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INCENTIVIZING DRUG DEVELOPMENT: NOVEL REFORMS OF
PHARMACEUTICAL INNOVATION †

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The Food and Drug Administration (“FDA”) has embraced its position as the Gatekeeper of the pharmaceutical industry. However, the agency’s regulatory requirements have stifled innovation in key therapeutic areas. Promoting robust drug development in these “neglected” areas has become a distinct congressional goal. On July 9, 2012, Congress passed the Generating Antibiotic Incentives Now (“GAIN”) Act as part of the Food and Drug Administration Safety and Innovation Act. GAIN increases the exclusivity period of a Qualified Infectious Disease Product (“QIDP”) by five years and provides fast track and priority review by the FDA. The bipartisan legislation responded to the National Strategy on Combating Antibiotic Resistant Bacteria and encouraged the development of drug products to treat serious and life-threatening infections. In 2012, Congress also passed the Rare Pediatric Disease Priority Review Voucher to fight rare pediatric diseases. Several other bills have been proposed to incentivize drug developers — including the groundbreaking 21st Century Cures Act, the Promoting Life-Saving New Therapies for Neonates Act of 2015, and the Advancing Targeted Therapies for Rare Diseases Act of 2015. I begin this article by describing several areas of concern in healthcare and the recent history of congressional reform incentivizing healthcare innovation, including novel legislative-regulatory mechanisms. Then, I describe the newest legislation in

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detail. I conclude by proposing flexible incentivizing mechanisms that fit neatly into the current regulatory framework.

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I. INTRODUCTION

The FDA is responsible for “advancing the public health by helping to speed innovations.”¹ Yet, the agency has frequently adopted stringent requirements that impose undue regulatory burdens on the healthcare industry. Encumbered with unwieldy

¹ *What We Do*, FDA, <http://www.fda.gov/AboutFDA/WhatWeDo/> (last visited Nov. 4, 2016).

statutory restrictions, regulators have struggled to keep up with rapidly evolving medical technologies. The current approval process has been cost prohibitive to development.² In response, professional organizations have urged the FDA to adopt the least-burdensome requirements and promote medical advancement.³ Responding to political pressure from health organizations and Congress, the FDA has significantly increased the pace of drug approvals to promote competitiveness in the drug industry.⁴ However, major issues still plague the regulatory process.

A major public health issue is the lack of available treatment options for rare diseases that disproportionately affect young children. More than one-third of infant deaths in the first year of life are due to rare diseases.⁵ Yet, about 95% of these rare diseases do not have a single FDA approved treatment.⁶ Equally troubling are the nearly 100,000 deaths every year due to healthcare-associated infections.⁷ Hospital-acquired infections cost payers billions of dollars annually and lead to significant mortality and morbidity.⁸ However, due to significant barriers and uncertainty in drug development, the largest players in the United States pharmaceutical industry have turned to more lucrative therapeutic areas.⁹

² THE INST. OF MED. OF NAT'L ACADS., *THE FUTURE OF DRUG SAFETY*, 166 (Alina Baciú et al. eds., 2007).

³ See, e.g., RICHARD WILLIAMS ET AL., *MERCATUS CTR. AT GEORGE MASON UNIV., US MEDICAL DEVICES: CHOICES AND CONSEQUENCES* (2015), <http://mercatus.org/publication/us-medical-devices-choices-and-consequences> (finding that high costs, uncertainty, delays, and rapid growth are identifiable problems with the current FDA approval system).

⁴ See generally U.S. FOOD & DRUG ADMIN., *FDA AND ACCELERATING THE DEVELOPMENT OF THE NEW PHARMACEUTICAL THERAPIES* (2015), <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm439082.htm>.

⁵ *RARE Diseases: Facts and Statistics*, GLOBAL GENES, <https://globalgenes.org/rare-diseases-facts-statistics> (last visited Oct. 27, 2016).

⁶ CALIFORNIA HEALTHCARE INSTITUTE, *COMBATING RARE DISEASES IN THE 21ST CENTURY 1* (2014), <http://rareadvocates.org/wp-content/uploads/2014/05/CHI-Rare-Disease-Policy-Report.pdf>.

⁷ *Preventing Healthcare-Associated Infections*, CENT. FOR DISEASE CONTROL, <http://www.cdc.gov/washington/~cdcatWork/pdf/infections.pdf> (last visited Nov. 4, 2016).

⁸ *Health Care-Associated Infections*, AGENCY FOR HEALTHCARE RESEARCH AND QUALITY: PSNET, <https://psnet.ahrq.gov/primers/primer/7/health-care-associated-infections> (last updated Jul. 2016).

⁹ Rumana Haque-Ahmed, *Developing Drugs for Rare Diseases in the US—Emerging Trends*, *REGULATORY FOCUS* 31, 31-32 (2011) (observing that “[u]ntil recently . . . large pharmaceutical firms were mostly absent. Today, pharmaceutical giants are entering this space.”).

The unique difficulties weighing against drug development for “neglected” diseases have not evaded concerned legislators. Congress has been considerably active—perhaps even successful—in legislating approaches to incentivize medical innovation. Congress has weighed input from governmental research groups, private stakeholders, and public organizations to craft versatile proposals. This paper focuses on these legislative efforts.

In Part I of this article, I present the medical foundation underpinning a serious need for congressional involvement in healthcare innovation. Two significant public health concerns are at the forefront of this discussion: the lack of effective antibiotic development targeting resistant “superbugs” and a growing need to inject novelty into the regulatory process for rare disease therapies. Part I also describes some of the major incentives that combat the aforementioned health crises. In Part II, this paper discusses three major congressional enactments of the past decade that have ameliorated certain regulatory gaps. These enactments are founded on the incentive mechanisms previously described and provide an overview of the legislative tools available in the legislative arsenal. Part III introduces recent noteworthy congressional proposals that have gained significant traction. These proposals address regulatory concerns while echoing patient needs. This list focuses on a diverse group of incentives that were reorganized in the comprehensive 21st Century Cures Act. I conclude, in Part IV, by discussing probable oversights of recently proposed congressional legislation and potential problems that could arise after implementation. I finish by outlining, in broad strokes, other useful incentive mechanisms that can be used in the healthcare industry.

II. BACKGROUND

A. Why should Congress promote medical innovation?

Developing therapies to help patients suffering from rare diseases has been an important public health concern for almost fifty years. Congress began to face considerable pressure from several activist organizations supporting rare disease sufferers in the 1970s and early 1980s.¹⁰ In response to meaningful media coverage, Congress passed the Orphan Drug Act in 1983 to incentivize the

¹⁰ John Henkel, *Orphan Drug Law Matures Into Medical Mainstay*, FDA CONSUMER, May-June 1999, at 29 (crediting the National Organization of Rare Disorders, a coalition of over 140 rare disease groups, and actor Jack Klugman for creating the initial media buzz that led Congress to pass the Orphan Drug Act).

pharmaceutical industry and assuage public sentiment.¹¹ In the decade before the Act, only ten such products were approved.¹² Since then, the FDA has approved more than 500 drug and biologic products for rare diseases.¹³ Yet, only about 5% of rare diseases are currently treatable with approved medicine in the United States.¹⁴

The National Institute of Health (“NIH”) defines a rare disease as a condition that affects fewer than 200,000 people.¹⁵ There are an estimated 7,000 rare diseases affecting Americans. Combined, these diseases are not rare at all—about 10% of the American population, around 25-30 million people, are affected by one or more rare diseases.¹⁶ The majority of rare diseases are genetic in origin and disproportionately affect children because of their rapid clinical progression.¹⁷

The small market and variability of these ailments make the cost of developing treatments prohibitive for pharmaceutical firms.¹⁸ Research and development of a new drug, combined with the cost of generating the information necessary for FDA approval, costs

^{11.} Orphan Drug Act of 1983, Pub. L. No. 97-414, § 1, 96 Stat. 2049, 2049 (1983).

^{12.} *Id.*; *Developing Products for Rare Diseases & Conditions*, FDA, <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm> (last updated Nov. 2, 2016) (describing the success of the Orphan Drug Act in “enabling the development and marketing” of drugs and biological in the United States).

^{13.} *Id.*

^{14.} Johanne Bissonette, *Close-up on Rare Diseases and Orphan Drugs*, UNIVALOR, <http://www.univalor.ca/en/media/article/close-rare-diseases-and-orphan-drugs>, (last visited Nov. 4, 2016) (estimating that only 400 rare diseases out of the known universe of 7000- 8000 rare diseases have an FDA approved treatment). *But see* WARREN KAPLAN ET AL., PRIORITY MEDICINES FOR EUROPE AND THE WORLD 2013 UPDATE 148 (2013), http://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf (finding that 400 products have been approved for rare disease treatment, but only for about 200 diseases).

^{15.} *FAQs About Rare Diseases*, NAT’L INST. OF HEALTH, <https://rarediseases.info.nih.gov/about-gard/pages/31/frequently-asked-questions> (last updated Aug. 11, 2016).

^{16.} *Id.*

^{17.} Gayatri R. Rao, *Rare Diseases in Children Pose Unique Challenges*, U.S. FDA: FDA VOICE (Feb. 27, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/02/rare-diseases-in-children-pose-unique-challenges>.

^{18.} *See* Christopher Ehinger, *Can Rare Diseases Be a Viable Option for the Pharma Industry?*, PHARMAPHORUM (Oct. 3, 2013), <http://pharmaphorum.com/views-and-analysis/can-rare-diseases-be-a-viable-option-for-the-pharma-industry/>.

more than \$2 billion.¹⁹ Developers weigh the prohibitive costs with the expected size of the market and often determine that drugs with small patient markets are unlikely to generate a good financial return.²⁰ Thus, patients affected with rare diseases are left vulnerable as potential treatments never reach the market. This spiral propagates poor health outcomes and increases national healthcare costs while patient access remains relatively stable.

Moreover, the small population available for clinical trials makes drug development for rare diseases arduous.²¹ Fewer drug trial participants can lead to limited treating physicians and treatment centers.²² The few patients that are available are geographically dispersed and hard to congregate in one study. Furthermore, clinicians do not have clearly established endpoints or clinical outcome tools for rare diseases because progression rates for genetic diseases vary considerably, even within the same disease.²³

Helping spark medical innovation for rare diseases is crucial, but another looming threat has recently emerged—the significant health threat from drug-resistant microbes.²⁴ Researchers have alerted both legislators and regulatory bodies to the importance of promoting antibiotic development.²⁵ There is a strong consensus among infectious disease researchers that the healthcare system is on the cusp of losing the war against microbes without significant and imminent government intervention in the research process.²⁶

19. See, e.g., Joseph DiMasi et al., *Cost to Develop and Win Marketing Approval for a New Drug Is \$2.6 Billion*, TUFTS CTR. FOR THE STUDY OF DRUG DEV. (Nov. 18, 2014), http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study (The total cost of discovering and marketing a new drug is subject to a wide range of estimates. A commonly accepted figure is \$2.6 billion.).

