiveness to support the drug's use for this person; and if providing access "will not interfere with the ... clinical investigations to support marketing approval."[105] The widespread use of expanded access is limited by an important factor: whether the manufacturer agrees to provide the drug, which—because it is not FDA-approved—cannot be obtained otherwise. FDA does not have the authority to compel a manufacturer to participate. Manufacturers may consider several factors in deciding whether to provide an investigational drug, such as available supply, perceived liability risk, limited staff and facility resources, and need for data to assess safety and effectiveness. Although FDA reports the number of investigational drug requests it receives, manufacturers do not.

Senate Legislation

The provision would add a new FFDCA Section 561A, "Expanded Access Policy Required for Investigational Drugs" to require a manufacturer to make its policies on responding to compassionate use requests publicly available. Required elements of the policy would include contact information for the manufacturer or distributor of the drug, request procedures, "the general criteria the manufacturer or distributor will use to evaluate such requests for individual patients, and for responses to such requests," and anticipated time to acknowledge request receipts. The new section would state that posting of policy would not guarantee patients access to an investigational drug. The provision would also allow a manufacturer or distributor to revise its policy at any time. This provision would become effective on the later of the date that is 60 days after the enactment of S. 2700 or "the first initiation of a phase 2 or phase 3 study ... with respect to such investigational drug."

Comparable Provisions in the 21st Century Cures Act

The House bill contains a comparable provision (H.R. 6, Title II, Subtitle E, Section 2082, "Expanded Access Policy").

Finalizing Draft Guidance on Expanded Access (§13)

Issue Background

FFDCA Section 561(b) allows a person, acting through a licensed physician, to request a manufacturer or distributor of an investigational product to provide that product under specified circumstances and conditions. The sponsor or clinical investigator must provide the HHS Secretary with information, as required by regulations. Although FDA has approved patient access in over 99% of the requests to which the sponsor has agreed, some sponsors have been reluctant to provide investigational drugs outside of the standard investigational new drug (IND)

[104] CRS Report R44134, *Access to Unapproved Drugs: FDA Policies on Compassionate Use and Emergency Use Authorization*.

[105] FFDCA §561(b).

processes because of the uncertainty of how FDA would consider potential adverse events associated with the expanded access use in its assessment of the drug's safety, which could influence whether an NDA is approved.

Senate Legislation

This provision would require that the HHS Secretary finalize the guidance "Expanded Access to Investigational Drugs for Treatment Use—Qs & As," issued in draft form in May 2013.[106] The provision would require that the final guidance "clearly define how the Secretary of Health and Human Services interprets and uses adverse drug event data reported by investigators in the case of data reported from use under a request submitted under" FFDCA Section 561(b).

Comparable Provisions in the 21st Century Cures Act

The House bill contains an identical provision (H.R. 6, Title II, Subtitle E, Section 2083, "Finalizing Draft Guidance on Expanded Access").

Amendments to the Orphan Drug Act (§14)

Issue Background

The Orphan Drug Act of 1983 (P.L. 97-414) was signed into law to incentivize development of drugs to treat rare diseases, which affect fewer than 200,000 individuals in the United States. Since the law's passage, FDA has approved over 400 new orphan drugs and biological products.[107] Incentives for sponsors of orphan drugs include seven years of market exclusivity, tax credits for clinical trial expenses, user fee waivers, and federal grants to cover costs of qualified clinical testing expenses.

The FFDCA contains provisions to grant market exclusivity for statutorily defined time periods (in months or years) to the holder of the NDA for a product that is, for example, a drug used in the treatment of a rare disease or condition, the first generic version of a drug to come to market, certain pediatric uses of approved drugs, and new qualified infectious disease products. During the period of exclusivity, FDA does not grant marketing approval to another manufacturer's product.

Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) allows the Secretary to make grants and enter into contracts with certain entities to assist in "defraying the costs of qualified clinical testing expenses incurred in connection with the development of drugs for rare diseases and conditions." Section 5 defines "qualified testing" as human clinical testing

> (i) which is carried out under an exemption for a drug for a rare disease or condition under section 505(i) of the Federal Food, Drug, and Cosmetic Act (or regulations issued under such section); (ii) which occurs after the date such drug is designated under section 526 of such Act and before the date on which an application with respect to such drug is submitted under section 505(b) or under section 351 of the Public Health Service Act; and (B) preclinical testing involving a drug is designated under section 526 of such Act and before

[106] FDA, "DRAFT Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use—Qs & As," May 2013, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf.

[107] FDA, Office of Orphan Products Development, see http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm.

the date on which an application with respect to such drug is submitted under section 505(b) or under section 351 of the Public Health Service Act.

Senate Legislation

This provision would amend Section 5 of the Orphan Drug Act (21 U.S.C. 360ee) to broaden the use of grants made by the Secretary to assist in "defraying the costs of developing drugs for rare diseases or conditions" and would include but not be limited to qualified testing expenses. This provision also would expand the definition of qualified testing to include "prospectively planned and designed observational studies and other analyses conducted to assist in the understanding of the natural history of a rare disease or condition and in the development of a therapy..."

