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## The 21st Century Cures Act: A Patient's Miracle or Demise?

Brittaney N. Edwards

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# The 21st Century Cures Act: A Patient’s Miracle or Demise?

**Brittaney N. Edwards**

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## I. INTRODUCTION

On December 13, 2016, Barack Obama signed the 21st Century Cures Act (Act) into law.<sup>1</sup> Congress designed the Act to expedite the U.S. Food and Drug Administration (FDA) approval process of pharmaceutical and medical device applications. Moreover, it intended the Act to increase patient access to innovative therapies.<sup>2</sup> Nevertheless, some stakeholders fervently contested the legislation.<sup>3</sup> In particular, many experts claimed that the Act's Title III provisions promoted evidentiary "shortcuts" that could cause the FDA to issue drug and device approvals based on insufficient data.<sup>4</sup>

In drug clinical trials, Title III allows researchers to use surrogate markers and real-world evidence.<sup>5</sup> For medical devices, Title III requires the FDA to exempt certain Class I and II devices from premarket review.<sup>6</sup> Moreover, Title III expands the FDA's obligation to approve all devices based on the least burdensome approach.<sup>7</sup> As a result, various experts believe that Title III advocates a less rigorous evidentiary standard that will erode the reliability and safety of FDA approved drugs and devices.<sup>8</sup>

This article analyzes the 21st Century Cures Act regarding its origin, clinical trial impact, and potential harms. Section II discusses the legislative history of the Act.<sup>9</sup> Section III explains the factors that caused the legislature to propose and adopt the Act.<sup>10</sup> Section IV discusses the FDA's basic drug and device approval process.<sup>11</sup> Section V analyzes the evidentiary changes that the Act makes to medical product development.<sup>12</sup> Section VI concludes that the 21st Century Cures Act may produce unanticipated harms.<sup>13</sup>

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<sup>1</sup> Joseph A. Goble, *The Potential Effect of the 21st Century Cures Act on Drug Development*, 24 J. MANAGED CARE SPECIALTY PHARMACY 677, 677 (2018). See *21st Century Cures Act*, Pub. L. No. 114-255, 130 Stat. 1033 (codified as amended in scattered sections of 21 U.S.C.).

<sup>2</sup> *21st Century Cures Act*, FDA (Jan. 31, 2020), <https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act>. See *21st Century Cures Act*, Pub. L. No. 114-255, 130 Stat. 1033 (codified as amended in scattered sections of 21 U.S.C.).

<sup>3</sup> Goble, *supra* note 1.

<sup>4</sup> *Id.*

<sup>5</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3011, § 507, 130 Stat. 1033, 1086 (2016) (codified as amended at 21 U.S.C. § 357); 21st Century Cures Act, Pub. L. No. 114-255, sec. 3022, § 505F, 130 Stat. 1033, 1096 (2016) (codified as amended at 21 U.S.C. § 355g).

<sup>6</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 3054, 130 Stat. 1033, 1126 (codified as amended in scattered sections of 21 U.S.C. § 360).

<sup>7</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 3058, 130 Stat. 1033, 1128–129 (codified as amended in scattered sections of 21 U.S.C. § 360).

<sup>8</sup> Stephen Barlas, *21st Century Cures Bill May Lead to Faster Drug/Device Approvals*, 42 PHARMACY & THERAPEUTICS 76, 76 (2017); see also Michael Gaybay, *21st Century Cures Act*, 52 HOSP. PHARMACY 264, 264 (2017) (expressing that health professionals are concerned that Title III "could result in approvals based upon lower quality data").

<sup>9</sup> See *infra* Section II.

<sup>10</sup> See *infra* Section III.

<sup>11</sup> See *infra* Section IV.

<sup>12</sup> See *infra* Section V.

<sup>13</sup> See *infra* Section VI.

## II. DEFINING THE 21ST CENTURY CURES ACT

### A. Legislative History

Public Law 114-255,<sup>14</sup> known as the 21st Century Cures Act,<sup>15</sup> was “one of the most-lobbied healthcare bills in recent history.”<sup>16</sup> The Bill prompted 400 organizations to hire more than 1,455 lobbyists,<sup>17</sup> and it yielded lobbying expenditures of “as much as half a billion dollars.”<sup>18</sup> Although the bill’s most prominent advocates were pharmaceutical manufactures,<sup>19</sup> its activists also included universities, medical schools, patient groups, and other related organizations.<sup>20</sup> By contrast, the Bill’s opponents were public interest groups, some liberal Democrats,<sup>21</sup> and some healthcare professionals.<sup>22</sup>

Supporters alleged that the proposed legislation “would ‘modernize’ the FDA[’s] . . . approval process” and accelerate “the delivery of cutting-edge, lifesaving medicines to patients.”<sup>23</sup> Conversely, opposers argued that the Bill’s provisions would weaken the FDA’s review standards and increase the risk of

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<sup>14</sup> Public laws are regulations that “affect society as a whole.” *Federal Register*, NAT’L ARCHIVES, <https://www.archives.gov/federal-register/laws> (last updated Dec. 28, 2017). Legal professionals cite public laws using “the abbreviation, Pub. L., the Congress number (e.g., 107), and the number of the law.” *Id.*

<sup>15</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 1000, 130 Stat. 1033, 1039 (2016) (stating that Division A of the act “may be cited as the ‘21st Century Cures Act’”).

<sup>16</sup> Sydney Lupkin, *Legislation That Would Shape FDA And NIH Triggers Lobbying Frenzy*, NPR (Nov. 25, 2016, 6:00 AM ET), <https://www.npr.org/sections/health-shots/2016/11/25/503176370/legislation-that-would-shape-fda-and-nih-triggers-lobbying-frenzy>.

<sup>17</sup> A lobbyist is an individual “who conducts activities [that are] aimed at influencing or swaying public officials and especially members of a legislative body on legislation.” *Lobbyist*, MERRIAM-WEBSTER, <https://www.merriam-webster.com/dictionary/lobbyist> (last viewed on Jan 1, 2020).

<sup>18</sup> Lupkin, *supra* note 16.

<sup>19</sup> Pharmaceutical companies employed most of the lobbyist that advocated the bill. *See* Sheila Kaplan, *Winners and losers of the 21st Century Cures Act*, STAT (Dec. 5, 2016), <https://www.statnews.com/2016/12/05/21st-century-cures-act-winners-losers/>; *see* Lupkin, *supra* note 16 (stating that AbbVie, a large pharmaceutical manufacture, spent \$7.7 million to support the bill, and that, Pharmaceutical Researchers of America (PhRMA), the leading pharmaceutical industry trade group, dedicated \$24.7 million of its \$30.3 million total lobbying expenditures to champion the bill).

<sup>20</sup> *See* Lupkin, *supra* note 16 (stating that “[h]ospitals and medical schools . . . supported the bill because the NIH funding could propel grants to medical and research institutions”); *see also* Barlas, *supra* note 8 (stating that the Advanced Medical Technology Association, the leading medical device trade group, supported the bill).

<sup>21</sup> William H. Manz, *21st Century Cures Act: A Legislative History of Public Law No. 114-255*, 1 WILLIAM S. HEIN & CO. INC. i, v (2018). Some public interest groups believed that the bill perpetuated “a trend of eroding standards at the Food and Drug Administration since the 1990s.” *Id.* (quoting Michael Carom, a Public Citizen member).

<sup>22</sup> *See* Robert M. Kaplan, *Is the 21st Century Cures Act a Solution or a Problem?*, THE REG. REV. (May 7, 2019), <https://www.theregreview.org/2019/05/07/kaplan-21st-century-cures-act/>.

<sup>23</sup> Trudy Lieberman, *With media watchdogs on the sidelines, pharma-funded advocacy groups pushed Cures Act to the finish line*, HEALTHNEWSREVIEW.ORG (Dec. 6, 2016), <https://www.healthnewsreview.org/2016/12/with-media-watchdogs-sidelined-pharma-funded-advocacy-groups-pushed-cures-act-to-the-finish-line/>. Fred Upton, a Republican congressman, asserted that the bill was ““an innovative game-changer and a truly once-in-a-generation opportunity to bring . . . [the U.S.] healthcare system light years ahead.” Manz, *supra* note 21.

harm to patients.<sup>24</sup> Many critics voiced “overarching concerns . . . that” pharmaceutical and medical device manufactures were “hijack[ing]”<sup>25</sup> the FDA’s duty to “ensur[e] the safety, efficacy, and security”<sup>26</sup> of new medical products.<sup>27</sup> Some of the Act’s challengers even likened portions of the law to “legaliz[e] fraud” that “undercut[] the development of real cures.”<sup>28</sup>

Despite its controversy, the Bill generated widespread bipartisan support,<sup>29</sup> and President Barack Obama signed the 21st Century Cures Act into law on December 13, 2016.<sup>30</sup> Because the FDA is in the early stages of implementing the Act’s requirements,<sup>31</sup> its impact on clinical trials, medical products, and patients are mostly unknown. As a result, it is imperative that regulators and the medical

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<sup>24</sup> See Kaplan, *supra* note 22.

<sup>25</sup> Reshma Ramachandran & Zachary Berger, *21st Century Cures Act will distort the meaning of ‘FDA approved’*, STAT (Dec. 1, 2016), <https://www.statnews.com/2016/12/01/21st-century-cures-act-fda-approval/>.

<sup>26</sup> *What We Do: FDA Mission*, FDA, <https://www.fda.gov/about-fda/what-we-do> (last updated Mar. 28, 2018).

<sup>27</sup> Ramachandran & Berger, *supra* note 25. Strong financial incentives likely drove the pharmaceutical and medical device industry to heavily lobby for the 21st Century Act. See Michelle Llamas, *21st Century Cures Act Benefits Big Pharma, Device Makers, Critics Say*, DRUGWATCH (Dec. 8, 2016), <https://www.drugwatch.com/news/2016/12/08/21st-century-cures-act-benefits-big-pharma/> (noting that the proposed legislation would save pharmaceutical and medical device manufactures “billions [of dollars] to bring new drugs and devices to market”).

<sup>28</sup> Manz, *supra* note 21, at vi (quoting Senator Elizabeth Warren); see Elizabeth Warren, delivering remarks on the 21st Century Cures Act (Nov. 28, 2016) (transcript available at <https://www.warren.senate.gov/newsroom/press-releases/senator-warren-delivers-remarks-on-the-proposed-21st-century-cures-bill>). Senator Elizabeth Warren and other opponents expressed strong disapproval about the portions of the Act that set less rigorous FDA approval standards, such as its provision that allows the FDA to approve the secondary use of a previously approved drug without requiring the manufacturer to “conduct[] a randomized clinical trial.” *Id.*

<sup>29</sup> Manz, *supra* note 21.

<sup>30</sup> Goble, *supra* note 1. The Energy and Commerce Committee, one of the oldest committees of the U.S. House of Representatives, introduced the initial draft of the 21st Century Cures Act as the “21st Century Cures Initiative” in April 2014. *About E&C*, HOUSE COMMITTEE ENERGY COM., <https://energycommerce.house.gov/about-ec> (last viewed Mar. 5, 2020); Kirsten Messmer & Robert Cumming, *21st Century Cures Act Innovation Breakthroughs, and Research in Under-Represented Populations*, THE EVIDENCE FORUM 1 (Nov. 2017), [https://www.evidera.com/wp-content/uploads/2017/10/02-21st-Century-Cures-Act-Innovation-Breakthroughs-and-Research\\_2017Nov.pdf](https://www.evidera.com/wp-content/uploads/2017/10/02-21st-Century-Cures-Act-Innovation-Breakthroughs-and-Research_2017Nov.pdf). Over a two-year period, the House of Representatives and the Senate negotiated a “bipartisan agreement to fund and accelerate cancer research and overall medical product discovery, development, and delivery (Division A, the 21st Century Cures Act); to help families in mental health crisis (Division B); and, to increase the choice, access, and quality in healthcare for Americans (Division C).” Messmer & Cumming, *supra*. Ultimately, the House and Senate voted in favor of the Act 392-26 and 94-5, respectively. Barlas, *supra* note 8.