20. See Ehinger, *supra* note 18.

21. See Anna Pariser, *Small Clinical Trials*, FDA (Sept. 22, 2014), <http://www.fda.gov/downloads/NewsEvents/MeetingsConferencesWorkshops/UCM415213.pdf>.

22. *Id.* at 4.

23. *Id.*

24. Helen W. Boucher et al., *10 × '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America*, 56 *CLINICAL INFECTIOUS DISEASES* 1685, 1685 (2013) (finding that progress in developing antibiotics for treating gram-negative bacilli remains “alarmingly elusive”).

25. *Id.* at 1691 (providing that the “IDSA . . . supports urgent approval of FDA guidance on pathogen-specific clinical trials, which will help development of new antimicrobial drugs that target infections caused by drug-resistant pathogens.”)

26. Ignasi Roca et al., *The Global Threat of Antimicrobial Resistance: Science for Intervention*, 6 *NEW MICROBES & NEW INFECTIONS* 22, 22 (2015)

Clinicians fear that patient mortality risk from routine infections will increase as antibiotic resistance renders our most common antibiotics useless.²⁷ The Center for Disease Control and Prevention (“CDC”) estimates there are over two million infections and over 23,000 deaths annually in the United States caused by antibiotic resistant bacteria.²⁸ Bacteria all around the world are becoming increasingly resistant to current therapies. A Chinese university reported that Enterobacteriaceae taken from some pigs and several human patients expressed a gene conferring resistance to the last line of antibiotics.²⁹ Two months later, researchers in British Columbia, Canada confirmed the resistance mechanism had spread to the province.³⁰

The antibiotic clinical pipeline has been dwindling in the face of substantial market challenges.³¹ Investing in antibiotic research is not a priority for drug manufacturers because antibiotics also have a poor return on investment.³² Ideally, they are taken for a short period of time and cure the infection.³³ By 2008, only five drug manufacturers among the top fifty drug companies had active

(providing that “[d]espite the urgent need to find new antibacterial products, many pharmaceutical companies have abandoned antibiotic drug discovery programs . . . Relaunching . . . antimicrobial drug discovery and development should be a global priority . . .”).

^{27.} C. Lee Ventola, *The Antibiotic Resistance Crisis*, 40 PHARMACY AND THERAPEUTICS 277, 283 (2015) (arguing that “[e]ven when effective treatments exist . . . patients with resistant infections require significantly longer hospital stays . . . and experience a higher incidence of long-term disability.”).

^{28.} Margaret Hamburg, *FDA’s Take on the Executive Order and National Strategy to Combat Antibiotic-Resistant Bacteria*, FDA: FDA VOICE (Sept. 18, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/09/fdas-take-on-the-executive-order-and-national-strategy-to-combat-antibiotic-resistant-bacteria>.

^{29.} The Lancet, *New Gene that Makes Common Bacteria Resistant to Last-line Antibiotic Found in Animals, Patients in China*, SCIENCEDAILY (Nov. 19, 2015), <https://www.sciencedaily.com/releases/2015/11/151119095828.htm> (discussing the emergence of polymyxin resistance mechanism via *mcr-1* genes).

^{30.} *One Case of mcr-1 Resistance Confirmed in British Columbia*, BC CTR. FOR DISEASE CONTROL (Jan. 25, 2016), <http://www.bccdc.ca/about/news-stories/news-releases/2016/health-alert-one-case-of-mcr-1-resistance-confirmed-in-british-columbia>.

^{31.} Jenni Laidman, *Despite Growing Crisis, Few New Antibiotics Are in Pipeline*, MEDSCAPE MED. NEWS (Apr. 22, 2013), http://www.medscape.com/viewarticle/802891#vp_1.

^{32.} Theresa Braine, *Race Against Time to Develop New Antibiotics*, 89 BULLETIN OF THE WORLD HEALTH ORG. 88, 88 (2011), <http://www.who.int/bulletin/volumes/89/2/11-030211/en> (stating that “[a]ntibiotics . . . have a poor return on investment because they are taken for a short period of time and cure their target disease.”).

^{33.} *Id.*

antibiotic discovery programs.³⁴ Currently, 86% of companies involved in antibiotic research and development are small to medium-sized enterprises.³⁵ It is no surprise then that only two new antibiotics were approved from 2008-2012, while sixteen were approved from 1983-1987.³⁶ In fact, no new class of antibiotics has been developed for gram-negative bacteria in over fifty years.³⁷

In response to growing fears, there is observable governmental support in identifying techniques to slow the emergence of resistant bacteria and accelerate research and development of new antibiotics and vaccines. In response to the President's Council of Advisors on Science and Technology ("PCAST") "Report to the President on Combating Antibiotic Resistance ("CAR")" in September 2014, the White House announced a National Action Plan for Combating Antibiotic Resistant Bacteria.³⁸ The PCAST report considers several mechanisms to incentivize antibiotic development.

B. What types of incentives have been proposed?

Congressional legislation promoting innovation can be classified into specific incentivizing mechanisms. This section summarizes techniques Congress uses to "push" industry to innovate drugs in certain areas of public need. The next section describes the actual congressional acts.

1. Priority Review Vouchers

^{34.} *Id.* (providing that "[o]nly five major pharmaceutical companies . . . still had active antibacterial discovery programs in 2008 . . .").

^{35.} Gail Dutton, *Biopharmas Drive Antibiotic Development*, GEN: GEN EXCLUSIVES (Aug. 4, 2013), <http://www.genengnews.com/insight-and-intelligence/biopharmas-drive-antibiotic-development/77899874>.

^{36.} Brad Spellberg & David Geffen, *New Antibiotic Development: Barriers and Opportunities in 2012*, ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, <http://www.tufts.edu/med/apua/news/news-newsletter-vol-30-no-1-2.shtml> (last visited Nov. 5, 2016).

^{37.} *Id.* (providing that "we have had no new classes of antibiotics to treat Gram-negative bacilli (GNB) for more than 40 years – amazingly, the fluoroquinolones were the last new class of antibiotics to treat GNB."); *see also* Robert C. Moellering, Jr., *The Fluoroquinolones: The Last Samurai?*, 41 CLINICAL INFECTIOUS DISEASES S111 (2005) (summarizing fluoroquinolones), http://cid.oxfordjournals.org/content/41/Supplement_2/S111.full.pdf.

^{38.} PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., REPORTING TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE, EXEC. OFFICE OF THE PRESIDENT (Sept. 18, 2014); THE WHITE HOUSE, NAT'L ACTION PLAN FOR COMBATING ANTIBIOTIC RESISTANT BACTERIA (2015) (announcing the President's response to the report).

The FDA drug approval process for a new drug application (“NDA”) averages about 14.5 months.³⁹ Although this is a significant improvement from close to two years in the early 1990s, the regulatory delays in approval are costly to pharmaceutical companies. Regulatory delays also mean that life-saving therapies take longer to reach patients.⁴⁰ The 1992 Prescription Drug User Fee Act (PDUFA) established a two-tiered system for drug approvals.⁴¹ The most common tier, standard review, applies to drugs that offer marginal improvements over existing therapies. The 2002 PDUFA amendments set a goal of ten month review time for drug applications in the standard review tier.⁴² The less common tier, priority review, is a designation given to new therapies that provide “significant therapeutic improvements”⁴³ or treat conditions that lack any treatment options. The FDA’s goal for completing a priority review is six months.⁴⁴ On average, priority review applications took about eleven months to approve in 2008, but the FDA met its goal in 2012 when the average review time dropped to six months.⁴⁵

A priority review voucher is a voucher issued by the FDA to a drug sponsor allowing the holder of the voucher to submit a NDA for priority review instead of standard review.⁴⁶ Priority review

^{39.} Kurt R. Karst, *New Reports on FDA Drug Approval Performance Emerge as House Committee Considers User Fee Reauthorization Legislation*, FDA L. BLOG (May 10, 2012), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/05/new-reports-on-fda-drug-approval-performance-emerge-as-house-committee-considers-user-fee-reauthoriz.html.

^{40.} Les Picker, *The Safety and Efficacy of the FDA*, NAT’L BUREAU OF ECON. RESEARCH, <http://www.nber.org/digest/jun06/w11724.html> (last visited Nov. 11, 2016) (reporting that more rapid access to drugs on the market has enabled hundreds of thousands of patient life-years).

^{41.} *FDA User Fees 2012: How Innovation Helps Patients and Jobs*, Hearing Before the S. Subcomm. on Health, Comm. on Energy and Commerce, FDA (Apr. 18, 2012), <http://www.fda.gov/NewsEvents/Testimony/ucm300568.htm> (statement of Janet Woodcock, Dir., Cent. for Drug Eval. and Research, Food and Drug Admin., U.S. Dep’t of Health and Human Servs.).

^{42.} *FAQ about the FDA Approval Process*, FDA <http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm279676.htm> (last visited Nov. 6, 2016).

^{43.} *See Priority Review*, FDA, <http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm> (last visited Nov. 6, 2016) (listing four factors that can be demonstrated for a finding of significant therapeutic improvement).

^{44.} *Id.*

^{45.} Steven Ross Johnson, *FDA Getting Quicker at Reviewing New Drugs, Study Participants Say*, MODERN HEALTHCARE: VITAL SIGNS BLOG (Jan. 28, 2015), <http://www.modernhealthcare.com/article/20150128/blog/301289927>.

^{46.} *FAQ About the FDA Approval Process*, *supra* note 42.

vouchers are considered very valuable because they help reduce the time to begin marketing a drug to the public. So far, Congress has passed two laws allowing manufacturers to obtain transferable priority review vouchers after a successful drug approval. These transferable vouchers can be—and consistently are—sold to other companies. Acquiring a priority review voucher has been shown to be very rewarding to the original submitter. A drug manufacturer sold one of them for \$350 million.⁴⁷ One large drug manufacturer, Sanofi-Aventis, purchased two vouchers—one for \$67 million and the other for \$245 million. Sanofi-Aventis then used one of these priority review vouchers to beat Amgen (another big drug developer) to the market in obtaining FDA approval of the first PCSK9 cholesterol therapy in the United States—Praluent.⁴⁸ Praluent is expected to generate annual sales of more than \$2 billion. Thus, the half-year that Sanofi “saved” in getting the drug approved might make a \$1 billion difference in revenue. With these staggering figures in mind, it becomes apparent why the larger drug manufacturers are willing to spend a quarter-billion dollars for a priority review voucher.