Comparable Provisions in the 21st Century Cures Act

H.R. 6 contains a related provision (Section 2151. Extension of Exclusivity Periods for a Drug Approved for a New Indication for a Rare Disease or Condition). Unlike the Senate bill which would broaden the use of grants for development of rare diseases, the House provision would add a new FFDCA Section 505I, which would add six months to the exclusivity period of an approved drug already on the market when FDA approves a supplemental application for that drug for a new indication to prevent, diagnose, or treat a rare disease or condition. The sponsor of a drug that receives the extended exclusivity under this provision would be required to notify the Secretary "of any discontinuance of the production of the drug for solely commercial reasons at least one year before such discontinuance." The six-month extension would not be available for a drug that had already received a six-month extension under this provision.

Standards for Regenerative Medicine and Advanced Therapies (§15)

Issue Background

Regenerative medicine is defined by NIH as "the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects."[108] The regulation of cells or tissues intended for implantation or infusion into a human patient is the responsibility of the FDA Center for Biologics Evaluation and Research (CBER). FDA refers to such cells as HCT/Ps, which stands for human cells, tissue, and cellular and tissue-based products. Stem cells are one example of HCT/P. CBER held a public workshop on standards development for cellular therapies and regenerative medicine products in March 2014.[109]

Senate Legislation

This section would amend the FFDCA by adding a new Section 506G, "Standards for Regenerative Medicine and Advanced Therapies." It would require the Secretary, in consultation with the National Institute of Standards and Technology and specified stakeholders, to facilitate the development of standards for regenerative medicine and advanced therapies through a

[108] NIH Fact Sheet, Regenerative Medicine, October 2010, at https://report.nih.gov/nihfactsheets/Pdfs/RegenerativeMedicine(NIBIB).pdf.

[109] FDA, Public Workshop: Synergizing Efforts in Standards Development for Cellular Therapies and Regenerative Medicine Products, March 31, 2014. Agenda, transcript, presentation slides at http://www.fda.gov/biologicsbloodvaccines/newsevents/workshopsmeetingsconferences/ucm364114.htm.

transparent public process. After the development of such standards, the Secretary would update relevant regulations and guidance through a transparent public process. The term "regenerative medicine and advanced therapies" is defined as including cell therapy, gene therapy, gene-modified cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products.

Comparable Provisions in 21st Century Cures Act (H.R. 6)

There is no comparable provision in H.R. 6.

Good Guidance Practices (§16)

Issue Background

Rules (or regulations) generally start with an act of Congress, and they are the means by which statutes are implemented and specific requirements are established. In lieu of or in addition to rulemaking, agencies may issue guidance that, although not legally binding, explains the agency's interpretation of, or policy on, a regulatory or statutory issue.[110] Guidance may be used, among other things, to provide an interpretation of either statute or regulation or to inform regulated entities as to how an agency intends to implement and enforce a program. According to FDA's website, the agency prepares guidance documents "primarily for industry, but also for other stakeholders and its own staff, and uses them to address such matters as the design, manufacturing, and testing of regulated products; scientific issues; content and evaluation of applications for product approvals; and inspection and enforcement policies."[111] FDA issues more than 100 guidances each year.[112]

FFDCA Section 701(a) provides FDA with the authority to promulgate regulations for the enforcement of the FFDCA. Section 701(h)(1)(A) directs the Secretary to "develop guidance documents with public participation and ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means." Some Members of Congress have expressed concern with FDA's use of guidance documents in lieu of the rulemaking process in certain instances.

Senate Legislation

This provision would amend FFDCA Section 701(h)(1)(C) by adding clause (iii), which would require the Secretary, when proposing or finalizing a guidance document, to include in that guidance document a statement

> explaining why the interpretation or policy set forth in such guidance is being provided in a nonbinding guidance document and not established through rulemaking, and identifying each specific statutory provision or regulation being interpreted in the guidance document or authorizing policy decision described in the guidance document.

[110] These types of guidance documents are sometimes referred to as "interpretive rules" or "policy statements." For an overview of legal issues surrounding the distinction between rules, interpretive rules, and policy statements, see CRS Report R44468, *General Policy Statements: Legal Overview*.

[111] FDA, Fact Sheet: FDA Good Guidance Practices, http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm285282.htm.

[112] Ibid.

Comparable Provisions in the 21st Century Cures Act

There is no comparable provision in H.R. 6.

Paperwork Reduction Act Waiver during a Public Health Emergency (§17)

Issue Background

PHSA Section 319 authorizes the HHS Secretary to determine the existence of a public health emergency, which in turn authorizes certain further actions to enhance response flexibility, such as waivers of requirements for grant-making and hiring.[113] The Paperwork Reduction Act (PRA) ensures that federal agencies do not overburden the public with federally sponsored data

[113] For more information, see HHS, "Public Health Emergency Declaration," http://www.phe.gov/Preparedness/legal/Pages/phedeclaration.aspx.

collections. Among other things, the PRA requires review and pre-clearance of federal data collection proposals by the Office of Management and Budget (OMB).[114]

Senate Legislation

Section 17 would add an additional provision to PHSA Section 319 to waive requirements for voluntary data collection under the Paperwork Reduction Act (PRA) when a public health emergency declaration is in effect (subject to certain conditions), allowing the HHS Secretary to more easily investigate outbreaks or other circumstances germane to the emergency response.

Comparable Provisions in the 21st Century Cures Act

There is no comparable provision in H.R. 6.

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[114] For more information, see HHS, "Frequently Asked Questions About PRA / Information Collection," http://www.hhs.gov/ocio/policy/collection/infocollectfaq.html.