<sup>31</sup> The 21st Century Act approves government funding to implement its provisions over a 10-year period. Margaret Rouse, *21st Century Cures Act*, TECHTARGET, <https://searchhealthit.techtargget.com/definition/21st-Century-Cures-Act> (last updated Feb. 2018); see *21st Century Cures Act*, *supra* note 2 (discussing the FDA’s 9-year work and implementation plan for the Act); see also 21st Century Cures Act, Pub. L. No. 114-255, §§ 1001–02, 130 Stat. 1033, 1040 (2016).

community reevaluate whether the Act will eviscerate the FDA approval process and disseminate harmful medical products to patients.<sup>32</sup>

## B. The Provisions & Purpose

The legislature designed the 21st Century Cures Act to expedite the FDA's approval of pharmaceutical and medical device applications, and it intended the Act to increase patient access to innovative therapies.<sup>33</sup> The Act contains the following three divisions: Division A (21st Century Cures Act)<sup>34</sup>;

<sup>32</sup> See Kaplan, *supra* note 22 (stating that the FDA developed “high standards” due to “terrible disasters such as thalidomide, diethylstilbestrol, and the Dalkon Shield intrauterine device[,]” and “the 21st Century Cures Act is deserving of . . . continu[ed] scrutiny” because it “lowers standards”).

<sup>33</sup> *21st Century Cures Act*, *supra* note 2. Congress defined the 21st Century Cures Act as a vehicle “[t]o accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.” 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat 1033 (codified as amended in scattered sections of 21 U.S.C.) (stating that the “short title” of Public Law 114-255 “may be cited as the ‘21st Century Cures Act’”); see Covington & Burling LLP, *21st Century Cures Act: Key Provisions (Title III - Development)*, COVINGTON 1 (Dec. 22, 2016), [https://www.cov.com/-/media/files/corporate/publications/2016/12/21st\\_century\\_cures\\_act\\_key\\_provisions\\_title\\_iii\\_development.pdf](https://www.cov.com/-/media/files/corporate/publications/2016/12/21st_century_cures_act_key_provisions_title_iii_development.pdf) (stating that “[t]he Act amends the Federal Food, Drug, and Cosmetic Act (“FDCA”) and Public Health Service Act (“PHSA”), among other laws, with the aim of accelerating the discovery, development, and delivery of new medicines and medical technologies”). The Act authorizes government spending of more than \$6.3 billion on medical research and development initiatives. Lisa Wesel, *\$6.3 Billion Approved for 21st Century Cures Act*, TRADELINE (Jan 1, 2017), <https://www.tradelineinc.com/reports/2017-1/63-billion-approved-21st-century-cures-act>. More specifically, the Act provides the FDA \$500 million to help it streamline its approval process. See 21st Century Cures Act, Pub. L. No. 114-255, § 1002, 130 Stat 1033, 1042 (2016); see also Wesel, *supra*. Moreover, the Act grants the National Institute of Health (NIH) \$4.8 billion to increase its grant distribution to research organizations. See 21st Century Cures Act, Pub. L. No. 114-255, § 1001, 130 Stat 1033, 1039 (2016); see also Wesel, *supra*. The NIH is “the nation’s medical research agency,” and it is a part of the U.S. Department of Health and Human Services. *Who We Are*, NAT’L INST. HEALTH, <https://www.nih.gov/about-nih/who-we-are> (last viewed on Oct. 20, 2019). The NIH “invests nearly \$41.7 billion annually in medical research for the American people,” and it distributes its funds to “more than 300,000 researchers at more than 2,500 . . . research institutions in every state.” *What We Do*, NAT’L INST. HEALTH, <https://www.nih.gov/about-nih/what-we-do/budget> (last updated June 29, 2020).

<sup>34</sup> Division A of the 21st Century Cures Act “provides funding for biomedical research—including the Precision Medicine Initiative (PMI) and the Cancer Moonshot Initiative—and for the opioid crisis response; modifies Food and Drug Administration (FDA) pathways for the approval of regulated medical products; and makes a number of reforms to the National Institutes of Health (NIH).” Amanda K. Sarata, *The 21st Century Cures Act (Division A of P.L. 114-255)*, CONG. RES. SERV. 1 (Dec. 23, 2016), <https://fas.org/sgp/crs/misc/R44720.pdf>. To support biomedical research, Division A granted the Precision Medicine Initiative, or the All of Us Program, \$1.455 billion “to gather data from ≥1 million people living in the United States to accelerate research and improve health by accounting for individual variations in lifestyle, environment, and biology.” Larry B. Goldstein, *Twenty-First Century Cures Act Semper Vigilans*, 49 *STROKE* 2555, 2555 (2018). In addition, Division A granted the Cancer Moonshot Initiative \$1.800 billion to prevent, detect, and “make more therapies available to more patients . . .” *Id.*

Division B (Helping Families in Mental Health Crisis)<sup>35</sup>; and Division C<sup>36</sup> (Increasing Choice, Access, and Quality in Health Care for Americans).<sup>37</sup>

Most experts agree that the Act's funding provisions are beneficial because they advance innovative research and mental health initiatives.<sup>38</sup> Nevertheless, numerous experts disagree about the aptness of the Act's other provisions.<sup>39</sup>

Most notably, Title III of Division A appears to be "the most controversial section of the Cures Act."<sup>40</sup> The Title III provisions "modernize regulations for new drug and device development . . . to streamline the . . . [FDA's] review of applications in a more 'industry-friendly' manner."<sup>41</sup> Some experts warn that the

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<sup>35</sup> Division B of the 21st Century Cures Act aids the "prevention, treatment, and recovery" of mental illness and substance abuse. 21st Century Cures Act, Pub. L. No. 114-255, Div. B, 130 Stat. 1033, 1202 (codified as amended in scattered sections of 42 U.S.C.). In relation, Division B addressed issues related to support initiatives, health care access, Medicaid Mental Health Coverage, HIPPA regulations, and the justice system. *Id.*

<sup>36</sup> Division C of the 21st Century Act addresses Medicare Part A, Medicare Part B, other Medicare provisions, and small employer health plan requirements. 21st Century Cures Act, Pub. L. No. 114-255, Div. C, 130 Stat. 1033, 1315 (codified as amended in scattered sections of 42 U.S.C.).

<sup>37</sup> Sarata, *supra* note 34. See Goldstein, *supra* note 34 (stating that the 311-page bill is composed of 3 divisions . . . 18 titles, and 23 subtitles).

<sup>38</sup> Messmer & Cumming, *supra* note 30; see Ramachandran and Berger, *supra* note 25 (stating that "[t]he legislation does include some redeeming features, such as increases in funding for the National institutes [*sic*] of Health and for addressing mental health and the opioid epidemic"); see also Goldstein, *supra* note 34 (stating that "[m]ultiple sections of the 21st Century Cures Act were causes for celebration," such as "funding for National Institutes of Health (NIH) Innovations projects"). But not all experts agree that the Act's funding provisions are beneficial. See Goble, *supra* note 1. Because the provisions transfer \$3.5 million of the Prevention and Public Health Fund's (PPHF) funding to the NIH, some experts believe that the provisions will impair the PPHF's "substantial" and "far reaching" work. *Id.*

<sup>39</sup> See Goble, *supra* note 1 (stating that the Act's controversial provisions "may lead to . . . serious unintended consequences"); see also Jessica K. Cohen, *21st Century Cures Act driving FDA changes*, MODERN HEALTHCARE (Sept. 7, 2019), <https://www.modernhealthcare.com/politics-policy/21st-century-cures-act-driving-fda-changes> (explaining that the central dispute about the Act is "[w]hether getting potentially life-saving treatments into the hands of patients is worth [the] possible safety risks associated with approving them more quickly").

<sup>40</sup> See Goble, *supra* note 1 (stating that "there is much controversy over" some of the Title III provisions because they "potentially diminish the robustness of the evidence base required for drug and medical device approvals"). See also Goldstein, *supra* note 34, at 2556 (stating that Title III of Division A "are among the law's more controversial provisions").

<sup>41</sup> Goble, *supra* note 1. Title III intends to advance medical product development through its "Subtitle A – Patient Focused Drug Development," "Subtitle B – Modern Trial Design and Evidence Development," "Subtitle – D Patient Access to Therapies and Information," "Subtitle – E Antimicrobial Innovation and Stewardship," "Subtitle – F Medical Device Innovations," and "Subtitle – G Improving Scientific Expertise and Outreach at the FDA." *Proposed FDA Work Plan for 21st Century Cures Act Innovation Account Activities*, FDA 13, <https://www.fda.gov/media/104756/download> (last viewed Mar. 5, 2019). For the drug development process, the most debated Title III provisions involve the "use of surrogate endpoints in clinical trials, modernization of clinical trial design, and use of real-world evidence for decision making." Goble, *supra* note 1.

Title III provisions introduce evidentiary “shortcuts” that may cause the FDA to issue drug and medical device approvals based on insufficient data.<sup>42</sup>

While many experts acknowledge that “expedited access to truly effective drugs may confer net benefits under these regulatory conditions,” Title III’s weak evidentiary requirements may lead to unexpected harms.<sup>43</sup> Thus, regulators and other stakeholders carefully evaluate the impact of certain Title III provisions.<sup>44</sup>

### III. FACTORS THAT PAVED THE WAY FOR THE ACT

It is vital to consider the factors that caused the legislature to create Title III to understand and evaluate its provisions. This section examines the factors that likely prompted the legislature to enact Title III. The relevant factors presumably were high research and development costs, burdensome medical device approvals, and lengthy drug approvals.

#### A. High Research and Development (R&D) Costs

Historically, medical product manufacturers paid high costs to fund their research and development (R&D) activities. The substantial R&D payouts diminished medical product manufacturers’ return on investment<sup>45</sup> and their capacity to research new products.<sup>46</sup>

In the pharmaceutical industry, drug R&D costs rose rapidly each year.<sup>47</sup> In 2003, it cost pharmaceutical manufacturers an average of \$1 billion to develop a single drug, including the cost of drug failures.<sup>48</sup> However, by 2013, the cost to

<sup>42</sup> Goble, *supra* note 1.

<sup>43</sup> *Id.* (footnotes omitted). See Goldstein, *supra* note 34, at 2556 (cautioning that a “less rigorous evaluation of new putative therapies could lead to the introduction of ineffective or hazardous treatment approaches”).

<sup>44</sup> See Goble, *supra* note 1 (stating “[w]hile many of the evidence evaluation provisions will take several years to implement, careful consideration must be given regarding the future of disease management in the United States”).

<sup>45</sup> “Return on investment (ROI) is a performance measure used to evaluate the efficiency of an investment” based on its costs. James Chen, *Return on Investment (ROI)*, INVESTOPEDIA, <https://www.investopedia.com/terms/r/returnoninvestment.asp> (last updated Apr. 27, 2020). To calculate ROI, use the following equation:  $ROI = \frac{\text{Current Value of the Investment} - \text{Cost of Investment}}{\text{Cost of Investment}}$ . *Id.*

<sup>46</sup> See Kenyon Farrow, *The 21st Century Cures Act’s “Pathway to Crisis” in Drug Safety*, TAGLINE 4 (Oct. 2015), <https://www.treatmentactiongroup.org/wp-content/uploads/2015/10/tagline-2015-October-Final.pdf> (explaining that shareholders are placing “greater pressure” on pharmaceutical manufacturers to “reduc[e] R&D costs” because it will allow “more drugs to [go to] market” and “boost company profits”).

<sup>47</sup> 2015 profile BIOPHARMACEUTICAL RESEARCH INDUSTRY, PHARMA 65 (Apr. 2015), [http://pharma-docs.pharma.org/sites/default/files/pdf/2015\\_pharma\\_profile.pdf](http://pharma-docs.pharma.org/sites/default/files/pdf/2015_pharma_profile.pdf).