2. Exclusivity

Exclusivity is a marketing right granted by the FDA upon approval of a drug.⁴⁹ Market exclusivity prevents the submission or effective approval of abbreviated new drug applications (“ANDAs”) from generic competitors.⁵⁰ Exclusivity is granted to a drug product holder when certain statutory requirements are met. The Drug Price Competition and Patent Term Restoration Act of 1984, colloquially known as the Hatch-Waxman Act, originally included two types of

^{47.} United Therapeutics, *United Therapeutics Corporation Agrees to Sell Priority Review Voucher to AbbVie for \$350 Million* (Aug. 19, 2015), <http://ir.unither.com/releasedetail.cfm?ReleaseID=928100>.

^{48.} *FDA Approves Praluent to Treat Certain Patients with High Cholesterol*, FDA (Jul. 24, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm>

^{49.} *Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, FDA, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962> (last updated Feb. 11, 2016) (“Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product.”).

^{50.} Renu Lal, *Patents and Exclusivity*, FDA / CDER SBIA CHRONICLES (May 19, 2015), <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM447307.pdf>.

exclusivity grants—new chemical entity exclusivity and “other significant change” (“OSC”) exclusivity.⁵¹ A new chemical exclusivity runs from the time of the NDA approval and grants up to five years of market exclusivity.⁵² The OSC exclusivity can last up to three years and is granted for a supplemental application containing reports of new clinical investigations⁵³ of a drug that are used for a new indication.⁵⁴

Congress had passed two other types of FDA market exclusivities before its recent wave of legislation. The Orphan Drug Act of 1983 allowed the FDA to grant the orphan drug exclusivity for seven years from the date on which the FDA approves an NDA.⁵⁵ Lastly, the FDA can also grant a pediatric exclusivity as a six-month add-on to another active exclusivity.⁵⁶ To qualify for a pediatric exclusivity, the applicant must: (1) submit a Written Request to the FDA detailing the studies needed and the time frame for their completion in the pediatric population; (2) submit study reports after the request; and (3) meet the deadlines and terms specified in the Written Request.⁵⁷ Congress has attempted to mirror

^{51.} *Id.*

^{52.} *Id.* The FDA grants a five-year period of exclusivity to new drug applications for products containing chemical entities never previously approved by FDA either alone or in combination.

^{53.} The FDA defines “new clinical investigations” as an investigation in humans, the results of which (1) have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety in a new patient population and (2) do not duplicate the results of another investigation relied upon by FDA to demonstrate a previously approved drug’s effectiveness or safety in a new patient population. *See* 21 C.F.R. § 314.108 (2015).

^{54.} *Lal, supra* note 50. The FDA grants a three-year period of exclusivity for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations conducted or sponsored by the sponsor *essential* to approval of the application.

^{55.} *FAQ on Patents and Exclusivity*, FDA, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm> (last updated Jul. 18, 2014). Receiving orphan drug *designation* requires that both the drug and the disease or condition meet certain criteria specified in FDA’s implementing regulations at 21 C.F.R. Part 316. The drug must treat a rare disease or treat a non-rare disease where the manufacturer cannot reasonably expect to recover the cost of developing the drug from sales in the United States.

^{56.} *Id.*

^{57.} *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric “Rule,” and their Interaction*, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm> (last updated Nov. 5, 2013) (“Pediatric exclusivity is an add-on

the success of market exclusivity incentives in newer proposals. For example, the Generating Antibiotics Now Act (GAIN) guarantees five years of additional market exclusivity for antibiotics that target qualified pathogens.

Another type of exclusivity that has been gaining support in drug regulation is “wildcard exclusivity.” Wildcard exclusivity incentives are not a new concept. The idea was first proposed in the 2005 US Biodefense and Pandemic Vaccine and Drug Development Act but was removed from the final version of the bill because of opposition from the generic drug manufacturer industry.⁵⁸ The omitted provision would have allowed pharmaceutical companies that develop bioterrorist countermeasures by researching commonly used medications for new indications, such as Anthrax, to extend patents on their popular and more profitable drugs.⁵⁹

Wildcard exclusivity was discussed as a mechanism for incentivizing cancer drug development by researchers from the London School of Economics in 2009⁶⁰ and by committee members in the PCAST report to President Obama in 2014.⁶¹ Recently, wildcard exclusivity discussion resurfaced during a public congressional hearing surrounding the 21st Century Cures Initiative.⁶²

A wildcard exclusivity voucher is similar to a transferable priority review voucher. The wildcard exclusivity voucher would permit a drug sponsor that obtains an FDA approval for a qualified drug product to grant a patent or exclusivity extension on another

to existing marketing exclusivity or patent protection...products with no patent life or exclusivity remaining cannot qualify”).

⁵⁸. Kathleen D. Jaeger, *Testimony Before the Joint Senate Judiciary and H.E.L.P. Committee Hearing On S. 666, BioShield II* 2-3, GENERIC PHARMACEUTICAL ASSOCIATION (Oct. 6, 2004), <http://www.help.senate.gov/imo/media/doc/Kathleen%20Jaeger.pdf>.

⁵⁹. Lindsay Frank, *Bioshield 2: A Shot in the Right Direction?*, 11 PUB. INT. L. REP. 19 (2006).

⁶⁰. ELIAS MOSSIALOS ET AL., POLICIES AND INCENTIVES FOR PROMOTING INNOVATION IN ANTIBIOTIC RESEARCH 115 (2009) <http://www.lse.ac.uk/LSEHealthAndSocialCare/impacts/LSEHealthNews/News%20Attachments/Policies%20and%20incentives%20report.pdf>.

⁶¹. PRESIDENT’S COUNCIL OF ADVISORS ON SCI. & TECH., *Report to the President on Combating Antibiotic Resistance* 40 (2014).

⁶². Daniel A. Kracov et al., *What to Expect in 2015: An Overview of Potential Pharmaceutical Regulatory, Policy and Enforcement Developments*, ARNOLD & PORTER LLP 17 (Jan. 2015), http://www.arnoldporter.com/resources/documents/eBook-FDA_WhatToExpectIn2015.pdf.

product of their choice.⁶³ The proposal would also permit the voucher holder to transfer or sell the voucher to another company. Like a transferable priority review voucher, a transferable patent extension could be a great economic incentive for innovative firms. The value of the voucher would depend on the length of the potential exclusivity period.

The transferable wildcard exclusivity incentive has several additional benefits. First, a bill permitting a wildcard exclusivity voucher would not require additional federal appropriation. Thus, the legislature would promote several drug development goals in much needed therapeutic areas without political debate about additional expenditures.⁶⁴ Second, the value of the free voucher would be based on the going rate on the market and would foster innovation from small companies that hope to sell the transferable voucher to another company.

One perceived pitfall of wildcard exclusivity is the increased cost to society of market exclusivity extensions. Since generic manufacturers would be precluded from bringing cheaper alternatives of a certain drug to market for an even longer time, the burden of higher costs would be shifted to payers – namely, private insurers and the government. Legislators are reluctant to “give away” benefits in the form of higher profits to the pharmaceutical industry.⁶⁵ Thus, this mechanism has never been seriously debated. While no current laws allow for transferable wildcard market

⁶³. Global Health Tech. Coalition Incentives & Innovative Financing Working Group, *Current and Proposed Incentive Mechanisms*, <http://www.healthresearchpolicy.org/sites/healthresearchpolicy.org/files/GHTC%20Incentive%20Mechanisms%20List.pdf> (last visited Nov. 6, 2016).

⁶⁴. Commentators have not adequately studied the cost-effectiveness of wildcard exclusivity grants because of the amorphous nature of the grant – questions arise regarding which medication would ultimately receive the added exclusivity protection and the length of the exclusivity. *But see* Brad Spellberg et al., *Societal Costs Versus Savings from Wild-Card Patent Extension Legislation to Spur Critically Needed Antibiotic Development*, 35 *INFECTION* 167, 167-74 (2007) (finding the overall societal savings of developing a treatment for the multi-drug resistant pathogen *Pseudomonas aeruginosa* would be \$4.6 billion in twenty years).

⁶⁵. Some commentators conclude that after weighing the intended result versus costs, antibiotics are one of the most cost-effective therapeutic agents. Thus, wildcard exclusivity would still be an enticing bargain for antibiotic development. *See, e.g.*, STEVEN PROJAN, *Stimulating Antibacterial Research and Development: Sense and Sensibility*, *ANTIBIOTIC DISCOVERY AND DEVELOPMENT* 1103, 1104 (J. Dougherty & Michael J. Pucci eds., 2007) (reasoning that insurers pay tens of thousands for cancer medications that increase patients’ life expectancy by several months and that spending a few thousand dollars on an antibiotic that cures a patient’s infection and adds decades of life is a “bargain”).

exclusivity, Congress has a powerful incentivizing tool in its toolshed when it decides to rapidly promote drug development.

III. INCENTIVIZING LEGISLATION FROM THE PAST DECADE

A. *Tropical Disease Priority Review Voucher*

In 2007, Congress passed the 2007 FDA Amendments Act (“FDAAA”).⁶⁶ The FDA described the FDAAA as a significant extension of FDA authority.⁶⁷ Among numerous statutory reforms, the FDAAA reauthorized the prescription drug user fee program and the medical device user fee program.⁶⁸ Included in its other major sections was Section 1102, which added section 524 to the Food Drug & Cosmetic Act (“FDCA”).⁶⁹

FDCA section 524 allows the FDA to award transferable priority review vouchers to sponsors of drugs that treat certain tropical diseases. Section 524(a)(3) originally listed 16 tropical diseases⁷⁰ eligible for review.

On December 26, 2014, in response to the Ebola outbreak in West Africa, President Obama signed into law an act amending the tropical disease priority review program to include Ebola in the list of covered tropical diseases.⁷¹ This Act considerably strengthened the Tropical Disease Voucher program by reducing the time a drug sponsor was required to notify the FDA prior to the sponsor’s intended use of a priority review voucher—from 365 days to ninety days.⁷² Drug manufacturers often decide to submit a drug for FDA approval close to the actual date of submission based on results from clinical studies. Thus, the 365 day notification period prior to submission had been cited as a major weakness in the original transferable voucher program.

Drug manufacturers were not willing to purchase a voucher that far in advance of submission. Consequently, smaller, more

^{66.} *Food and Drug Administration Amendments Act (FDAAA) of 2007*, FDA, <http://www.fdanews.com/ext/resources/files/07/07-29-30-FDAAA.pdf> (last updated Dec. 2, 2011).

^{67.} *Id.*

^{68.} *Id.*

^{69.} Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1102, 121 Stat. 823, 972 (2007).

^{70.} *Id.* The list includes more common diseases such as tuberculosis, malaria, and cholera among rarer diseases like leprosy, dengue fever, and onchocerciasis.

^{71.} Adding Ebola to the FDA Priority Review Voucher Program Act, Pub. L. No. 113-233, § 2, 128 Stat. 2127 (2014).