<sup>48</sup> Thomas Sullivan, *A Tough Road: Cost To Develop One New Drug Is \$2.6 Billion; Approval Rate for Drugs Entering Clinical Development is Less Than 12%*, POL’Y & MED., <https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html> (last updated Mar. 21, 2019). See 2015 profile BIOPHARMACEUTICAL RESEARCH INDUSTRY, *supra* note 47. The average cost to develop one drug, including the cost of drug failures, was \$179 million in the 1970s, \$413 million in the 1980s, and \$1.0 billion in the early 2000s. *Id.* at 35. Regarding drug failures, only 12% of compounds would progress to Phase I of a clinical trial. *Id.* Moreover, even where the FDA approved a drug, only 2 out of 10 marketed drugs yielded revenue returns that equaled or

develop a drug rose to an average of \$2.6 billion.<sup>49</sup> Correspondingly, in 2014, PhRMA<sup>50</sup> members spent a total aggregate of approximately \$51.2 billion on R&D,<sup>51</sup> and their U.S. R&D expense comprised 23.4% of their U.S. sales.<sup>52</sup> According to Joseph A. DiMasi, the director of economic analysis at the Tufts Center for the Study of Drug Development, the rising R&D cost were primarily due to “increases in out-of-pocket costs for individual drugs and higher failure rates for drugs tested in human subjects.”<sup>53</sup>

Like pharmaceutical manufacturers, medical device manufacturers paid costly R&D expenses.<sup>54</sup> In 2012, the top 100 medical device companies spent over \$540 million on average for their R&D activities.<sup>55</sup> Moreover, many medical device manufacturers increased their R&D budget each year.<sup>56</sup> Between 2010 and

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exceeded their R&D costs. *Id.* at KEYFACTS 2015. Thus, approximately eighty percent of a pharmaceutical manufacturer's marketed drugs returned little to no profits.

<sup>49</sup> The \$2.6 billion figure included an “approximate average out-of-pocket cost of \$1.4 billion” and an opportunity cost of \$1.2 billion to bring a drug to market. Sullivan, *supra* note 48; see Sammy Almashat, *Pharmaceutical Research Cost: The Myth of the \$2.6 Billion Pill*, PUBLICCITIZEN (Sept. 1, 2017), <https://www.citizen.org/news/pharmaceutical-research-costs-the-myth-of-the-2-6-billion-pill/> (explaining that the \$2.6 billion average represented a manufacturer's actual cost of \$1.4 billion to develop a drug and its opportunity cost of \$1.2 billion to “forg[o] investments with annual returns of 10.5%”); see also Richard Harris, *R&D Costs For Cancer Drugs Are Likely Much Less Than Industry Claims, Study Finds*, NPR (Sept. 11, 2017), <https://www.npr.org/sections/health-shots/2017/09/11/550135932/r-d-costs-for-cancer-drugs-are-likely-much-less-than-industry-claims-study-finds> (discussing how some consumer advocacy groups believed that it cost pharmaceutical manufacturers significantly less than \$2.6 billion to develop a drug, but industry participants strongly disagreed with the consumer groups because the heightened cost of drug failures drastically raised the cost of drug R&D activities). According to experts, it cost drug manufacturers an additional \$312 million to perform post-approval R&D, meaning that the total R&D cost of each approved drug was around \$3 billion. Sullivan, *supra* note 48.

<sup>50</sup> Pharmaceutical Research and Manufacturers of America (PhRMA) is a trade group that “represents the country's leading innovative biopharmaceutical research companies.” *About*, PhRMA, <https://www.phrma.org/About> (last viewed Mar. 5, 2020).

<sup>51</sup> 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47. As a group, PhRMA members spent \$41.1 billion in the United States and \$10.1 billion abroad on R&D in 2014. *Id.* Between 2010 and 2014, PhRMA members collectively spent over two hundred billion dollars on R&D investments in the U.S. and abroad. *Id.*

<sup>52</sup> *Id.* at 66. According to PhRMA, “[t]he pharmaceutical industry is one of the most research-intensive industries in the United States,” and “[p]harmaceutical firms invest as much as five times more in research and development, relative to their sales, than the average US manufacturing firm.” *Id.* at 36 (citing *Research and Development in the Pharmaceutical Industry*, CONGRESSIONAL BUDGET OFFICE (Oct. 2006), <https://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/76xx/doc7615/10-02-drugr-d.pdf>). As a collective, PhRMA members' overall R&D expense totaled \$1.9 billion in 1980, \$8.4 billion in 1990, \$26.0 billion in 2000, and \$50.7 billion in 2010. *Id.*

<sup>53</sup> Sullivan, *supra* note 48. DiMasi explained that “increased clinical trial complexity, larger clinical trial sizes, higher cost of inputs . . . greater focus on . . . chronic and degenerative diseases, changes in protocol design . . . and testing on comparator drugs,” likely led to rising put-of-pocket costs. *Id.*

<sup>54</sup> *Medical device companies: Who spends the most on R&D?*, MASSDEVICE (Aug. 14, 2012), <https://www.massdevice.com/medical-device-companies-who-spends-most-rd/>.

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

2011, St. Jude Medical, Coviden, and Stryker spent an additional \$74 million, \$107 million, and \$68 million on their R&D investments respectively.<sup>57</sup>

It is reasonable to conclude that high R&D costs can limit pharmaceutical and medical device manufacturers' financial resources and innovation. Fortunately, Title III accelerates medical product development, and it leads to lower R&D costs.<sup>58</sup> Arguably, the lower R&D costs could benefit public health because it could lead to more innovative products. However, stakeholders must consider whether a shorter R&D process could compromise the quality of medical products and risk the welfare of patients.

## B. Burdensome Medical Device Approval Process

Before the 21st Century Cures Act, medical device approval was time-consuming and costly. It took medical device manufacturers an average of three to seven years to bring “new medical devices from concept to market.”<sup>59</sup> Moreover, it cost manufacturers \$32 million on average to “develop[] and get[] a medical device to market.”<sup>60</sup> Unsurprisingly, most of the cost was related to the FDA's approval requirements.<sup>61</sup> According to experts, some medical devices generated higher costs than others.<sup>62</sup> A study revealed that the FDA took 7.2

<sup>57</sup> *Id.*

<sup>58</sup> See *21st Century Cures Act*, *supra* note 2 (noting that the legislature intended the Act to accelerate the discovery, development, and approval stages of R&D); see also Scott Gottlieb, *Implementation of the 21st Century Cures Act: Progress and the Path Forward for Medical Innovation*, FDA (Dec. 6, 2017), <https://www.fda.gov/news-events/congressional-testimony/implementation-21st-century-cures-act-progress-and-path-forward-medical-innovation-12062017-12062017> (explaining that Title III allowed the FDA to exempt numerous medical devices from its 510(k) review pathway as “to decrease regulatory burdens . . . and reduce the costs of innovation”).

<sup>59</sup> Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices*, 1 JACC: BASIC TRANSLATIONAL SCI. 277, 277 (2016). The average time to bring a medical device to market spans the manufacturer's conception of the device to the FDA's approval for the manufacturer to market the device. *Id.*

<sup>60</sup> See Richard Williams, *Maze of FDA Regulations Slows Medical Innovation to a Crawl*, MERCATUS CTR. (Oct. 21, 2015), <https://www.mercatus.org/publications/regulation/maze-fda-regulations-slows-medical-innovation-crawl> (stating that manufacturers paid \$24 million on average “to deal with the FDA's requirements,” and the \$24 million constituted “75 percent of the overall cost” to bring a device to the market).

<sup>61</sup> *Id.* User fees are one of the FDA's various approval requirements. *Medical Device User Fee Amendments (MDUFA)*, FDA, <https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa> (last updated Aug. 4, 2020). The Center for Devices and Radiological Health (CDRH), an FDA subsidiary, performs the premarket review of most medical devices. Judith A. Johnson, *FDA Regulation of Medical Devices*, CONGRESSIONAL RESEARCH SERVICE 1, 1 (Sept. 14, 2016) <https://fas.org/sgp/crs/misc/R42130.pdf>. “[C]ongressional appropriations and user fees collected from device manufacturers” fund the CDRH's operations. *Id.* A standard user fee can cost \$4,603 to \$340,995 per medical device application depending on the application type. *Medical Device User Fee Amendments (MDUFA)*, *supra*. In 2016, the FDA collected \$134 million in medical device use fees. *HHS FY 2016 Budget in Brief – FDA*, DEP'T OF HEALTH & HUMAN SERVS. <https://www.hhs.gov/about/budget/budget-in-brief/fda/index.html> (last updated Feb. 13, 2015). The fees constituted approximately 30% of its medical device fiscal year budget. *Id.*

<sup>62</sup> Michael Blanding, *New Medical Devices Get To Patients Too Slowly*, HARV. BUS. SCH. (Aug. 10, 2015), <https://hbswk.hbs.edu/item/new-medical-devices-get-to-patients->

months longer to approve some “first mover” devices compared to “follow-on” devices, and the delay added \$6.7 million to these manufacturers’ costs.<sup>63</sup> Many experts claimed that the FDA had an “obsolete regulatory framework” that made the medical device approval process “slow, expensive, [and] uncertain.”<sup>64</sup>

As a remedy, Title III requires the FDA to use the “least burdensome” evidentiary standards to simplify the medical device approval process.<sup>65</sup> Conceivably, less onerous evidentiary standards could accelerate approval times, reduce development costs, and incentivize medical device development.

However, a closer analysis cautions against the FDA using lower evidentiary standards for medical device approvals. Even before the Act, the FDA used minimalistic criteria<sup>66</sup> to approve medical devices. Therefore, the Act’s lower review standards could lead to poor quality assurance and more dangerous products.

### C. Long Drug Approval Process

In the past, a potential new medicine underwent a “lengthy, complicated, multistep process” that “continue[d] even after” it received FDA approval.<sup>67</sup> As a result, drug manufacturers spent more than 10 years to develop a new drug,<sup>68</sup> increasing their development costs and limiting their ability to pursue new projects.

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<sup>63</sup> *Id.* According to a study, novel high-risk devices “in any given category . . . took on average 34 percent longer to be approved than the next device in that category.” *Id.*

<sup>64</sup> Williams, *supra* note 60. Due to the unique features of different medical devices, “including how they work, how they are applied to the patient, and how their effectiveness is measured,” the FDA spent a significant amount of time creating testing criteria for “each new device.” Blanding, *supra* note 62. Moreover, the FDA had administrative tasks that slowed its review of medical devices. Stephen Barlas, *Critics Assail FDA Medical Device Approval Process*, 36 P&T 395, 395 (2011). Because the Medical Device Amendments of 1976 “required the FDA to categorize all medical devices into Class I, II, or III” designations, the FDA struggled to classify and reapprove 140 “pre-amendment” devices.” *Id.* Similarly, the FDA struggled to approve some recent products in a timely manner. *See* Williams, *supra* note 60 (stating that the FDA did not approve three devices that were submitted in 1998 until 2007); *see also* Blanding, *supra* note 62 (noting that the FDA approved the Edwards Lifescience’s transcatheter heart valve four years after the European Union approved the device, making the United States “the 40<sup>th</sup> country to do so”).

<sup>65</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3058, § 513, 130 Stat. 1033, 1128–29 (2016) (codified as amended in scattered sections of 21 U.S.C. 360).

<sup>66</sup> *See infra* Section III.

<sup>67</sup> 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 37.

<sup>68</sup> *Id.* at 35. The time to develop a drug spans from when the drug is “identified to when it receive[d] approval from the US Food and Drug Administration (FDA).” *Id.* Similarly, an article reported that the average time “from preclinical testing in animal models to approval of a new drug in the United States takes 12 to 16 years.” Goldstein, *supra* note 34, at 2556. Furthermore, PhRMA reported that clinical research was becoming more complex due to clinical trial regulations increasing patient enrollment criteria, the number of “site visits and procedures,” the length of clinical trials, and the quantity of data collection. 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 42. With respect to increased data collection, the form that researchers use to collect data “expanded in length by 227% between 2000 and 2011, reflecting the growing challenges of conducting clinical trials.” *Id.*

In response, Title III requires the FDA to accept drug applications based on surrogate markers<sup>69</sup> and real-world evidence,<sup>70</sup> as opposed to conventional RCT evidence.<sup>71</sup> Plausibly, surrogate markers and real-world evidence could hasten the approval process because their evidentiary burdens are less rigorous and time-consuming compared to RCT evidence.<sup>72</sup>

Nevertheless, non-RCT evidence could erode the reliability of a drug's clinical trial data.<sup>73</sup> Traditionally, the robust drug development process<sup>74</sup> has required RCT evidence because it is more scientifically stringent, and it safeguards the integrity of clinical data.<sup>75</sup> Because alternative evidentiary standards could be less reliable, surrogate markers or real-world evidence could force the FDA to make its drug approvals based on inaccurate clinical data.

#### IV. FDA APPROVAL PROCESS AND PRIOR EVIDENTIARY STANDARDS

##### A. Medical Device Approval

###### 1. Medical Device Classification

Unlike new pharmaceuticals, not all new medical devices have received clinical testing.<sup>76</sup> Instead, the FDA has used a risk classification scheme to determine whether a medical device requires clinical testing.<sup>77</sup> The FDA has

<sup>69</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3011, § 507, 130 Stat. 1033, 1086–91 (2016) (codified as amended in scattered sections of 21 U.S.C. 357).

<sup>70</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3022, § 505F, 130 Stat. 1033, 1096–98 (2016) (codified as amended in scattered sections of 21 U.S.C. 355(g)).

<sup>71</sup> RCT refers to a randomized control trial (RCT). See Ted J. Kaptchuk, *The double-blind, randomized, placebo-controlled trial*, 54 J. CLINICAL EPIDEMIOLOGY 541, 541 (2001) (stating that RCTs are the golden standard of scientific evidence because it protects against biased data).

<sup>72</sup> See Matthew Herper, *Attempt to replicate clinical trials with real-world data generates real-world criticism, too*, STAT (July 3, 2019), <https://www.statnews.com/2019/07/03/replicate-clinical-trials-real-world-evidence/> (explaining that a researcher replicated the results of a RCT trial using real-world “data from insurance databases to monitor a heart drug’s safety,” and it “cut the time to get data in half – at a considerably lower cost” compared to the RCT); see also *21st Century Cures Act*, *supra* note 2 (noting that the legislature designed the Act to accelerate the discovery, development, and approval stages of R&D).

<sup>73</sup> According to one expert, non-RCT evidence is not “useless as a hypothesis-generating approach” but “it is certainly not something that ought to be used for regulatory decisions” or “clinical decisions.” Matthew Herper, *supra* note 72 (quoting Dr. Steven Nissen, a leading cardiologist at the Cleveland Clinic). Similarly, another expert cautioned that non-RCT evidence is more prone to bias, and he considered it risky to “to supplant [RCT evidence because it] . . . has really generated huge amounts of important data.” *Id.* (quoting Dr. David Nathan, the director of the Diabetes Center and Clinical Research Center at Massachusetts General Hospital).

<sup>74</sup> See *infra* Section III.

<sup>75</sup> Kaptchuk, *supra* note 71.

<sup>76</sup> *Considerations for the Design and Execution of Medical Device Trials*, PREMIER RES. (July 3, 2018), <https://premier-research.com/blog/perspectivesmedical-devices-vs-drug-trials/>.

<sup>77</sup> *Id.*

categorized medical devices into Class I,<sup>78</sup> II,<sup>79</sup> and III<sup>80</sup> designations.<sup>81</sup> The class type has “define[d] the regulatory requirements,” and the “[r]egulatory control

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<sup>78</sup> Class I devices represent low-risk products. *US FDA Medical Device Classification*, EMERGO, <https://www.emergobyul.com/services/united-states/fda-device-classification> (last viewed Mar. 5, 2020). The FDA refers to Class I requirements as “general controls.” *Id.* Class I devices include simple products, such as “adhesive bandages, scalpels, and manual stethoscopes.” *Id.* The FDA alleges that Class I products “must be suitable for their intended use, be adequately packaged and properly labeled, and be manufactured under a “quality system,”” but some experts contend that Class I oversight is minimal and functions more like a “self-registration process.” *Why ‘Approved’ Medical Devices in the U.S. May Not Be Safe or Effective*, HEALTHNEWSREVIEW.ORG <https://www.healthnewsreview.org/toolkit/tips-for-understanding-studies/medical-devices/> (last viewed Mar. 5, 2020). The FDA allows a manufacturer to register most Class I devices without FDA clearance. *US FDA Medical Device Classification*, *supra*. According to the FDA, “35% of medical device types are Class I[,] and . . . 93% of these are exempt from pre-market review.” Bennett Napier, *FDA and Dental Products*, NAT’ ASS’N DENTAL LABORATORIES (May 14, 2020), <https://dentallabs.org/fda-and-dental-products/#:~:text=Class%20I%20%E2%80%93%20These%20are%20devices,exempt%20from%20pre%20market%20review.&text=Class%20III%20%E2%80%93%20These%20are%20devices,risk%20of%20illness%20or%20injury>.

<sup>79</sup> Class II devices represent medium-risk products, and the FDA refers to Class II requirements as “special controls.” *US FDA Medical Device Classification*, *supra* note 78. Class II devices are more complex devices, such as “endoscopes, powered wheelchairs, syringes, and total joint implants,” and their misuse or malfunction may cause medium harm. *Id.* According to the FDA, “53% of device types” are Class II devices, and “[m]ost require FDA review through premarket notification (510(k)).” *Are Medical Device Manufacturers Risking Your Safety?*, WATER KRAUS & PAUL (May 16, 2019), <https://www.waterskraus.com/medical-device-manufacturers-risking-safety/>; *see US FDA Medical Device Classification*, *supra* note 78 (stating that “[s]ome Class II devices only need to be registered, but many require [FDA] clearance”). A 510(k) clearance, or a Premarket Notification (PMN), refers to Section 510(k) of the FDCA, and it allows the FDA to clear a device without any “evidence of [its] safety or efficacy” where a manufacturer claims that its device is “substantially equivalent” to an existing device on the market. *Why ‘Approved’ Medical Devices in the U.S. May Not Be Safe or Effective*, *supra* note 78.

<sup>80</sup> Class III devices represent high-risk products, and the FDA explains that “[t]hese devices usually sustain or support life, are implanted, or present potential high risk of illness or injury.” *Learn if a Medical Device Has Been Cleared by FDA for Marketing*, FDA (Dec. 29, 2017), <https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing>. Class III devices are sophisticated devices, such as “implantable pacemakers and breast implants.” *Id.* Only nine percent of all devices are Class III, and the FDA must review the devices “through [the] premarket approval (PMA) or humanitarian device exemption (HDE)” pathway. *Are Medical Device Manufacturers Risking Your Safety?*, *supra* note 79.

<sup>81</sup> *Overview of Device Regulation*, FDA, <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation> (last viewed Mar. 5, 2020).

[has] increase[d] from Class I to Class III.”<sup>82</sup> In the United States, the FDA only has required Class III devices<sup>83</sup> to undergo clinical testing.<sup>84</sup>

As a result, the FDA has not subjected a significant number of medical devices to rigorous review.<sup>85</sup> Before Title III, the FDA exempted “[a]round three-fourths of Class I devices, and a small percent of Class II devices” from “safety . . . efficacy, . . . [and] clinical trial” testing.<sup>86</sup> Moreover, where the FDA did not exempt Class I or II devices, it often approved the products based on weak clinical evidence.<sup>87</sup> As a result, the FDA only restricted its “most stringent” approval process to all Class III devices.<sup>88</sup> But even many Class III devices escaped thorough review because they were pre-amendment devices<sup>89</sup> or other devices that had a “less rigorous” approval process.<sup>90</sup>

<sup>82</sup> *Id.*

<sup>83</sup> Before 1976, medical devices were predominately unregulated “and the vast majority were not subject to any premarket review.” Jonas Z. Hines et. al., *Left to Their Own Devices: Breakdowns in United States Medical Device Premarket Review*, 7 PLOS MED. 1, 1 (2010); see Benjamin N. Rome et. al., *Approval of High-Risk Medical Devices in the US: Implications for Clinical Cardiology*, 16 CURRENT CARDIOLOGY REP. 489, 491 (2014) (explaining that “medical devices had no official premarket requirements and were subject to state-level oversight via consumer-protection statutes” before the MDA). Congress passed the Medical Device Amendments (MDA) of 1976 “to prevent the distribution of dangerous and ineffective devices by creating a . . . premarket review mechanism.” Hines et. al., *supra*. The MDA required the FDA to classify devices according to their risk and to use premarket approval (PMA) for the most dangerous devices. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 470 (1996). Despite Class III devices representing the highest risk, many Class III devices did not receive PMA. *Medtronic, Inc.*, 518 U.S. at 470. Before the MDA, medical device manufacturers placed over 1,700 kinds of devices into commercial distribution, and it was unreasonable for the manufacturers to withdraw the devices from the market. Hines et. al., *supra* at 5. As a result, Congress “allow[ed] pre-1976 devices to remain on the market without FDA approval until the requisite . . . [review was] completed.” *Medtronic, Inc.*, 518 U.S. at 470. Thus, around 140 pre-amendment devices remained on the market until the FDA “finalized a rule calling for a PMA application for that type of device.” Hines et. al., *supra* at 5. The MDA also allowed devices that were “‘substantially equivalent’ to preexisting [Class III] devices to avoid the PMA process until the FDA initiated the [review] process for the underlying device.” *Medtronic, Inc.*, 518 U.S. at 470; see *515 Program Initiative*, FDA, <https://www.fda.gov/about-fda/cdrh-transparency/515-program-initiative> (last updated Dec. 19, 2017) (acknowledging that the “FDA regulated over 170 Class III device types through the 510(k) program” after the MDA). Although all Class III devices would *eventually* receive PMA, the FDA failed to publish a CFR to establish a PMA requirement for numerous Class III devices over the decades. *515 Program Initiative*, *supra*. In 2019, three percent of pre-amendment devices remained unclassified as Class I, II, or III altogether. *Are Medical Device Manufacturers Risking Your Safety?*, *supra* note 79. Consequently, numerous Class III devices on the market lacked PMA. *Id.*

<sup>84</sup> Rome et. al., *supra* note 83; see Norman, *supra* note 59, at 278 (stating that “Class I and II devices” have a “less stringent regulatory processes than Class III devices”).

<sup>85</sup> Norman, *supra* note 59, at 278.

<sup>86</sup> *Id.*

<sup>87</sup> *Id.*

<sup>88</sup> *Are Medical Device Manufacturers Risking Your Safety?*, *supra* note 79. The most rigorous medical device approvals require clinical trials. Norman, *supra* note 59, at 278.

<sup>89</sup> See, *supra* note 83.

<sup>90</sup> Norman, *supra* note 59, at 278. Where a Class III device had a predicate, it could “generally be approved by [a] less rigorous . . . process.” *Id.* A predicate referred to a device that had “only minor” differences compared to a new device. *Id.* Where a new medical device did *not* have a

Regulators and stakeholders must examine the FDA's prior review standards to meaningfully evaluate the changes that Title III has made to medical device approvals. This section provides a comprehensive overview of the FDA's approval process leading up to Title III. For non-exempt devices, the basic approval applications were the 510(k) Premarket Notification (PMN) Pathway, Humanitarian Device Exemption (HDE) Pathway, or Premarket Approval (PMA) Pathway.<sup>91</sup>

## 2. 510(k) Premarket Notification (PMN)

Premarket Notification (PMN) was an expedited clearance<sup>92</sup> pathway that required its applicants to “show[] that [their] device [was] substantially equivalent<sup>93</sup> to an existing device that . . . already” received FDA clearance or approval.<sup>94</sup> Where the FDA determined that a PMN device was substantially equivalent to its predicate, it cleared the device for commercial distribution.<sup>95</sup>

Although PMN featured mostly moderate risk and some high-risk devices,<sup>96</sup> the FDA typically did not require the devices to demonstrate “direct

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predicate, it received a Class III designation automatically. *Id.* Nevertheless, an applicant could ask the FDA to reclassify a new device to Class I or II. *Id.* If the FDA reclassified a Class III device, it called the device a de novo device. *Id.* Like Class III devices that had a predicate, the FDA subjected de novo devices to “a less rigorous [review] process.” *Id.*

<sup>91</sup> *Id.*

<sup>92</sup> According to the FDA, a manufacturer had to have the FDA clear or approve their device to legally market or sell it in the United States “unless it [was] . . . exempt.” See *Premarket Notification 510(k)*, supra note 95. FDA clearance referred to PMN devices that the FDA considered “substantially equivalen[t] to another legally U.S. marketed device.” *Id.* By contrast, FDA approval referred to PMA or HDE devices that the FDA found to have met particular safety or efficacy standards. Tom Rish, *How FDA Distinguishes Between Clearance vs. Approval vs. Granted*, GREENLIGHT GURU (Nov. 3, 2020), [https://www.greenlight.guru/blog/fda-clearance-approval-granted#:~:text=Clearance%3A%20When%20a%20medical%20device,rigorous%20review%20and%20approval%20process.&text=This%20is%20a%20relatively%20new%20term%20in%20the%20FDA%20lexicon](https://www.greenlight.guru/blog/fda-clearance-approval-granted#:~:text=Clearance%3A%20When%20a%20medical%20device,rigorous%20review%20and%20approval%20process.&text=This%20is%20a%20relatively%20new%20term%20in%20the%20FDA%20lexicon.). See *PMA Approvals*, FDA, <https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals> (last updated Aug. 24, 2018); see also *HDE Approvals*, FDA, <https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/hde-approvals> (last updated Aug. 24, 2018).