^{72.} *Id.*

innovative biotech firms had not been induced to develop treatments for tropical diseases. The original tropical disease voucher statute had also limited the number of transfers of the voucher to one time.⁷³ To make the voucher program more enticing, this limit was removed in the 2014 amendment.⁷⁴

Furthermore, the amended act allowed the FDA to determine which diseases to designate as tropical diseases for the purpose of the program. Section 524(a)(3)(R) originally defined a tropical disease as “any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary.”⁷⁵ The amended act changed “regulation by” to “order of.”⁷⁶ Thus, the task of defining the key terms of section 524(a)(3)(R) was left to the Secretary of the Department of Health and Human Services.

On August 20, 2015, in response to this delegation, the FDA published a final order adding two other tropical diseases and proposed definitions to the several key phrases in the statute to help determine which diseases met the definition of a tropical disease.⁷⁷ The phrases were: (1) “developed nation,” (2) “no significant market,” and (3) “disproportionately affects poor and marginalized populations.”⁷⁸

The FDA proposed that a country’s presence on the World Bank’s list of high income economies be used as evidence that it is a “developed nation” and its presence on the list’s low income economies as evidence that it should not be considered a “developed nation.”⁷⁹ Then, the FDA proposed a two-factor test to determine whether a “significant market” exists in the developed country. The two factors are: (1) prevalence of the disease in

^{73.} Food and Drug Administration Amendments Act of 2007, *supra* note 69.

^{74.} Adding Ebola to the FDA Priority Review Voucher Program Act, *supra* note 71 (“There is no limit on the number of times a priority review voucher may be transferred before such voucher is used.”).

^{75.} Food and Drug Administration Amendments Act, *supra* note 69.

^{76.} Adding Ebola to the FDA Priority Review Voucher Program Act, *supra* note 71.

^{77.} Section 524(a)(3)(R) defines tropical diseases not included in the original list as “[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations.”

^{78.} Designating Additions to the Current List of Tropical Diseases in the FDCA, 80 Fed. Reg. 50,559-61 (Aug. 20, 2015) (to be codified at 21 C.F.R. pt. 317).

^{79.} *Id.* at 50,560.

developed nations and (2) the existence of a sizeable indirect market for the drug that would constitute a financial incentive for drug development.⁸⁰ The FDA stressed the importance of the second factor in determining market incentives: “People in high-income economies are more likely to be able to afford disease treatments and, thus, drug companies have an incentive to create products that will be in demand in those countries.”⁸¹

Finally, the FDA proposed a four-factor test to determine whether the disease “disproportionately affects poor and marginalized populations.” The FDA considers these four factors in relation to the countries where the disease is found: (1) the impact of the disease on a given population via the “disability-adjusted life year” measurement; (2) the relative burden of the disease; (3) the burden of the disease on infants, children, or other marginalized segments of the population; and (4) designation by the World Health Organization (“WHO”) as a neglected tropical disease.⁸²

B. Rare Pediatric Disease Priority Review Voucher

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (“FDASIA”).⁸³ The FDASIA reauthorized the FDA’s authority to collect fees from sponsors, enhanced the FDA’s ability to monitor the drug supply chain, created the “Breakthrough Therapy Designation,” and required that the FDA consult with the Office of the National Coordinator to develop a proposed strategy for regulating health information technology.⁸⁴

The FDASIA also included Section 908, which added section 529 to the FDCA. Under section 529, the FDA can award priority review vouchers to sponsors of certain rare pediatric diseases.⁸⁵ The FDA defines a “rare pediatric disease” similarly to a rare disease, but in pediatric patients – thus, a rare pediatric disease is a disease

^{80.} *Id.* at 50,560-61.

^{81.} *Id.* at 50,560.

^{82.} *Id.* at 50,561.

^{83.} *Food and Drug Administration Safety and Innovation Act (FDASIA), Regulatory Information*, FDA (Oct. 6, 2015), <http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/FDASIA/ucm20027187.htm>.

^{84.} *Id.*

^{85.} *Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry* (Nov. 17, 2014), <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>.

that affects fewer than 200,000 individuals primarily⁸⁶ aged zero to eighteen years. To qualify, the drug sponsor cannot seek approval for an adult indication in the original rare pediatric disease application.⁸⁷ These drugs could also qualify for a six-month add-on market exclusivity provided by section 505(A) of the Food and Drug Administration Modernization Act of 1997 (“FDAMA”).

One concern with off-label treatments for pediatric populations is the lack of clinical evidence for children’s dosages. These dosages are not adequately studied because of small patient populations. Thus, physicians extrapolate the adult dose by adjusting the original dose based on a child’s body weight.⁸⁸ However, this fails to consider developmental differences in children beyond body mass.⁸⁹ FDCA section 539(a)(4)(D) as amended contemplates this very issue, adding a requirement that the application rely on “clinical data derived from studies examining a pediatric population and dosages of the drug intended” for pediatrics.⁹⁰ The FDA has further interpreted this requirement to require adequate pediatric labeling.⁹¹

A request for FDA designation as a treatment for a rare pediatric disease must be made at the same time as an orphan drug designation request.⁹² However, orphan designation is not a prerequisite for receiving the Rare Pediatric Priority Review Voucher. The statute requires the FDA to make a decision on designation no later than sixty days after submission of a timely request for rare pediatric disease designation.⁹³ The FDA states that a sponsor does not need to specifically request rare disease

^{86.} *Id.* The Draft Guidance defines “primarily” as greater than 50% of the affected population based on the year of *diagnosis*. For genetic diseases that do not manifest until an older age, the guidance allows a product’s diagnosis to include intent to treat a genetic disorder or prevent clinical progression.

^{87.} *Id.*

^{88.} Gayatri Rao, *Rare Diseases in Children Pose Unique Challenges*, FDA VOICE (Feb. 27, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/02/rare-diseases-in-children-pose-unique-challenges>.

^{89.} *See generally* Cheston M. Berlin, Jr., *Pharmacokinetics in Children*, MERCK MANUAL, <http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children> (last updated Sept. 2013) (children have different rates of drug absorption because they have an underdeveloped gastrointestinal system, higher percentage of water content, and varying concentrations of enzymes involved in metabolism).

^{90.} 21 U.S.C. § 360aa (2012).

^{91.} *Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry*, *supra* note 85 at 5.

^{92.} *Id.* at 8.

^{93.} *Id.*

designation, but should request a rare disease priority review voucher.⁹⁴

The voucher can be transferred and sold without limits.⁹⁵ However, the drug sponsor that proceeds to use the voucher must relay their intent to use the voucher to the FDA at least ninety days before submitting a drug application.⁹⁶ Since the program's inception in 2012, the FDA has awarded six priority drug vouchers.⁹⁷ One of these vouchers was sold for \$245 million to Sanofi-Aventis in 2015.⁹⁸ The original statute, however, had a sunset clause limiting the voucher's availability.⁹⁹ The pharmaceutical industry has a great incentive in the pediatric rare disease priority review program, but there is lots of uncertainty about future availability because the program has yet to be reauthorized permanently.¹⁰⁰

C. *Generating Antibiotic Incentives Now (GAIN)*

The GAIN provisions (sections 801-806) were also enacted as part of the FDASIA, further amending the Food, Drug, and Cosmetic Act.¹⁰¹ The provisions were enacted as part of President Obama's national strategy on combating antibiotic resistance and

^{94.} *Id.* at 14.

^{95.} Food, Drug, and Cosmetic Act, § 529(b)(2), 21 U.S.C. § 360ff(b)(2)(A) (2012).

^{96.} Food, Drug, and Cosmetic Act, § 529(b)(4)(A), 21 U.S.C. § 360ff(b)(4)(B)(i) (2012).

^{97.} Alexander Varond, *Nearing its Sunset, Pediatric Voucher Program Gains Momentum*, FDA L. BLOG (Dec. 13, 2015), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/12/nearing-its-sunset-pediatric-voucher-program-gains-momentum.html (five different drug manufacturers have collectively received six total priority review vouchers from the FDA).

^{98.} Chelsey Dulaney, *Retrophin Sells FDA Voucher to Sanofi for \$245 Million*, WALL ST. J. (May 27, 2015), <http://www.wsj.com/articles/retrophin-sells-fda-voucher-to-sanofi-for-245-million-1432732325>.

^{99.} Food, Drug, and Cosmetic Act, § 529(b)(4)(A), 21 U.S.C. § 360ff(b)(4)(B)(i) (2012) (“The Secretary may not award any priority review vouchers under paragraph (1) after the last day of the 1-year period that begins on the date that the Secretary awards the third rare pediatric disease priority voucher under this section.”)

^{100.} There are several congressional proposals that will renew the Rare Pediatric PRV if passed. These proposals will be discussed in the next section of the paper.

^{101.} FDA Safety and Innovation Act, Pub. L. No. 112-144, §§ 801-06, 126 Stat. 993 (2012).

encouraging research and development.¹⁰² GAIN incentivizes the development of antimicrobial treatments that treat qualified pathogens. First, GAIN defines qualifying pathogens as those pathogens that have “the potential to pose a serious threat to public health.”¹⁰³ Although the statute includes several qualifying pathogens, it delegates the authority to the Secretary of the Department of Health and Human Services to develop a list of qualifying pathogens and a methodology based on several considerations.¹⁰⁴

The statute requires the Secretary consider: (1) the impact on public health due to drug-resistant organisms in humans; (2) the rate of growth of drug-resistant organism in humans; (3) the increase in resistance rates in humans; and (4) morbidity and mortality in humans.¹⁰⁵ Further, the Secretary is required to consult with the CDC, FDA, medical professionals, and the clinical research community when establishing and maintaining the list.¹⁰⁶ Lastly, the Secretary must review and modify the list at least every five years.¹⁰⁷ On June 5, 2014, the FDA passed a final rule implementing GAIN and listing 18 qualifying pathogens.¹⁰⁸ However, three additional pathogens were added to the list in response to comments received during the rulemaking period.¹⁰⁹

GAIN grants a significant incentive—an additional five years of exclusivity for antibiotics designated under the law as a “qualifying infectious disease product” upon the approval of a new drug application by the FDA.¹¹⁰ The five year market exclusivity is in addition to five year exclusivity as a new chemical entity (NCE), three year clinical investigation exclusivity, and seven-year orphan drug exclusivity.¹¹¹ The exclusivity can also be combined with the

^{102.} Margaret A. Hamburg, *FDA’s Take on the Executive Order and National Strategy to Combat Antibiotic-Resistant Bacteria*, FDA VOICE (Sept. 18, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/09/fdas-take-on-the-executive-order-and-national-strategy-to-combat-antibiotic-resistant-bacteria>.

^{103.} Food, Drug, and Cosmetic Act, § 505E(f)(1), 21 U.S.C. § 355f(f)(1) (2012).

^{104.} *Id.*

^{105.} Food, Drug, and Cosmetic Act, § 505E(f)(2)(B), 21 U.S.C. § 355f(f)(2)(B) (2012).