<sup>93</sup> A new device was substantially equivalent to a predicate device if “[i]t [had] the same intended use as the predicate device,” and it either had “the same technological characteristics” or the same safety and efficacy profile as the predicate device. Elaine Silvestrini, *FDA 510(k) Clearance – Dangerous Fast-Track Approval Process*, <https://www.drugwatch.com/fda/510k-clearance/> (last updated May 14, 2019).

<sup>94</sup> Norman, supra note 59, at 280 (explaining that PMN was “a fast-track process for devices” that had “an acceptable predicate”); see Corinna Sorenson & Michael Drummond, *Improving Medical Device Regulation: The United States and Europe in Perspective*, 92 MULTIDISCIPLINARY J. POPULATION HEALTH & HEALTH POL’Y 114, 125 (stating that the FDA intended PMN to accelerate the approval of “devices deemed substantially equivalent to devices previously cleared by the FDA”); see also Silvestrini, supra note 93 (emphasizing that the PMN pathway allowed companies “to fast-track product development without having to go through expensive and time-consuming testing and clinical trials”).

<sup>95</sup> *Premarket Notification 510(k)*, FDA, <https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k> (last updated Mar. 13, 2020). Where the FDA found a PMN device was not substantially equivalent to its predicate, the device had to enter the FDA's most stringent approval pathway. Norman, supra note 59 at 280.

<sup>96</sup> Most PMN approvals were Class II devices, but PMN approvals also included some Class I and III devices. See Johnson, supra note 61, at 20 (revealing that PNM approvals were more than

evidence of [their] safety and effectiveness.”<sup>97</sup> As a matter of fact, the FDA cleared PMN devices even where their predicate was another PMN device or a voluntarily recalled device.<sup>98</sup> More disturbingly, 21 CFR § 807.78 clarified that PMN clearance did “not in any way denote official approval of . . . [a] device.”<sup>99</sup> Instead, PMN clearance only indicated that the FDA considered the device “no less safe and no less effective than a predicate.”<sup>100</sup>

Various experts feared that the FDA used PMN to clear “too many high-risk devices.”<sup>101</sup> Indeed, ninety-five to ninety-eight percent of marketed devices were PMN devices in the United States.<sup>102</sup> From 2004 to 2014, the FDA only subjected a mere two percent of devices to its most demanding review standards.<sup>103</sup> Correspondingly, the United States Government Accountability Office (GAO) reported that more than twenty percent of Class III devices received PMN clearance.<sup>104</sup> Furthermore, the FDA gave numerous high-risk devices, like implantable products, a Class II classification despite their potential danger.<sup>105</sup>

Correspondingly, some PMN approvals led to harmful results and device withdrawals.<sup>106</sup> In 2008, DePuy ASR XL Acetabular Cup System (ASR XL), a Class III metal-on-metal hip implant device, received PMN approval.<sup>107</sup> ASR XL’s predicates dated “back more than five decades” over “a total of 95 different devices,” and none of the predicates had all of the device’s characteristics.<sup>108</sup> Several of the ASR XL’s metal-on-metal predicates did not closely resemble its

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eighty percent Class II devices, around ten percent Class I devices, and less than five percent Class III devices between 1996 and 2009).

<sup>97</sup> Sorenson & Drummond, *supra* note 94. “[O]nly 10% to 15% of [PMN] submissions contain[ed] any clinical data.” *Id.*; see Silvestrini, *supra* note 93 (stating that PMN did not require a device to undergo “clinical trials and testing”); see also Norman, *supra* note 59, at 280 (emphasizing that countless years could lapse “between . . . [a] current device . . . and the clinical evidence supporting it” because old PMAs could support “a series of similar devices”). Its weak evidentiary requisites seem to bolster the argument that PMN did not evaluate whether a “product [was] safe or effective;” instead, “it just agree[ed] with the maker’s claim that the device [was] similar” to a predicate. Silvestrini, *supra* note 93.

<sup>98</sup> See Sorenson & Drummond, *supra* note 94; Silvestrini, *supra* note 93 (revealing that the FDA to accepted PMN predicates that it “never determined . . . [were] safe,” and predicates that it knew were defective); see also Brent M. Ardaugh et. al., *The 510(k) Ancestry of a Metal-on-Metal Hip Implant*, 368 NEW ENG. J. MED. 97, 98 (2013) (explaining that voluntarily recalled devices could serve as a predicate “as long as the FDA did not formally remove these devices from the market or a court did not find them adulterated or misbranded”).

<sup>99</sup> 21 C.F.R. § 807.97. Moreover, the federal rule emphasized that “[a]ny representation that create[d] an impression of official approval of a . . . [PMN device] because . . . [it] compl[ie]d with the . . . [PMN] regulations [was] misleading and constitute[d] misbranding.” *Id.*

<sup>100</sup> Ardaugh et. al., *supra* note 98.

<sup>101</sup> Sorenson & Drummond, *supra* note 94.

<sup>102</sup> Silvestrini, *supra* note 93.

<sup>103</sup> Sorenson & Drummond, *supra* note 94.

<sup>104</sup> *Id.*

<sup>105</sup> Silvestrini, *supra* note 93. Consequently, the FDA used PMN to clear around four hundred implantable devices annually. *Id.*

<sup>106</sup> Ardaugh et. al., *supra* note 98.

<sup>107</sup> *Id.*

<sup>108</sup> *Id.*

design, and the others “had poor clinical performance.”<sup>109</sup> Moreover, these predicates were linked to earlier predicates that “were discontinued . . . well before” the ASR XL’s “clearance” due to their high reversion rate.<sup>110</sup> After numerous patient injuries established the ASR XL’s high reversion rate, its manufacturer voluntarily withdrew the device.<sup>111</sup> Like ASR XL, experts linked other PMN devices to patient harms and subsequent recalls.<sup>112</sup>

Unfortunately, the 21st Century Cures Act may force the FDA to clear more devices without thoroughly examining their safety and efficacy. Title III requires the FDA to exempt certain Class I and II devices from premarket review.<sup>113</sup> Thus, many more Class I and II devices may escape at least some type of evaluation. In addition, Title III requires the FDA to approve all device applications based on the least burdensome approach.<sup>114</sup> Therefore, PMN approvals may reference predicates that have weaker safety and efficacy evidence. Regulators and stakeholders must consider whether the Title III provisions will lower the safety and efficacy of certain Class I and II devices.

### 3. Humanitarian Device Exemption (HDE)

Humanitarian Device Exemption (HDE) was an expedited approval pathway that exempted Humanitarian Use Devices (HUDs) from demonstrating a “reasonable assurance of effectiveness.”<sup>115</sup> Congress intended the HDE “to encourage the discovery and use of devices . . . [that could treat or diagnose] diseases or conditions that affect[ed] or . . . manifested in fewer than 4,000

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<sup>109</sup> *Id.*

<sup>110</sup> *Id.*

<sup>111</sup> *Id.*

<sup>112</sup> Diana Zuckerman et. al., *17 Medical Device Recalls and the FDA Approval Process* 1006, 1006-09 (2001). From 2005 to 2009, the FDA recalled one hundred fifteen devices. *Id.* at 1007. One hundred thirteen of the devices were Class I recalls, meaning that the recalls represented the highest risk based on postmarket complaints and adverse reports. *Id.* The FDA only used its most rigorous approval process to review nineteen percent of the recalls. *Id.* By contrast, the FDA used its less rigorous PMN process to review seventy-one percent of the recalls. *Id.* at 1008. Thirty-five of the total recall devices were cardiovascular devices, yet two-thirds of the devices were PMN clearances and only thirty-four percent of the devices were PMA approvals. *Id.* Furthermore, twelve percent of the overall PMN recalls were Class III devices that should have undergone a more stringent PMA review. *Id.* The researchers noted that “[w]hile even the more rigorous PMA criteria” was “often scientifically inadequate to ensure patient safety,” its “standards [were] clearly superior to . . . [PMN] standards.” *Id.* at 1009. These findings suggested that the FDA was inappropriately allowing too many high-risk devices to receive PMN approval.

<sup>113</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 3054, 130 Stat 1033 (codified as amended in scattered sections of 21 U.S.C.).

<sup>114</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3058, § 513, 130 Stat 1033, 1128–29 (codified as amended in scattered sections of 21 U.S.C. 360).

<sup>115</sup> *Humanitarian Device Exemption (HDE) Program—Final Guidance*, FDA 6 (Oct. 21, 2019), <https://www.fda.gov/media/131886/download>. A HUD’s small target population likely justified its lower evidentiary requirements. *Id.* Because HUDs targeted rare diseases, manufacturers likely struggled to locate an adequate number of clinical trial participants to generate clinically significant data. *Id.* Under the FDA’s most rigorous evidentiary standards, fewer HUDs likely would have entered the market because it would have taken an unreasonable amount of time and resources for a manufacturer to enroll enough clinical trial participants. *Id.* Therefore, HUDs defensibly required a lower evidentiary standard to safeguard the availability of innovative treatment options for rare diseases and conditions. *Id.*

individuals in the United States per year.”<sup>116</sup> As a result, the FDA did not require HDE applicants to demonstrate “scientific evidence of efficacy.”<sup>117</sup> Instead, the FDA only required the applicants to establish that their HUD provided a “probable [health] benefit” that “outweigh[ed] [its] risk of injury or illness.”<sup>118</sup>

Compared to the FDA’s most stringent review criteria, HUDs had a lower evidentiary burden because the FDA only assessed their relative safety, but not their efficacy.<sup>119</sup> Moreover, the FDA could approve HUDs based on clinical,

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<sup>116</sup> *Current Regulations: 21CFR 814 Subpart H: Humanitarian Use Devices*, FDA, <https://www.fda.gov/industry/humanitarian-use-device-laws-regulations-and-guidances/current-regulations-21cfr-814-subpart-h-humanitarian-use-devices> (last updated Feb. 16, 2018); see Janice Hogan, *Does the Humanitarian Device Exemption Process Work (And Is It Worth Pursuing)?*, MED DEVICE ONLINE (Feb. 25, 2016), <https://www.meddeviceonline.com/doc/does-the-humanitarian-device-exemption-process-work-and-is-it-worth-pursuing-0001> (stating that Congress created the HDE pathway “to encourage the development of and facilitate access to devices for . . . rare conditions and diseases” in 1990). In addition to its limited target population requirement, the HDE requires that the exemption was necessary to make the HUD commercially available, the HUD was not equivalent to a non-exempt device, and the HUD was beneficial compared to its risks. *Medical Devices; Humanitarian Use Devices Part V*, FDA, <https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/medical-devices-humanitarian-use-devices-part-v> (last updated Sept. 15, 2015). The Safe Medical Devices Act of 1990 (the SMDA) amended section 520(m) of the Food, Drug and Cosmetic Act (FDCA), and “authorize[d] the FDA . . . to exempt a HUD from the effectiveness requirements of sections 514 and 515” of the FDCA. *Id.*

<sup>117</sup> Norman, *supra* note 59, at 281.