^{106.} *Id.*

^{107.} Food, Drug, and Cosmetic Act, § 505E(f)(2)(C), 21 U.S.C. § 355f(f)(2)(C) (2012).

^{108.} *Establishing a List of Qualifying Pathogens Under the Food and Drug Administration Safety and Innovation Act*, 79 Fed. Reg. 32,464 (June 5, 2014).

^{109.} *Id.* at 32,472-74.

^{110.} Food, Drug, and Cosmetic Act, § 505E(a), 21 U.S.C. § 355f(a) (2012).

^{111.} *Id.*

six month pediatric exclusivity from the FDAMA. Furthermore, for a qualifying product that also has NCE exclusivity, GAIN amends the period during which an ANDA¹¹² cannot be submitted by extending the period from four years after the product is approved to nine years. Lastly, as part of its designation, drug applications for qualifying products receive priority review and fast track designation at the sponsor's request.¹¹³

The GAIN Act does have several limitations. It does not apply to the approval of a subsequent application filed by a drug sponsor that results in a new indication, strength, or dosing schedule. However, the provisions have already created a sizeable boost to the antibiotic development pipeline. At least thirty-nine different molecules have been designated a qualifying product by the FDA¹¹⁴ as of September 2014 and six antibiotics have been approved as a qualifying product through the GAIN.¹¹⁵

IV. THE RECENT BUZZ OF NEW INCENTIVIZING LEGISLATION FOR SPECIFIC CONDITIONS

In addition to the three laws discussed above, Congress has been very active in finding ways to incentivize pharmaceutical innovation for specific therapeutic needs. Several bills have been proposed and some have garnered widespread approval. This section discusses some of this legislation.

A. *Promoting Life-Saving New Therapies for Neonates Act of 2015*

On September 16, 2015, two US Senators, Dr. Bill Cassidy (R-LA) and Bob Casey (D-PA) introduced the Promoting Life-Saving New Therapies for Neonates Act ("PLS Act") of 2015 to increase treatment options for newborns.¹¹⁶ Representative Cassidy stated that a major impetus prompting the legislation was the lack of drug development for neonates—only one drug specifically indicated for the neonatal population had been approved in the past sixteen

^{112.} The ANDA must have a Paragraph IV certification to an Orange Book listed patent.

^{113.} Food, Drug, and Cosmetic Act, § 524A, 21 U.S.C.A. § 355 (2012).

^{114.} Janet Woodcock, *Three Encouraging Steps Toward New Antibiotic*, FDA VOICE (Sept. 23, 2014), <http://blogs.fda.gov/fdavoices/index.php/tag/gain-act/>.

^{115.} *FDA Approves New Antifungal Drug Cresemba*, FDA (Mar. 6, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm437106.htm>.

^{116.} Promoting Life-Saving New Therapies for Neonates Act of 2015, S. 2041, 114th Cong. (2015).

years.¹¹⁷ The PLS Act defines a neonatal drug as a drug developed “for the prevention or treatment of a disease or condition of a preterm or full-term neonate.”¹¹⁸ A drug sponsor for a qualified drug product receives a hybrid “Neonatal Drug Exclusivity Voucher” that awards a transferable voucher entitling the holder to a one year add-on of transferable extension to all existing patents and marketing exclusivities, including any extensions.¹¹⁹

There are certain limitations on voucher eligibility and use. A voucher cannot be “transferred to, or used for” drugs whose patents and exclusivities have expired. This is statutorily similar to the pediatric exclusivity extension, where the extension works only as an “add-on.” Also, drug sponsors may also not combine vouchers received from the tropical disease PRV and the rare disease PRV. Lastly, a drug sponsor must notify the Secretary at least fifteen months prior to loss of patent and exclusivities for which the voucher will be redeemed. This fifteen-month notification period would not be a drawback for this legislation. Unlike a lengthy notification period prior to application submission, drug manufacturers will know when their patents and exclusivities expire and have enough financial data to make a savvy business decision regarding voucher application.

The PLS Act requires that the Secretary of the Department of Health and Human Services (“DHHS”), in consultation with the NIH, Pediatric Advisory Committee, and International Neonatal Consortium and other stakeholders, publish a list of critical research priorities related to diseases common to neonates.¹²⁰ Furthermore, the PLS Act requires that the Secretary issue a guidance specific to the neonatal drug exclusivity voucher program and update the critical research priorities list every three years.¹²¹ The Act somewhat parallels the Rare Pediatric Disease Priority Review Voucher because it requires that a new drug application rely on clinical data

^{117.} *Cassidy, Casey Introduce Legislation to Boost Lifesaving Treatments for at Risk Newborns*, BILL CASSIDY (Sept. 17, 2015), <http://www.cassidy.senate.gov/newsroom/press-releases/cassidy-casey-introduce-legislation-to-boost-lifesaving-treatments-for-at-risk-newborns>.

^{118.} Promoting Life-Saving New Therapies for Neonates Act of 2015, *supra* note 116.

^{119.} *Id.*

^{120.} *Id.*

^{121.} *Id.*

derived from studies examining a neonatal population to obtain the voucher.¹²²

The PLS Act seems vague in delegating duties to the Secretary. For example, it requires the Secretary to “perform other activities necessary to support neonatal drug applications.” This passage might prove unworkable for the FDA. Congress will need to clarify this abstract requirement if the Act ultimately passes and the clarification is likely to be based on input from the FDA. Another drawback is that the Act also prohibits additional fees, outside of the regular NDA application, for the exercise of a voucher under the PLS Act. Considering how lucrative the use of this voucher has been for drug developers seeking to exclude competitors for an entire year, an additional fee¹²³ is unlikely to be cost-prohibitive. The FDA could use the additional resources to efficiently conduct the priority review while not increasing the risk of patient harm.

B. Antibiotic Development to Advance Patient Treatment (“ADAPT”) Act

On December 12, 2013, the ADAPT Act was introduced by ten bipartisan members of the House Energy and Commerce Committee.¹²⁴ The ADAPT Act is thought to augment GAIN and is often referred to as its immediate successor. The Act creates a pathway for faster approval of antimicrobial drugs intended for serious or life-threatening diseases by allowing FDA approval using limited size studies and alternative clinical endpoints. The FDA has often acknowledged that patients with bacterial infections are too sick to enroll in clinical trials and there are inherent limitations in conducting a clinical trial involving very sick patients.¹²⁵

^{122.} The Rare Pediatric Disease PRV requires that the drug sponsor rely on studies in the pediatric population and similarly submit to the FDA adequate labeling instruction specifically for the pediatric population.

^{123.} *But see Fee for Using a Rare Pediatric Disease Priority Review Voucher in Fiscal Year 2016*, 81 Fed. Reg. 37,360 (Sept. 30, 2015) (section 529(c)(2) of Food, Drug, and Cosmetic Act allows the FDA set the amount of the *rare pediatric disease priority review* user fee based on the “average cost incurred . . . in the review of a human drug application subject to a priority review in the previous fiscal year, and the average cost incurred . . . in the review of a human drug application not subject to a priority review in the previous fiscal year. This requirement allows the FDA to allocate additional expenses for generating a priority review decision.”).

^{124.} Antibiotic Development to Advance Patient Treatment Act of 2013, H. 3742, 113th Cong. (2013).

^{125.} Edward M. Cox, *FDA’s Multi-pronged Approach Helps Meet the Challenge of Bringing New and Innovative Antibiotics to Patients Who Need Them*, FDA VOICE (Jul. 28, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/07/fdas-multi-pronged-approach->

First, ADAPT creates a mechanism known as the Limitation Population Antibacterial Drug (“LPAD”) pathway.¹²⁶ Under this pathway, the FDA may approve an antimicrobial drug to treat a limited population of patients if there is an unmet medical need. The Act further states:

[I]n determining whether to grant such approval for a limited population of patients, may rely on traditional endpoints, alternative endpoints, or a combination of traditional and alternative endpoints; datasets of limited size; pharmacologic or pathophysiologic data; data from phase 2 clinical studies; and such other confirmatory evidence as the Secretary deems necessary.¹²⁷

ADAPT thus makes clinical trials more scientifically feasible for rare infections by allowing smaller studies and flexible clinical endpoints. The proceeding section of ADAPT requires a mandatory label on the drug stating that the “drug is indicated for use in a limited and specific population of patients.”¹²⁸ ADAPT also includes broader governmental initiatives. The Act requires that the CDC use an appropriate monitoring system to monitor the use of antimicrobials in life-threatening infections and determine antimicrobial resistance trends.¹²⁹ The data from these studies have to be publically available.

Unlike the previously discussed legislation, the ADAPT Act does not require a shorter review time by the FDA. However, the two antibiotic Acts, GAIN and ADAPT, are meant to work together. Some drug products that would meet the statutory requirement with “the potential to pose a serious threat to public health” under GAIN would also be considered “serious and life-threatening” for ADAPT purposes. Thus, drug sponsors would have two financial incentives for developing antibiotics—lower costs for clinical studies and a longer period of market exclusivity.

Certain provisions in the ADAPT Act might be ineffective or contrary to the FDA mission. The ADAPT Act does not impose responsibilities for antibiotic stewardship for antibiotics developed under this pathway.¹³⁰ This can lead to overuse of these antibiotics

helps-meet-the-challenge-of-bringing-new-and-innovative-antibiotics-to-patients-who-need-them.

^{126.} Antibiotic Development to Advance Patient Treatment Act of 2013.

^{127.} *Id.* § 2(a).

^{128.} *Id.*

^{129.} *Id.* § 2(c).

^{130.} *Core Elements of Hospital Antibiotic Stewardship Programs*, CTR FOR DISEASE CONTROL AND PREVENTION, <http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html> (last updated May 25, 2015) (defining antibiotic stewardships as hospital-based

and contribute to resistant microbes. The reduced requirement for diverse clinical trial participants encourages hand-picking of healthier patients that have better treatment outcomes than the actual population. Also, the Act would jeopardize the recent efforts of the FDA and NIH in promoting diverse clinical trials that include women, children, and elderly subjects.¹³¹ While supporting the broader goals of the Act, the Infectious Disease Society of America (“IDSA”) cautioned that labeling must be prominent to enforce “judicious use” of novel antibiotics.¹³²

C. 21st Century Cures Act

Many of the ADAPT Act provisions were ultimately incorporated into the 21st Century Cures Act (“Cures Act”). The Cures Act is a major bipartisan congressional initiative that aims to revolutionize healthcare research, development, and delivery. The Cures Act will overhaul the FDA regulatory landscape and speed up innovation of new treatments with the goal of reducing patient access “lag time.”

The bill was approved by the House on July 20, 2015 and is currently in Senate.¹³³ However, the length of the bill, even in its edited form, is still about 200 pages. The Cures Act has not gathered

programs that “optimize the treatment of infections and reduce adverse events associated with antibiotic use,” that “help clinicians improve the quality of patient care,” that “improve patient safety through increased infection cure rates, reduced treatment failures, and increased frequency of correct prescribing for therapy and prophylaxis, and . . . reduce antibiotic resistance.”)