<sup>118</sup> *Id.*; see *Medical Devices; Humanitarian Use Devices Part V*, *supra* note 116 (stating that HDE applications had to demonstrate that “the device w[ould] not expose patients to an unreasonable or significant risk of illness or injury” and that its use provided a “probable [health] benefit” that “outweigh[ed] the risk of injury or illness . . . , taking into account” other devices and alternative treatments); see also *Getting a Humanitarian Use Device to Market* FDA, <https://www.fda.gov/medical-devices/humanitarian-device-exemption/getting-humanitarian-use-device-market> (last updated Dec. 12, 2019) (explaining that the FDA’s parameters only required HDE applicants to provide enough information to allow it to conclude that the HUD “w[ould] not expose patients to an unreasonable or significant risk of illness or injury” and that its potential health benefits “outweigh[ed] the risk of injury or illness from its use”).

<sup>119</sup> Norman, *supra* note 59, at 281. The FDA’s most stringent approval criteria required a device to demonstrate both safety and effectiveness. See 21 CFR § 860.7 (2015). A device demonstrated a reasonable assurance of *safety* when the FDA determined that its use provided “probable [health] benefits” that “outweigh[ed] any probable risks” based on “valid scientific evidence.” See 21 CFR § 860.7(d)(1) (2015). The FDA *safety* required a device’s valid scientific evidence to “demonstrate the absence of unreasonable risk of illness or injury.” *Id.* Separately, a device provided a reasonable assurance of *effectiveness* when the FDA determined that “a significant portion of the target population” used the device according to its intended uses, warnings, and instructions, and the use provided “clinically significant results” that were “based upon valid scientific evidence.” See 21 CFR § 860.7(e)(1) (2015). The valid scientific evidence an applicant needed to demonstrate their device’s *effectiveness* “consist[ed] principally of well-controlled investigations . . . unless the [FDA] Commissioner authorize[d] reliance upon other valid scientific evidence which the Commissioner has determined [was] sufficient.” 21 CFR § 860.7(e)(2) (2015). In 21 CFR § 860.7(f), the FDA identified “the essentials of a well-controlled clinical investigation” that most applicants needed to demonstrate that their device gave a reasonable assurance of *efficiency*, including standard scientific controls against biased data. See 21 CFR § 860.7(f) (2015).

nonclinical, or experiential evidence that lacked traditional, scientific rigor.<sup>120</sup> However, HUD approvals were not necessarily an effortless endeavor. Although “HDEs [were] exempt from the effectiveness requirement[,]” HDE applicants still had to provide “all the other information” that the FDA required on PMA applications.<sup>121</sup> As a result, HDEs “virtually always require[d]” HUDs to have “clinical data of some kind” to demonstrate their “safety and probable benefit.”<sup>122</sup>

Nevertheless, the 21st Century Cures Act may eliminate the few evidentiary hurdles HUDs must satisfy. Title III requires FDA approval of all device applications, including HDEs, based on the least burdensome approach.<sup>123</sup> As a result, the FDA could permit HUDs to submit even weaker evidence of their reasonable safety. Regulators and stakeholders must consider whether the Title III provisions will adversely impact the safety of HUDs and the welfare of patients.

#### 4. Premarket Approval (PMA) Pathway

Premarket Approval (PMA) was “the most stringent type of device marketing application,” and the FDA used it to “evaluate the safety and effectiveness of Class III medical devices.”<sup>124</sup> The FDA required PMAs to contain enough “valid scientific evidence” to provide a “reasonable assurance that [a] device [was] safe and effective.”<sup>125</sup>

Before its approval, a PMA device underwent preclinical testing to establish its basic safety and efficacy.<sup>126</sup> After preclinical testing, a PMA device

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<sup>120</sup> *Medical Devices; Humanitarian Use Devices Part V*, *supra* note 116. The FDA acknowledged that HUDs were unique due to their small target population, and it exercised its discretion to exclude HUDs from the valid evidence requirements of 21 CFR § 860.7. *Id.* However, the FDA encouraged the HDE applicants to use valid scientific evidence “whenever possible,” and it clarified that it could require an HDE applicant to perform clinical testing occasionally if it was necessary to demonstrate the HUD was beneficial. *Id.* Moreover, the FDA tightly controlled the commercial distribution of approved HUDs. Norman, *supra* note 59, at 281. In particular, the FDA confined the market price of HUDs to “fees, . . . research and development expenses, and other closely defined costs” to protect against manufacturers profiting “from devices with unproven efficacy.” *Id.* If a manufacturer priced a HUD for more than \$250, it had to have an “independent certified accountant” identify the additional costs and justify the amounts. *Id.* Furthermore, the FDA only allowed manufacturers to distribute approved HUDs to facilities with a local independent review board (IRB) to monitor the clinical use of the device. *Id.*

<sup>121</sup> Stephen P. Rhodes & Elisa D Harvey, *HUDs and HDEs: Common Misconceptions and Current Challenges*, REG. FOCUS 21 (Jan. 2011), <https://www.cardiomedllc.com/wp-content/uploads/2014/06/HUDs-and-HDEs.pdf>; *see Medical Devices; Humanitarian Use Devices Part V*, *supra* note 116 (explaining that the HDE was comparable to the premarket approval (PMA) except the HDE did not require “clinical data” regarding the effectiveness of the device).

<sup>122</sup> Rhodes & Harvey, *supra* note 121.

<sup>123</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3058, § 513, 130 Stat 1033, 1128–29 (2016) (codified as amended in scattered sections of 21 U.S.C. 360).

<sup>124</sup> *Premarket Approval (PMA)*, FDA (May 16, 2019), <https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma>; *see* Norman, *supra* note 59, at 278 (explaining that PMA was “the strictest device marketing application,” and it was “required . . . for any new device” that lacked a predicate unless the FDA agreed to reclassify it as a Class I or Class II device, otherwise known as a “de novo device”).

<sup>125</sup> 21 CFR § 860.7(4)(c)(1) (2015).

<sup>126</sup> Owen Faris, *Clinical Trials for Medical Devices: FDA and the IDE Process*, CTR. DISEASE RADIOLOGICAL HEALTH Slide 6, <https://www.fda.gov/media/87603/download> (last viewed Mar. 5, 2020). Preclinical trial investigations consisted of bench testing and animal testing. *Id.* In medical devices, bench testing was a process that “tease[d] out mechanical and design flaws in devices,”

needed an FDA-approved investigational device exemption (IDE) to enter human clinical studies.<sup>127</sup> Upon IDE approval, a device often entered an exploratory study and a pivotal study.<sup>128</sup> First, the device entered a feasibility study to establish its “preliminary safety and performance information.”<sup>129</sup> Feasibility studies required researchers to enroll ten to thirty patients.<sup>130</sup> Next, the device entered a pivotal study to demonstrate that it was safe and effective for its intended use.<sup>131</sup> Pivotal studies required researchers to enroll 150-300 patients.<sup>132</sup> Following FDA approval, a PMA device entered a postmarketing study to determine its “long-term” safety and efficacy.<sup>133</sup>

Nevertheless, medical device clinical investigations were rather lax compared to traditional clinical trials.<sup>134</sup> In particular, the FDA often approved PMA devices “based on a single clinical study”<sup>135</sup> that lacked traditional scientific

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and it measured a device’s durability “without having to implant the device in a human.” *Bench testing important for patient safety, successful device development*, HEALIO (Oct. 2009), <https://www.healio.com/cardiology/arrhythmia-disorders/news/print/cardiology-today/%7B74d1523a-0e0d-413c-9c3f-02a7c78d5b56%7D/bench-testing-important-for-patient-safety-successful-device-development>.

<sup>127</sup> Norman, *supra* note 59; *see* Faris, *supra* note 126, at Slide 8 (stating that the FDA needed to approve an IDE before an applicant used the device in human clinical studies).

<sup>128</sup> John Lehmann, *DRUG AND MEDICAL DEVICE CLINICAL TRIALS 101*, IMARC (Oct. 19, 2016), <https://www.imarcresearch.com/blog/medical-device-clinical-trials-101>.

<sup>129</sup> Brandy Chittester, *Medical Device Clinical Trials – How Do They Compare with Drug Trials?*, GXP LIFELINE (Feb. 14, 2014); *see* Faris, *supra* note 126, at Slide 10 (explaining that feasibility studies could “support . . . a future pivotal study or . . . answer basic research questions[,]” but the FDA did “not intend[] [them] to be the primary support for a marketing application”).

<sup>130</sup> Chittester, *supra* note 129; *see* Faris, *supra* note 126, at Slide 10 (stating that feasibility studies often involved ten to forty participants, but the sample size was occasionally larger than forty participants). Unlike a drug clinical trial where researchers administered the drug to “a small number of healthy subjects,” a device clinical trial only used the device in participants who had “the disease or condition being studied.” Chittester, *supra* note 129.

<sup>131</sup> Chittester, *supra* note 129. The FDA mainly intended pivotal studies to provide the “clinical support for a marketing application.” Faris, *supra* note 126, at Slide 10.

<sup>132</sup> Chittester, *supra* note 129. The sample size and endpoints of pivotal studies were “statistically driven” and “designed to demonstrate a ‘reasonable assurance of safety and effectiveness.’” Faris, *supra* note 126, at Slide 11.

<sup>133</sup> Chittester, *supra* note 129.

<sup>134</sup> Sorenson & Drummond, *supra* note 94, at 125–26. Randomized control trials (RCTs) were considered the “gold standard of evidence.” Sarata, *supra* note 34, at 55 n.126. RCTs often placed clinical trial participants into different groups randomly. *Id.* RCTs gave one group the new treatment and the other group a current treatment or placebo. *Id.* The RCT randomization helped distribute patient variances “equal[ly] across each group” to better discern the effect of the treatment. *Id.*; *see* Tom Frieden, *Why the ‘gold standard’ of medical research is no longer enough*, STAT (Aug. 2, 2017), <https://www.statnews.com/2017/08/02/randomized-controlled-trials-medical-research/> (explaining that randomization made the tested groups “virtually identical in age, gender, socioeconomic status, and other variables” to reduce bias and confounding variables). Moreover, RCTs used clinically meaningful endpoints that were measured against an “actual patient benefit.” Sarata, *supra* note 34, at 55 n.126.

<sup>135</sup> Sorenson & Drummond, *supra* note 94, at 126; *see* Faris, *supra* note 126, at Slide 9, 11. (stating that pivotal trials provided PMA evidence, and medical device researchers often performed a “single pivotal trial”).

rigor.<sup>136</sup> In particular, device studies frequently used small sample sizes<sup>137</sup> because the FDA only required a device to *reasonably* assure it was safe and effective.<sup>138</sup> Furthermore, clinical testing often lacked standard controls and procedural uniformity.<sup>139</sup> Most clinical trials were not “randomized or blinded” studies that used “an active control group and hard end points.”<sup>140</sup> Moreover, many studies lacked homogeneity “in the way they account[ed] for patients . . . and data,” making it difficult to compare the safety and efficacy of different devices.<sup>141</sup>

Understandably, medical devices had weaker standards because traditional standards were less practicable for most Class III devices.<sup>142</sup> Class III devices included implantable devices, such as pacemakers and breast implants,<sup>143</sup> that made conventional requirements problematic due to “the risk of the implantation or procedure itself.”<sup>144</sup> Thus, medical device researchers struggled to randomize studies because it was “often unethical” to “give[] [patients] a placebo, or ‘sham’ operation.”<sup>145</sup> Similarly, researchers had difficulty using “‘blind’ or ‘double blind’

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<sup>136</sup> Sorenson & Drummond, *supra* note 94, at 126.

<sup>137</sup> Large sample sizes are required to apply a higher confidence level to the accuracy of clinical trial data. See Sarah Littler, *The Importance and Effect of Sample Size*, SELECT STATISTICAL SERVICES, <https://select-statistics.co.uk/blog/importance-effect-sample-size/> (last visited Mar. 5, 2020) (explaining that a large sample size increases the confidence level of the data, decreases uncertainty, increases “precision,” and increases the ability of a researcher to make meaningful inferences); see also Chittester, *supra* note 129 (stating that device clinical trials typically required a small sample size compared to drug clinical trials because the FDA applied a lower safety and efficacy standard to devices).