^{131.} See generally Robert M. Califf, *2016: The Year of Diversity in Clinical Trials*, FDA VOICE (Jan. 27, 2016), <http://blogs.fda.gov/fdavoices/index.php/2016/01/2016-the-year-of-diversity-in-clinical-trials> (discussing FDA efforts in 2016 that would improve patient inclusion and diversity in clinical trials by stating that “[o]ne challenge that remains for FDA is ensuring that research participants are representative of the patients who will use the medical product.”).

^{132.} Letter from Barbara E. Murray, President, Infectious Disease Society of America, to Representatives Phil Gingrey and Gene Green, U.S. House of Representatives (Dec. 12, 2013), http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20/Letters/To_Congress/IDSA%20Letter%20on%20LPAD%20to%20Gingrey%20and%20Green.pdf (“it is important that drugs approved under this pathway be used judiciously, particularly given that they will be approved for limited populations, not the broad population of patients suffering non-serious infections that can be treated effectively with existing drugs.”)

^{133.} *21st Century Cures: What You Need to Know*, HOUSE ENERGY & COMMERCE COMM. (last visited Oct. 26, 2016), <http://energycommerce.house.gov/cures>.

bipartisan support in the Senate. Thus, the Senate Committee on Health, Education, Labor and Pensions has split the Cures Act into several smaller bills that would be deliberated on different days.¹³⁴ This section covers some of the major initiatives included in the larger bill.

The originally proposed bill was divided into three main titles—Discovery, Development, and Delivery.¹³⁵ Title IV was added later to incorporate Medicaid and Medicare reforms but its goals are beyond the scope of this paper. The first substantive title of the 21st Century Cures Act is “Discovery.” “Discovery” is further subdivided into eight subtitles.¹³⁶ The title focuses on changing the way the NIH helps researchers innovate and provides funding for NIH efforts.¹³⁷

First, in Subtitle A, the Act increases funding for the NIH and establishes the NIH Innovation Fund.¹³⁸ Subtitle B requires that the NIH develop a strategic plan every five years focused on increasing the efficiency of biomedical research and identify areas of particular need.¹³⁹ Subtitle B also creates a Biomedical Research Working Group to provide recommendations to the NIH.¹⁴⁰ Subtitle C helps researchers in the NIH with loan repayment programs with the goal of luring talented researchers to government work.¹⁴¹

The Act introduces a pediatric research network in Subtitle E to foster clinical research for pediatric rare diseases.¹⁴² Finally, Section H establishes a nonprofit entity known as the “Council for 21st Century Cures.”¹⁴³ This council will be a public-private partnership headed by an Executive Director and will not be an agency of the United States government. The Act tasks the council with helping the “discovery, development, and delivery in the United States of cures, treatments, and preventive measures.” The FDA, NIH, and

^{134.} Jeff Overley, *Senate Panel Splits Approach To 21st Century Cures*, LAW360 (Jan. 19, 2016), <http://www.law360.com/articles/748360/senate-panel-splits-approach-to-21st-century-cures>; Zachary Brennan, *Senate Committee Advances Seven Bills Linked to Drug, Device Regulations and Research*, REGULATORY FOCUS (Feb. 9, 2016), <http://www.raps.org/Regulatory-Focus/News/2016/02/09/24277/Senate-Committee-Advances-Seven-Bills-Linked-to-Drug-Device-Regulations-and-Research/#sthash.dGoKyE5.dpuf>.

^{135.} 21st Century Cures Act, H.R. 6, 114th Cong. (2015).

^{136.} *Id.*

^{137.} *Id.* tit. 1 (“Discovery”).

^{138.} *Id.* §§ 1001-02.

^{139.} *Id.* §§ 1021-29.

^{140.} *Id.*

^{141.} *Id.* §§ 1041-42.

^{142.} *Id.* §§ 1081-83.

^{143.} *Id.* § 1141.

Centers for Medicare and Medicaid Services (“CMS”) would each hold a seat on the board of the council.

While Title I focuses more on clinical research, innovation, and the NIH, Title II (“Development”) focuses on modernizing the FDA regulatory landscape.¹⁴⁴ Subtitle A focuses on incorporating patient preferences into FDA regulatory meshwork. The Subtitle defines “Patient Experience Data” as data collected from patient care that includes information about the impact of a disease or therapy on patients’ lives.¹⁴⁵ The Act requires the FDA to methodically consider the experience of patients living with a particular disease, the patients’ burden, and impact on quality of life and publish guidance within two years on how companies can use “patient-experience data” in drug development.¹⁴⁶

Subtitle B strengthens the use of biomarkers¹⁴⁷ in FDA approvals. This section creates a structured framework at the FDA for submission and qualification of biomarkers and surrogate markers for specific purposes. The Act requires a new FDA guidance on biomarker use. Subtitle B also creates an “Accelerated Approval Development Plan” that uses surrogate endpoints as a basis for accelerated approval when an unmet medical need exists in the patient population.¹⁴⁸ Subtitle D is an important, but widely debated, section of the Cures Act because it requires that the FDA utilize evidence from clinical experiences to help support a new indication in an already approved drug. Eligible data might come from observational trials and therapeutic use.¹⁴⁹

Subtitle E reaffirms to the FDA the “sense of Congress” and tells the agency that it should expedite approval of breakthrough therapies by approving drugs as early as possible in the clinical development process.¹⁵⁰ Subtitle E amends the FDA’s compassionate use policies to require manufacturers of investigation drugs in phase two or three of the drug approval process to make their expanded access policy publicly available.¹⁵¹ This Subtitle does not require that the manufacturer provide expanded access but only expands access to information regarding the manufacturer’s policies.

^{144.} *Id.* tit.2 (“Development”).

^{145.} *Id.* § 2001(a).

^{146.} *Id.* § 2001(b).

^{147.} *Id.* § 2021(b) (defining “biomarkers” as a characteristic that is objectively measured as an indicator of normal biological processes or biological responses to a therapeutic intervention and includes surrogate endpoints).

^{148.} *Id.* § 2022.

^{149.} *Id.* §§ 2061-63.

^{150.} *Id.* §§ 2081-83.

^{151.} *Id.*

Subtitle G complements the GAIN and ADAPT provisions and creates a “limited population pathway” for development of antibiotics and antifungals along with specific labeling requirements.¹⁵² It also requires specific monitoring by the CDC and FDA. Then, the Subtitle provides economic incentives to antibiotic developers through higher payments under Medicare for qualified antibiotic products that are associated with high rates of mortality and morbidity.¹⁵³

Subtitle I provides incentives for orphan products and products developed for limited populations.¹⁵⁴ The Act would grant a one-time six month extension of exclusivity for an approved drug if the sponsor obtains approval of a new indication for a rare disease or condition.¹⁵⁵

The next three sections focus on medical technology innovation.¹⁵⁶ First, the Cures Act grants priority review for medical devices that are eligible for a new “breakthrough” designation by the FDA. The definition of breakthrough devices parallels breakthrough drugs. These devices must treat conditions without alternative treatments or provide a significant advantage over already approved devices. However, a device can also be a breakthrough device if its availability is in “the best interest of the patients.” The Act requires that FDA staff use the “least burdensome appropriate means concept” to review medical device applications and permit all “valid scientific evidence.”¹⁵⁷ Finally, the Act creates an advisory committee tasked with finding a better way to classify medical devices and allow presentation of a device to an advisory panel before classification. The Act then restricts FDA regulation of mobile health software by stating that the FDA will not be permitted to regulate health software except in cases where the software “poses a significant risk to patient safety.”¹⁵⁸

Title III of the 21st Century Cures Act focuses on delivery. The amended draft focuses on interoperability standards of health information technology and requires publication of application programming interfaces and real world data. Subtitle B reinforces the use of tele-health for delivering quality health care services and

^{152.} *Id.* §§ 2121-23.

^{153.} *Id.*

^{154.} *Id.* §§ 2151-52.

^{155.} *Id.* (reauthorizing the rare pediatric disease review voucher program until Dec. 31, 2018).

^{156.} *Id.* §§ 2201-43.

^{157.} *Id.* § 2223(a).

^{158.} *Id.* § 2242.

requires payment of these services by Medicare.¹⁵⁹ The other provisions of Title III and Title IV, which include prescription drug abuse prevention programs, removal of certain disclosures from physicians for payments received, and health insurance payment reforms, are outside the scope of this paper.

D. Promoting Access for Treatments Ideal in Enhancing New Therapies Act of 2015 (“PATIENT”) and Other Acts

The PATIENT Act is a stand-alone bill derived from section 1241 of the 21st Century Cures Act. The PATIENT Act was reintroduced by Representative Gus Bilirakis.¹⁶⁰ The substantive provisions of PATIENT extend the period of three-year exclusivity for “other significant change” exclusivity by two more years if the drug sponsor provides specific information to the FDA in its application.¹⁶¹

The drug sponsor must show that the new clinical investigation conducted can: (1) reasonably be expected to promote greater patient adherence to an approved treatment regime compared to an older formulation; (2) reduce the public-health risks associated with the drug relative to an older formulation; (3) reduce side effects and adverse events; (4) provide systemic benefits; or (5) provide other benefits comparable to items one through four above.¹⁶²

The Act then requires the Secretary of DHHS to promulgate regulations to carry out the amendments of the PATIENT Act within 180 days.¹⁶³ Interestingly, the statute requires that the FDA consult with applicants regarding eligibility for the extension. In this consultation, the FDA and the sponsor must discuss how the sponsor hopes to meet the Act’s requirements.¹⁶⁴

Congressmen have introduced two other bills that could incentivize development in rare disease therapeutics. The first bill is the Advancing Targeted Therapies for Rare Diseases Act of 2015.¹⁶⁵ This Act allows drug sponsors to rely upon their own data for rare genetic diseases.¹⁶⁶ Specifically, the proposal allows “the sponsor of

^{159.} *Id.* § 3021.

^{160.} *See* Promoting Access for Treatments Ideal in Enhancing New Therapies Act of 2015, H.R. 1353, 114th Cong. (2015).

^{161.} *Id.* § 2(a).

^{162.} *Id.*

^{163.} *Id.* § 2(c).

^{164.} *Id.* § 2(b).

^{165.} *See generally* Advancing Targeted Therapies for Rare Diseases Act of 2015, S. 2030, 114th Cong. (2015).

^{166.} *Id.*

a genetically targeted drug to rely upon data and information previously developed by the same sponsor.”¹⁶⁷ Thus, a drug manufacturer for a genetic disease would be allowed to use their own data for people who have different mutations of the same disease. On February 9, 2016, the Senate Health, Education, Labor and Pensions Committee approved the bill as a standalone from the Cures Act.¹⁶⁸

Another important incentivizing proposal is the Advancing Hope Act of 2015 which would reauthorize, permanently, the Rare Pediatric Disease PRV and add new treatments for pediatric cancers and sickle cell diseases to the list of qualifying products.¹⁶⁹ The provisions of the Cures Act, if passed, are likely to encompass most of the changes of this bill.