<sup>138</sup> Owen Faris & Jeffery Shuren, *An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials*, 376 NEW ENG. J. MED. 1350, 1352 (2017). Unlike new drugs where an applicant had to provide “‘substantial evidence’” of the drug’s effectiveness, new device applicants merely had to provide a reasonable assurance of the device’s safety and effectiveness. Hines et. al, *supra* note 83, at 2. As a result, new drugs often required “two or more well-controlled clinical studies,” while new devices often only required a single study. *Id.*

<sup>139</sup> See Faris, *supra* note 126, at Slide 9 (stating that medical device trials often lacked blinding, randomization, controls, and uniform endpoints).

<sup>140</sup> Sorenson & Drummond, *supra* note 94, at 126; see Hines et. al, *supra* note 83, at 2 (discussing how the FDA refused to issue new drug approvals where the drug’s effectiveness was solely based on “uncontrolled studies or partially controlled studies,” but it agreed to issue PMA approvals where a device’s effectiveness “reli[ed] upon other valid scientific evidence . . . even in the absence of well-controlled investigations”) (citing 21 CFR § 314.126(e) and 21 CFR § 860.7(e)(2)).

<sup>141</sup> Sorenson & Drummond, *supra* note 94, at 126.

<sup>142</sup> *Id.*

<sup>143</sup> *Are Medical Device Manufacturers Risking Your Safety?*, *supra* note 79.

<sup>144</sup> Faris & Shuren, *supra* note 138, at 1351.

<sup>145</sup> Chittester, *supra* note 129; see Faris & Shuren, *supra* note 138, at 1352 (stating that in certain instances it was “difficult or even unethical to randomly assign participants” to treatment groups that did not receive the new device).

controls”<sup>146</sup> because it was “nearly impossible to blind subjects or investigators” to the assigned treatment.<sup>147</sup>

However, several experts asserted that the PMA pathway had a major loophole that provided PMA approvals much like the controversial PMN pathway.<sup>148</sup> Following an original PMA approval, the FDA could approve multiple PMA supplement applications.<sup>149</sup> PMA supplement approvals allowed manufacturers to make substantial postmarket changes to PMA devices.<sup>150</sup> Most of the “PMA supplement review tracks” required no more than preclinical or weak clinical trial data.<sup>151</sup> As a result, “cumulative iterations of device changes” allowed PMA devices to “‘drift’ away from the originally approved device.”<sup>152</sup> By 2014, the FDA had approved seventy PMA orthopedic devices.<sup>153</sup> However, the FDA also approved “[a] total of 765 postmarket changes . . . for these 70 devices[,]” and most of the approvals only required preclinical or limited clinical trial evidence.<sup>154</sup> Unsurprisingly, the seventy devices were linked to twelve FDA recalls, meaning almost 20% of the modified devices were defective.<sup>155</sup> The

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<sup>146</sup> Chittester, *supra* note 129. A blind control made clinical trial participants “unaware” of whether their treatment was a new product, current product, or a placebo. *Id.* A double blind control made clinical trial participants and the treating physician unaware of whether the participant was receiving a new product, current product, or a placebo. *Id.*

<sup>147</sup> *Id.*; see Faris & Shuren, *supra* note 138, at 1351 (stating that occasionally it was “infeasible to conduct a blinded trial of an implantable device because it [was] impractical or unethical to use a sham control for the target patient population”).

<sup>148</sup> Samuel et. al., *How do Orthopaedic Devices Change After Their Initial FDA Premarket Approval?*, 474 CLINICAL ORTHOPEDICS RELATED RES. 1053, 1054–55 (2015); see Rome et. al., *supra* note 83, at 489 (stating that the PMA process “raised concerns about whether physicians and patients should sometimes be more wary about” the safety and efficacy of PMA devices).

<sup>149</sup> Samuel et. al., *supra* note 148. Due to the MDA failing to address the postmarket review standards for PMA devices, the FDA created a rule that allowed manufacturers to “supplement the design of existing devices.” Rome et. al., *supra* note 83, at 492. Congress adopted the FDA’s rule into the FDA Modernization Act (FDAMA) of 1997. *Id.*

<sup>150</sup> Samuel et. al., *supra* note 148.

<sup>151</sup> *Id.* Major changes to a device’s design often only required preclinical data “with ‘limited confirmatory clinical data’ needed in some cases.” Rome et. al., *supra* note 83, at 493. Only extreme changes, such as label modifications that broadened a device’s use “or remov[ed] contraindications[,]” required new clinical evidence. Samuel et. al., *supra* note 148, at 1055.

<sup>152</sup> Samuel et. al., *supra* note 148, at 1054.

<sup>153</sup> *Id.* at 1057.

<sup>154</sup> *Id.* According to the midpoint, the FDA approved 6.5 postmarket modifications per orthopedic device. *Id.* Some devices featured a higher number or rate of postmarket changes than other PMA devices. *Id.* Over 30.5-year period, the New Jersey LCS® Total Knee System incorporated the highest number of postmarket changes. *Id.* It received “135 device changes . . . , or 4.4 device changes per device-year.” *Id.* The Ceramax ® Ceramic Hip System received highest rate of postmarket approvals per year. *Id.* In a 4.4 period, the FDA approved 4.5 supplement applications for the device annually. *Id.* Like orthopedic devices, “many high-risk cardiac devices [were] actually approved as PMA ‘supplements,’ or changes to already-approved device models, often without the new use of clinical data to support the altered device design.” Rome et. al., *supra* note 83, at 490.

<sup>155</sup> Samuel et. al., *supra* note 148, at 1059.

various recalls highlight the significance of the FDA's evidentiary standards and caution against the FDA using additional evidentiary shortcuts.<sup>156</sup>

Unfortunately, the 21st Century Cures Act may further undermine the scientific rigor of the FDA's PMA process even more. Title III requires the FDA to approve all device applications, including PMAs, based on the least burdensome approach.<sup>157</sup> As a result, the FDA could permit original PMA applications to contain weaker evidence of a device's reasonable safety and effectiveness. Regulators and stakeholders must consider whether the Title III provisions will viscerate the PMA process and increase the number of FDA device recalls.

## B. Pharmaceutical Approval

### 1. New Drug Application (NDA)

In the United States, all new drugs were subject to the "regulation and control" of the FDA's new drug application (NDA)<sup>158</sup> before they could enter the market.<sup>159</sup> An NDA not only required new drugs to demonstrate their safety, but it also required them to establish "substantial evidence" of their effectiveness.<sup>160</sup> The FDA usually required new drugs to undergo "at least two adequate and well-controlled studies." It expected both studies to establish a new drug's effectiveness independently.<sup>161</sup> As a result, NDA approvals [were] slow

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<sup>156</sup> In *Riegel v. Medtronic*, the Supreme Court affirmed the district court's finding that federal law barred the plaintiff's "claims of strict liability; breach of implied warranty; and negligence in the design, testing, inspection, distribution, labeling, marketing, and sale of" a defective catheter because the "MDA's pre-emption clause bar[red] common law claims challenging the safety and effectiveness" of PMA-approved devices. 552 U.S. 312, 315 (2008); see 21 U.S.C.A. § 360k (West) (stating that the MDA preempted state laws that were "different from, or in addition to" its provisions if it was "relate[d] to the safety or effectiveness of . . . [a] device or to any other matter included" in its provisions). Instead, the Court found that the plaintiff could only bring a common-law tort claim where the "claim[] [was] premised on a violation of FDA regulations" because "the state duties in such a case 'parallel,' rather than add to, federal requirements." *Medtronic*, 552 U.S. at 330 (citing *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996)). Therefore, device manufacturers receive "immunity . . . against most lawsuits for injuries or deaths resulting from PMA-approved devices" where "the manufacturer did not design the device properly or sufficiently warn patients about its risks." *Rome et. al.*, *supra* note 83, at 490. Because Congress limited a patient's ability to recover damages where a faulty device injured them, the FDA must diligently apply evidentiary standards that mitigate patient harm to protect public welfare.

<sup>157</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3058, § 513, 130 Stat. 1033, 1128–29 (2016) (codified as amended in scattered sections of 21 U.S.C. 360).

<sup>158</sup> An NDA "includes all data concerning a drug," including its manufacturing and quality control process. Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 1*, 1 JACC: BASIC TRANSLATIONAL SCI. 170, 178 (2016). As a result, the average NDA was 100,000 pages. *Id.*

<sup>159</sup> *New Drug Application*, FDA, <https://www.fda.gov/drugs/types-applications/new-drug-application-nda> (last updated June 10, 2019).

<sup>160</sup> 21 CFR § 314.126(a). In 1938, Congress passed the Food, Drug and Cosmetic Act (FDCA), and it required drug manufacturers to demonstrate that their drugs were safe before they could market them. *Promoting Safe & Effective Drugs for 100 Years*, FDA (Apr. 23, 2019), <https://www.fda.gov/about-fda/histories-product-regulation/promoting-safe-effective-drugs-100-years>. In 1962, Congress passed the Kefauver-Harris Drug Amendments, and it required drug manufacturers to provide "substantial evidence" that their drug was effective. *Id.*

<sup>161</sup> *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, FDA 3 (May 1998), <https://www.fda.gov/media/71655/download>.

and costly, and the FDA “face[d] constant, often contradictory pressure to shorten the approval process, while still preserving or enhancing the safety and efficacy of drugs.”<sup>162</sup>

The 21st Century Cures Act pressures the FDA to accelerate and streamline its approval process.<sup>163</sup> Thus, it is essential to review the FDA’s original approval process to understand whether the Act’s provisions will compromise the safety and efficacy of new drugs. Before the Act, NDA approval required preclinical trials, investigational new drug (IND) approval, and meticulous clinical trials.

### **i. Preclinical Trials**

Eligible compounds<sup>164</sup> underwent preclinical testing to determine their suitability for human clinical trials.<sup>165</sup> In preclinical trials, researchers “conduct[ed] a series of laboratory and animal studies”<sup>166</sup> over multiple years to evaluate a compound’s “bioactivity, safety, and efficacy.”<sup>167</sup> Researchers used toxicology<sup>168</sup> and bioanalytical<sup>169</sup> tests to support a compound’s potential clinical trials.<sup>170</sup> Simultaneously, researchers designed a compound’s clinical trial and prepared its investigational new drug (IND) application.<sup>171</sup>

### **ii. Investigational New Drug (IND) Application**

Under United States federal law, a new drug could not enter human clinical trials unless it obtained an investigational new drug (IND) application.<sup>172</sup>

<sup>162</sup> Norman, *supra* note 158, at 178.

<sup>163</sup> Lieberman, *supra* note 23.

<sup>164</sup> Before the preclinical trial stage, researchers undertook drug discovery activities to “identify potential biological targets for possible future medicines.” *2015 profile BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 37. Researchers selected and investigated a biochemical mechanism in a disease to detect possible targets. *Id.* Subsequent to identifying potential targets, researchers tested “[u]p to 5,000 to 10,000 molecules” for the most promising compounds. Pacific BioLabs, *Stages of Drug Development*, <https://pacificbiolabs.com/stages-of-drug-development> (last viewed Jan. 1, 2020). The testing consisted of “rigorous screening” methods that tracked target interactivity and target symptoms to isolate eligible compounds. *Id.*

<sup>165</sup> *2015 profile BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 38. Preclinical testing “analyzes the bioactivity, safety, and efficacy of the formulated drug product.” Pacific BioLabs, *supra* note 164. “Only a few compounds” pass the preclinical testing phase and move onto the clinical trial stage. *2015 profile BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 38.

<sup>166</sup> *2015 profile BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 38.

<sup>167</sup> Pacific BioLabs, *supra* note 164.

<sup>168</sup> *Id.* Preclinical toxicology tests “assess[ed] the onset, severity, and duration of toxic effects, their dose dependency and degree of reversibility (or irreversibility).” Pacific BioLabs, *In Vivo Toxicology: Toxicology Studies*, <https://pacificbiolabs.com/in-vivo-toxicology> (last viewed Jan. 26, 2021).