V. REFORMING LEGISLATIVE INCENTIVE MECHANISMS THAT INNOVATE DRUG DEVELOPMENT

A. *Dissecting (and Improving) Current Legislation*

The rare pediatric priority review voucher program has been a success. The FDA has already approved six pediatric products with the designation.¹⁷⁰ The last approved product, Kanuma, is indicated for an extremely rare disease that affects only one to two in one million newborns.¹⁷¹ Some limitations exist, but the limitations are statutory and not inherent to the incentivizing mechanism. The sunset provision on the Rare Pediatric Disease Priority Review Voucher effectively enjoins the FDA from granting additional vouchers. Legislators realized the importance of the review program

^{167.} *Id.*

^{168.} Shannon Muchmore, *Senators Argue Mandatory NIH Funding in 21st Century Cures Companion Bills*, MODERN HEALTHCARE (Feb. 9, 2016), <http://www.modernhealthcare.com/article/20160209/NEWS/160209857>.

^{169.} Advancing Hope Act of 2015, H.R. 1537, 114th Cong. (2015).

^{170.} Alexander Gaffney, *Regulatory Explainer: Everything You Need to Know About the FDA’s Priority Review Vouchers*, REGULATORY AFFAIRS PROF’L SOC. (Nov. 3, 2016), <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers/>.

^{171.} *FDA Approves First Drug to Treat a Rare Enzyme Disorder in Pediatric and Adult Patients*, FDA (Dec. 8, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476013.htm> (“Patients with LAL deficiency, also known as Wolman disease and cholesteryl ester storage disease [CESD], have no or little LAL enzyme activity. . . [t]his results in a build-up of fats within cells.”)

and recently extended the program for six more months.¹⁷² However, it is uncertain whether Congress will permanently authorize the statute. Until then, drug manufacturers must weigh the risk that there will not be a final stopgap while expending resources on developing a pediatric product.

The Rare Tropical Disease Priority Review Voucher had significant limitations initially but congressional amendments rectified most concerns. The amendments allowed unlimited transfers of the voucher and a shorter notice period to the FDA. However, there are certain business risks when using a priority review voucher. An obvious risk is that the FDA does not have to approve a product that uses a voucher but only needs to make a decision within six months. In fact, in 2011, the FDA rejected the first drug application submitted through a priority voucher.¹⁷³ Another known limitation is that the six-month priority review period is not a guarantee by the FDA. The FDA's goal is to complete 90% of all priority reviews within six months, but for certain drugs, such as those affecting the nervous system, the timeframe is much longer.¹⁷⁴

Researchers are wary about entrepreneurs gaming the system by ushering an older drug quickly through the FDA approval process to obtain the voucher, then turning around and selling the voucher for a quick profit. Some commentators have found that Congress has fallen short of incentivizing "novel" therapies. The large drug manufacturers, raking in tens of billions of dollars in annual revenues, are not really incentivized to spend billions to develop a new drug for the value of a voucher. To the contrary, drug developers have won valuable vouchers by obtaining approval for older drugs that were used elsewhere.¹⁷⁵ If the rationale behind vouchers is improved patient access, the results are debatable. Final

¹⁷² Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 765, 129 Stat. 2242, 2286 (2015) ("Section 529(b)(5) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360ff(b)(5)) is amended by striking 'the last day' and all that follows through the period at the end and inserting 'September 30, 2016'.")

¹⁷³ Thomas M. Burton, *FDA Panel Votes Against Gout Drug*, WALL ST. J., (Jun. 22, 2011), <http://www.wsj.com/articles/SB10001424052702304887904576400062633107174>.

¹⁷⁴ *CNS Drugs Take Longer to Develop and Have Lower Success Rates than Other Drugs*, TUFTS CTR. FOR THE STUDY OF DRUG DEV. (Nov. 4, 2014), http://csdd.tufts.edu/news/complete_story/pr_ir_nov_dec_ir.

¹⁷⁵ Aaron S. Kesselheim, Lara R. Maggs & Ameet Sarpatwarl, *Experience With the Priority Review Voucher Program for Drug Development*, 314 JAMA 1687 (2015) (finding that when the FDA approved Knight Pharmaceutical's tropical disease voucher for miltefosine, the application was based on older studies of a drug originally used as a cancer treatment).

approval of a drug does not lead to affordable patient access because the legislation does not limit the cost of the drug once it is on the market.¹⁷⁶ Similarly, the recently reintroduced PATIENT Act poses a potential roadblock to innovation. While the Act has the right intent in supporting public health innovation, it might create a reverse incentive where companies provide little information in the beginning but obtain multiple approvals showing significant improvements and thus obtain exclusivity for their products.¹⁷⁷

The GAIN provisions aimed at incentivizing antibiotic development have significant limitations. First, no GAIN provisions encourage appropriate use of antibiotics to prevent bacterial resistance to newly developed products. Thus, GAIN can begin a vicious cycle of worsening antibiotic resistance that the Act was meant to address. The IDSA proposed a stewardship program during the enactment of the bill, but Congress failed to incorporate the proposals.¹⁷⁸ The recently proposed ADAPT Act, while strengthening GAIN, does not resolve this issue.

Not all Qualified Infectious Disease Products intended to treat qualifying infectious diseases are automatically eligible for qualifying product status. The provisions allow the FDA to define the eligible products to include only those intended to treat “serious or life-threatening infections.” Also, the GAIN Acts market exclusivity grants are not strong incentives for manufacturers because they have little effect on present day earnings. Additional earnings through longer market exclusivity are not realized until twenty to thirty years after expensive drug development efforts. However, the present-day expenses incurred to develop a new product are enormous.

During the congressional hearings on GAIN, the IDSA also noted that the FDA approval pathway for novel antibiotics should be simplified so the drug industry does not have a disincentive in unpredictable and costly antibacterial research. This robust approval pathway was mirrored in the ADAPT Act’s “LPAD” Pathway.

^{176.} *Id.* at 1688 (citing one approved drug that costs \$380,000 per year).

^{177.} Kurt Karst, *The PATIENT Act’s Proposed Exclusivity-Stacking Two-Year Extension: Is it an Incentive, a Reverse Incentive . . . or Both?*, FDA L. BLOG (Mar. 30, 2015), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/03/the-patient-acts-proposed-exclusivity-stacking-two-year-extension-is-it-an-incentive-a-reverse-incentive.html.

^{178.} Kevin Outterson, *All Pain, No GAIN: Need for Prudent Antimicrobial Use Provisions to Complement the GAIN Act*, ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, <http://www.tufts.edu/med/apua/news/news-newsletter-vol-30-no-1-4.shtml> (last visited Oct. 18, 2016).

B. Deciphering the 21st Century Cures Act's Legislative Patchwork

The 21st Century Cures Act is very promising, even when broken down into several smaller bills. The Act shows a distinct congressional plan in improving healthcare innovation. However, there are significant concerns with the Act. If the ultimate goal is to improve access, quality, and choice while reducing healthcare expenditures, parts of the Act are questionable. The Act proceeds with the assumption that FDA approval is the bottleneck for drug development. However, studies have shown that pace of FDA approvals are quickly improving.¹⁷⁹ Thus, legislators' concerns might be misplaced. Faster approval times can be dangerous because the FDA lacks strong post-market studies after a drug is approved.¹⁸⁰ A 2015 United States Government Accounting Office report on drug safety found that the agency itself lacked the system and resources to meet certain post-market safety reporting responsibilities and conduct systematic oversight.¹⁸¹ This lack of an effective monitoring system is especially important for drugs that use expedited pathways for approval.¹⁸²

One contested issue of the Cures Act is the use of biomarker¹⁸³ and surrogate data to determine efficacy of drug products in clinical

^{179.} See Alexander Gaffney, *Report Finds FDA Slow to Approve CNS Drugs, But Getting Faster*, REGULATORY AFFAIRS PROF'L SOC'Y (Nov. 5, 2014), <http://www.raps.org/Regulatory-Focus/News/2014/11/05/20689/Report-Finds-FDA-Slow-to-Approve-CNS-Drugs-But-Getting-Faster>; see also Brittany La Couture, *Introduction to the FDA Drug Approval Process and Off Label Use*, AM. ACTION FORUM (Oct. 22, 2015), <http://americanactionforum.org/research/primer-introduction-to-the-fda-drug-approval-process-and-off-labal-use>.

^{180.} See generally U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-16-192, DRUG SAFETY: FDA EXPEDITES MANY APPLICATIONS, BUT DATA FOR POSTAPPROVAL OVERSIGHT NEED IMPROVEMENT 22-29 (2015), <http://www.gao.gov/assets/680/674183.pdf>.

^{181.} *Id.*

^{182.} *Id.* at 29 ("FDA's monitoring efforts once drugs reach the market are particularly important for those drugs that have used certain expedited programs to reduce the development time before approval, where there may be greater potential for previously unrecognized safety issues to appear once a drug is more widely used."); see also Jeffrey Avorn & Aaron S. Kesselheim, *The 21st Century Cures Act – Will It Take Us Back in Time?* 372 NEW ENG. J. MED. 2473 (2015), <http://www.nejm.org/doi/full/10.1056/NEJMp1506964> (finding that more than two thirds of drugs are approved based on clinical studies lasting less than six months, a problem when the drug is to be taken chronically).

^{183.} There are many approved drugs that meet biomarker measures but do not correspondingly improve patient outcomes. For example, ezetimibe, a cholesterol lowering agent, is able to reduce body cholesterol but might not, by itself, correspondingly improve heart disease outcomes. See Binh An P. Phan,

trials. These non-traditional clinical endpoints increase the likelihood of finding false positives pointing to drug efficacy even when the drug does not improve patient outcomes.¹⁸⁴ Forcing the FDA to rely on biomarkers rather than actual patient outcomes further diminishes FDA standards when combined with less restrictive clinical studies.¹⁸⁵ For example, section 2062¹⁸⁶ of the Act allows the use of lower-quality evidence by the FDA, requiring the agency to develop a process to approve new uses for existing drugs on evidence based on “experience” and “registries” rather than randomized placebo-controlled trials. A safer and more cost-effective solution would be to improve the quality of predictive biomarkers by funding NIH research.

Another concern with the Cures Act is the suggested definition of “valid scientific evidence” required for medical device approval. Medical device sponsors would be able to rely on “well-documented case histories” in the expedited approval pathway.¹⁸⁷ Sponsors could also rely on data published in “peer-reviewed journals.”¹⁸⁸ However, since the “hard data” behind the publication are not submitted directly to the FDA, the law would require the FDA to submit a request to obtain that information.

Another major area of concern is the significant limitation the Act imposes on the FDA’s ability to monitor mobile health technologies. Mobile health apps are considered a “sleeping giant” in healthcare and have the potential to disrupt healthcare delivery.¹⁸⁹ However, certain mobile health apps are traditional medical devices that could pose serious risks to patients if they are not properly tested and regulated.¹⁹⁰ The FDA has been working closely with stakeholders for the last five years to delineate a workable risk-based classification system and regulatory mechanism.¹⁹¹ These amendments effectively wipe out these efforts and interrupt private-public engagement between the FDA and medical mobile app

Thomas D. Dayspring & Peter P. Toth, *Ezetimibe Therapy: Mechanism of Action and Clinical Update*, 8 VASCULAR HEALTH & RISK MGMT. 415, 419-424 (2012).

^{184.} *Id.*

^{185.} Avorn & Kesselheim, *supra* note 182, at 2474

^{186.} 21st Century Cures Act, H.R. 6, 114th Cong. § 2062 (2015).

^{187.} *Id.* § 2222

^{188.} *Id.*

^{189.} *See, e.g.*, ERIC TOPOL, THE CREATIVE DESTRUCTION OF MEDICINE: HOW THE DIGITAL REVOLUTION WILL CREATE BETTER HEALTH CARE (2012).

^{190.} *See generally* Kevin Khachatryan, *Medical Device Regulation in the Information Age: A Mobile Health Perspective*, 55 JURIMETRICS 477 (2015).

^{191.} *Id.*

manufacturers.¹⁹² For example, the FDA had deregulated medical device data systems (“MDDS”) in 2011 by changing these systems from class III to class I devices.¹⁹³ In 2014, the FDA decided that it would no longer regulate MDDS to help “encourage greater innovation in the development and maturation of these systems.”¹⁹⁴

Serious adverse effects will follow drugs rushed through the FDA approval process. Dangerous, but rare, side effects and important safety information are not revealed in limited clinical trials but take years of post-approval studies to identify. Thus, shortening the length of studies and reducing the required size of study participants can be deleterious to the FDA regulatory pathway leading to Black Box Warning “dilution” as the FDA attempts to address serious safety concerns post-hoc.

C. Congress Should Consider “Novel” Incentivizing Mechanisms in Healthcare

1. Tax Incentives

Congress has not amended the tax code to provide tax credits for drug developers since the Orphan Drug Act in 1983. But the economic incentives in the Act were a powerful stimulus for rare disease research. The Orphan Drug Act provides a 50% tax credit¹⁹⁵ for the “qualified” cost of conducting human clinical testing.¹⁹⁶ The credit covers “expenditures incurred during the clinical testing phases for orphan drugs being evaluated for their therapeutic potential.”¹⁹⁷ Congress made the tax credit permanent in 1997.¹⁹⁸

^{192.} FDA, MOBILE MEDICAL APPLICATIONS – GUIDANCE FOR INDUSTRY (2015), <http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf>.

^{193.} Bakul Patel, *FDA Encourages Medical Device Data System Innovation*, FDA: FDA VOICE (June 20, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/06/fda-encourages-medical-device-data-system-innovation>.

^{194.} *Id.*

^{195.} 26 U.S.C. § 45C (2015). To qualify for a tax credit, the clinical testing must: (1) meet the requirements for an investigation new drug under Federal Food, Drug, and Cosmetic Act §505(i); (2) be conducted by or on behalf of the taxpayer; (3) take into account the extent of how much the trials were for a rare disease or condition; and (4) occur before FDA approval but after FDA designation.

^{196.} Form 8820- Orphan Drug Credit, INTERNAL REVENUE SERV. (Dec. 2012), <https://www.irs.gov/pub/irs-pdf/f8820.pdf>.

^{197.} Enrique Seoane-Vazquez et al., *Incentives for Orphan Drug Research and Development in the United States*, 3 ORPHANET J. RARE DISEASES 33 (2008).

^{198.} Taxpayer Relief Act of 1997, Pub. L. 105-34, § 604, 111 Stat. 788, 863 (1997).

One tax credit proposed by the drug industry is the “Neglected Disease Tax Credit” which would provide a 50% tax credit for pre-clinical research expenses for neglected disease treatments.¹⁹⁹ The proposal defines a “Neglected Disease” as one of ten specific neglected diseases identified by the WHO.²⁰⁰ However, a workable statute would leave the definition of a “neglected disease” open to interpretation by the Secretary of the DHHS and would authorize a review mechanism at a defined frequency to reevaluate disease epidemiology. Thus, if a disease is no longer neglected it could be removed from the list.

A recently proposed legislation, the Reinvigorating Antibiotic and Diagnostic Innovation Act of 2015 attempts to use tax credits to bolster antibiotic research correspondingly with GAIN.²⁰¹ Similar to the Orphan Drug Act, this new legislation would amend the tax code to allow tax credits for 50% of the clinical testing expenses. To qualify, the clinical trial expenses must be related to (1) infectious disease products that are intended to treat a serious or life-threatening infection or a qualifying pathogen listed by the FDA as having the potential to pose a serious threat to public health; and (2) diagnostic devices that identify a serious or life-threatening bacterial infection within 4 hours.²⁰² This Act also allows transfers of unused tax credits to a “qualified diagnostics research taxpayer.”²⁰³

2. Prizes

The use of “prizes” as an inducement for innovation and research is widespread in many scientific fields.²⁰⁴ Both public

^{199.} Jason Chong, *Neglected Disease Drug Development: Incentives for Success*, BIOTECHBLOG, <http://www.biotechblog.com/2011/06/01/neglected-disease-drug-development-incentives-for-success/> (last visited Oct. 10, 2016).

^{200.} *Id.*

^{201.} Reinvigorating Antibiotic and Diagnostic Innovation Act of 2015, H.R. 3539, 114th Cong. (2015)

^{202.} *Id.* § 3-45T(d)(1).

^{203.} *Id.* § 3-45T(e). The Act defines a “qualified diagnostics research taxpayer” as a domestic corporation that derives income from “research or development on diagnostic tests used to identify or detect the presence, concentration or characteristics of a serious or life-threatening infectious disease or pathogen.”

^{204.} For a thorough history of innovation inducement prizes, see NAT’L RESEARCH COUNCIL OF THE NAT’L ACADS., INNOVATION INDUCEMENT PRIZES AT THE NATIONAL SCIENCE FOUNDATION (2007), <http://www.nap.edu/catalog/11816/innovation-inducement-prizes-at-the-national-science-foundation> (“[T]he U.S. Defense Advanced Research Projects Agency (DARPA) has sponsored a series of prizes awarded to teams that develop programmed land vehicles.”)

agencies and private sponsors have offered innovation inducement prizes as reward for specific challenges. Often, the prize is granted by a public agency sponsored with private funds.²⁰⁵ Congress has also entertained the use of prizes. The AMERICA Competes Act recognized Obama's "Strategy for American Innovation" and granted broad statutory authority to federal agencies in rewarding prize money.²⁰⁶ In September 2010, the U.S. General Services Administration launched challenge.gov which features specific challenges and prizes sponsored by various federal agencies.²⁰⁷

There are several advantages to prize incentives. Prizes attract a diverse competitor pool that is often different from the limited pool of researchers in a specific field. More importantly, the costs to the prize sponsor are concrete, yet the rewards could far outweigh investment. Also, research and development could be shifted from a governmental program to non-governmental organizations. To be sure, there are also certain limitations in using prizes in drug development. It is difficult to delineate the conditions necessary to win a prize in the healthcare field. A common endpoint, drug approval by the FDA, would be too burdensome for smaller firms. On the other extreme, mere identification of new chemical moieties would be too speculative. In such a scenario, prizes could be granted for molecules that would never be approved as drugs by the FDA. Thus, no public benefit with accrue. The National Science Foundation suggests that in specific fields it would be ideal to confer with scientists and "elicit from them desirable objectives for innovations that, if realized, could substantially advance nanotechnology applications."²⁰⁸

There are several ways to determine when a prize should be awarded. A common approach is the "first-to-succeed" prize offered to the first drug developer that achieves a certain goal. The Medical Innovation Prize Fund Act grants a prize to the "first person to

^{205.} *Id.* at 10 (describing the National Academy of Engineering's \$1 million prize, funded by a private party, for a team that can remove arsenic drinking water).

^{206.} Tom Kalil & Robynn Sturm, *Congress Grants Broad Prize Authority to All Federal Agencies*, THE WHITE HOUSE: WHITE HOUSE BLOG (Dec. 21, 2010, 5:24 PM), <https://www.whitehouse.gov/blog/2010/12/21/congress-grants-broad-prize-authority-all-federal-agencies>.

^{207.} OFFICE OF SCI. & TECH. POLICY, IMPLEMENTATION OF FEDERAL PRIZE AUTHORITY: PROGRESS REPORT 4 (2012), https://www.whitehouse.gov/sites/default/files/microsites/ostp/competes_report_on_prizes_final.pdf.

^{208.} NAT'L RESEARCH COUNCIL OF THE NAT'L ACADS., *supra* note 204, at 35-36 (discussing the importance of well-chosen objectives).

receive market clearance with respect to the drug or biological product.”²⁰⁹ The “Best Progress” award could be used to incentivize treatment improvement and help towards a specific treatment goal.

The idea to offer prizes for healthcare innovation has been discussed extensively by academia and often proposed in legislation.²¹⁰ In 2001, Eli Lilly created a company called InnoCentive to administer prizes to solve specific life science problems.²¹¹ Senator Bernard Sanders reintroduced a Medical Innovation Prize Fund Act in Senate in 2013. The proposal is based on the older Medical Innovation Prize Act of 2007 that failed because of the substantial cost to the government, projected to be around \$80 billion.

VI. CONCLUSION

Incentivizing drug and medical device development is a distinct congressional goal. Congress frequently introduces bills to alleviate drug development concerns in specific populations. Often, these legislators respond to political pressure from rare disease activist groups or scientific organizations. Congress has been very innovative in crafting specific solutions. Some of the bills have already made a significant difference in drug development. The true solution to the problem, however, seems to be a broader mechanism involving reduced regulatory barriers leading to drug approval and up-front financial incentives to innovators to reduce the bottleneck in innovation. However, when meeting these broad objectives, it is crucial that carefully devised FDA standards promoting safety are not dismantled without serious thought.

^{209.} The US Medical Innovation Prize Fund Act of 2007, S. 627, 113th Cong. (2013).

^{210.} See, e.g., *id.*; James Love & Tim Hubbard, *Prizes for Innovation in New Medicines and Vaccines*, 18 ANNALS HEALTH L. 155 (2009).

^{211.} *About Us*, INNOCENTIVE, <https://www.innocentive.com/about-innocentive> (last visited Oct. 28, 2016).