<sup>169</sup> Pacific BioLabs, *supra* note 164. Bioanalytical tests helped researchers evaluate the chemical and biochemical properties of a compound throughout its development. *Id.*

<sup>170</sup> *Id.*

<sup>171</sup> *Id.*

<sup>172</sup> *Investigational New Drug (IND) or Device Exemption (IDE) Process (CBER)*, FDA, <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-ind-or-device-exemption-ide-process-cber> (last updated May 14, 2019).

IND applications requested information about (1) preclinical studies and prior human use;<sup>173</sup> (2) drug production; and (3) clinical trial requirements. Once an IND was valid,<sup>174</sup> the drug could enter clinical trials “to demonstrate [its] safety and efficacy” in humans.<sup>175</sup> The NDA clinical trials comprised three phases, and the FDA required a drug to “successfully complete each phase.”<sup>176</sup>

### iii. Clinical Trials

In Phase I, researchers administered the new drug to a small group of healthy participants to examine its safety in humans.<sup>177</sup> Researchers conducted single dose,<sup>178</sup> single ascending dose,<sup>179</sup> and multiple ascending dose<sup>180</sup> trials to determine the drug's dosing, side effects, and toxicity.<sup>181</sup> Phase II studies evaluated a drug's effectiveness, and it continued investigating its safety.<sup>182</sup> The studies enrolled one hundred to three hundred patients,<sup>183</sup> and the experiments typically used a placebo treatment group.<sup>184</sup> Researchers used Phase III studies to generate “statistically significant” evidence that a drug was safe and effective.<sup>185</sup> The studies enrolled one thousand to three thousand patients, and the tests often

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<sup>173</sup> Norman, *supra* note 158, at 172.

<sup>174</sup> See *IND Application Procedures: Overview*, FDA, <https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-overview> (last updated Oct. 9, 2015) (stating that “[a]n IND application [may go] into effect: 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigations described in the application are subject to a Clinical Hold; or on earlier notification by FDA that the clinical investigations in the IND may begin”).

<sup>175</sup> 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 38.

<sup>176</sup> *Id.* at 39.

<sup>177</sup> Norman, *supra* note 158, at 176; see 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 39 (explaining that researchers administered a new drug to twenty to eighty participants “to determine the safety of the compound and how it is best metabolized or processed in the body”).

<sup>178</sup> Norman, *supra* note 158, at 176. Participants received a single dose of a drug, and the dose was one-tenth or less of the drug's highest preclinical trial dose that lacked adverse effects. *Id.* If the participants experienced a “severe reaction,” the researchers stopped the drug's clinical trial. *Id.*

<sup>179</sup> *Id.* In single ascending dose studies, approximately three participants received a higher single dose than the initial single dose study. *Id.* The researchers increase the single dosing across small groups of participants “until either pre-calculated pharmacokinetic safety levels are reached or until adverse effect begin appearing.” *Id.* Where unreasonable side effects were present, the dose that preceded the side effects was the drug's “maximum tolerated dose.” *Id.*

<sup>180</sup> *Id.* In multiple ascending dose studies, participants received “multiple low doses of the drug, and biological samples (blood, fluids, urine) [were] collected and analyzed.” *Id.*

<sup>181</sup> *Id.* at 175.

<sup>182</sup> *Id.* at 176; see 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 39 (stating that Phase II studies mainly addressed a drug's safety, but they also “determine [its] effectiveness . . . and optimal dosing”).

<sup>183</sup> 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 39. Unlike Phase I, Phase II and III administered the drug to its target population. *Id.*

<sup>184</sup> Norman, *supra* note 158, at 176.

<sup>185</sup> 2015 profile *BIOPHARMACEUTICAL RESEARCH INDUSTRY*, *supra* note 47, at 39.

used alternative treatment groups.<sup>186</sup> Where a drug's results demonstrated its safety and effectiveness, it could obtain an NDA approval.<sup>187</sup>

## 2. Clinical Trial Misconduct & Fraud

Because Title III introduces less rigorous evidentiary standards, it may make drug clinical trials more vulnerable to manipulation. Thus, it is important to discuss clinical trial misconduct and fraud. Historically, some principal investigators committed "scientific misconduct or fraud" to evade the rigors of the clinical trial process.<sup>188</sup> From 1977 to 2012, publishers retracted over two thousand scientific publications, and most of the retractions were biomedical publications that involved fraudulent data.<sup>189</sup> Two exemplary cases involved Dr. Robert Fiddes and Dr. Scott Rueben.

In the 1990's, Dr. Robert Fiddes, the former director of the Southern California Research Institute, oversaw multiple clinical trials to secure NDA approvals.<sup>190</sup> Unfortunately, Dr. Fiddes committed "scientific fraud on an impressive scale for over a decade" to produce his clinical trial data.<sup>191</sup> Specifically, Dr. Fiddes's clinical trials included unqualified, fabricated, and coerced patients.<sup>192</sup> Moreover, Dr. Fiddes manipulated clinical data and falsified "blood pressure [data], EKG[] [values], and other results."<sup>193</sup> In fact, Dr. Fiddes used blood and urine samples that did not belong to enrolled participants.<sup>194</sup> Eventually, Susan Lester, one of Dr. Fiddes's study coordinators, reported his misconduct to the FDA.<sup>195</sup> In 1997, a court convicted Dr. Fiddes of fraud, and he received a 15-month prison sentence.<sup>196</sup>

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<sup>186</sup> Norman, *supra* note 158, at 176; *see Chittester, supra* note 129 (stating that new drug clinical trials often were randomized, had blind controls, used large populations, included placebos, and compared "the new product to current therapies").

<sup>187</sup> Norman, *supra* note 158, at 176

<sup>188</sup> *See* Stephen L. George & Marc Buyse, *Data fraud in clinical trials*, 5 CLINICAL INVESTIGATION 161, 161 (2015) (stating that "[h]ighly publicized cases of fabrication or falsification of data in clinical trials had] occurred in recent years, and it [was] likely that there [was] additional undetected or unreported cases"). Clinical data fraud included "selective reporting . . . failure to follow written protocol, emphasis on secondary rather than primary outcomes, use of improper statistical methods, failure to publish [clinical trial results] and so on." *Id.*

<sup>189</sup> *Id.* at 163.

<sup>190</sup> *Id.* at 164.

<sup>191</sup> *Id.*; *see FR DATE: 11/06/2002*, FDA, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-debarment-list-drug-product-applications/fr-date-11062002> (last updated Aug. 19, 2014) (stating that Dr. Fiddes "direct[ed], and encourage[ed] the submission of false information to sponsors in required reports for clinical studies used by FDA to evaluate the safety and effectiveness of drug products").

<sup>192</sup> George & Buyse, *supra* note 188, at 164.

<sup>193</sup> *Id.*

<sup>194</sup> *Id.* Dr. Fiddes paid one of his employees \$25 per urine sample and used it in his clinical trial "as if it were a sample from an actual patient." *Id.*

<sup>195</sup> *Drug Trial Dangers?*, CBSNEWS (Mar. 30, 2001), <https://www.cbsnews.com/news/drug-trial-dangers>.

<sup>196</sup> George & Buyse, *supra* note 188, at 164.; *see FR DATE: 11/06/2002, supra* note 191 (stating that the FDA was "debar[ing] Dr. Robert A. Fiddes for 20 years from providing services in any capacity to a person that has an approved or pending drug product application" due to his fraud conviction).

Similarly, Scott Reuben, the former Professor of Anesthesiology at Baystate Medical Center,<sup>197</sup> falsified clinical data relating to “post-operative multimodal analgesia therapy.”<sup>198</sup> Dr. Reuben entered contracts to manage multiple clinical trials, and he “published articles in various medical journals based on the purported results of the research.”<sup>199</sup> In 2000, Dr. Reuben claimed that the combination of “COX2 inhibitors, such as Vioxx, Celebrex, and Pfizer's Bextra (valdecoxib)” and certain nerve pain relievers aided the recovery of orthopedic surgery patients.<sup>200</sup> Some experts estimate that his purported research “led to the sale of billions of dollars['] worth of the potentially dangerous drugs.”<sup>201</sup> Unfortunately, Dr. Reuben fabricated the research results, and his suggested drug use likely stalled patient recovery and increased their risk of a cardiac event.<sup>202</sup> In 2016, the FDA “permanently debarr[ed] [Dr. Reuben] from providing services in any capacity to a person with an approved or pending drug product application.”<sup>203</sup>

Title III allows the FDA to issue NDA approvals based on less rigorous evidence, such as surrogate markers and real-world evidence. Arguably, the Act's less stringent evidentiary criteria will increase a research investigator's ability to submit biased and misleading clinical trial data. Regulators and stakeholders must ensure that Title III does not increase clinical data fraud to protect vulnerable patients.

## V. HOW THE ACT IS CHANGING DRUG & MEDICAL DEVICE DEVELOPMENT

Division A's Title III provisions change the clinical data standards that pharmaceutical and medical device manufacturers must satisfy to accelerate the FDA approval process.<sup>204</sup> In drug clinical trials, Title III allows researchers to use surrogate markers and real-world evidence.<sup>205</sup> Separately, Title III requires the

<sup>197</sup> Paul F. White et. al., *The Scott Reuben Saga One Last Retraction*, 112 ANESTHESIA & ANALGESIA 512, 512 (2011).

<sup>198</sup> *Scott Reuben Notice*, 76 FEDERAL REGISTER 7102, 7103 (2011).

<sup>199</sup> *Id.* Dr. Reuben published at least twenty-one articles that “were pure fiction.” Brendan Borrell, *A Medical Madoff: Anesthesiologist Faked Data in 21 Studies*, SCI. AM. (Mar. 10, 2009), <https://www.scientificamerican.com/article/a-medical-madoff-anesthesiologist-faked-data/>.

<sup>200</sup> Borrell, *supra* note 199.

<sup>201</sup> *Id.*

<sup>202</sup> *Id.*

<sup>203</sup> *Scott Reuben Notice*, *supra* note 198. According to preclinical animal studies, COX2 inhibitors possibly impeded bone regeneration. Borrell, *supra* note 199. In 2004, Vioxx and Bextra were discontinued because they increased a patient's risk of having a cardiac event or stroke. *Id.* Another study indicated that Celebrex also increased a patient's risk of having a cardiac event. *Id.*

<sup>204</sup> Gaybay, *supra* note 8; *see Sarata, supra* note 34, at summary (stating that Division A, Title III “modif[ies] the drug and device approval pathways”).

<sup>205</sup> 21st Century Cures Act, Pub. L. No. 114–255, sec. 3011, § 507, 130 Stat 1033, 1186–91 (2016) (codified as amended at 21 U.S.C. 357); 21st Century Cures Act, Pub. L. No. 114–255, sec. 3022, § 505F, 130 Stat. 1033, 1196–98 (2016) (codified as amended at 21 U.S.C. 355(g)); *see Barlas, supra* note 8 (stating that the legislation “forc[es] the FDA to permit pharmaceutical companies to gain approval of new indications for existing drugs with evidence assembled short of expensive clinical trials and short of conventional ‘endpoints’”); *see also Gaybay, supra* note 8 (acknowledging that Title III “discusses the use of biomarkers, surrogate measures, patient

FDA to exempt certain Class I and II devices from premarket review.<sup>206</sup> Title III also expands the FDA's obligation to approve devices based on the least burdensome approach.<sup>207</sup> Some experts believe that Title III provides a less rigorous data standard that will erode the reliability and safety of FDA approved pharmaceuticals and medical devices.<sup>208</sup>

## A. Increasing Drug Development Laxity

### 1. Permitting Use of Surrogate Markers

Title III, Subtitle B § 3011 “is perhaps the most controversial provision” of the 21st Century Cures Act because it endorses “certain evidence types . . . that call into question” the reliability of data for new drug approvals.<sup>209</sup> In particular, Subtitle B authorizes manufacturers to use drug development tools to “support[] or obtain[] approval or licensure . . . of a drug” or to “support[] the investigational use of a drug.”<sup>210</sup>

Subtitle B specifies that a drug development tool “includes—(A) a biomarker; (B) a clinical outcome assessment; and (C) any other method, material, or measure that . . . aids drug development and regulatory review.”<sup>211</sup> Because surrogate endpoints are a common biomarker,<sup>212</sup> it can help explain the potential risks of drug development tools.

Unlike traditional clinical endpoints, “favorable effects on surrogate[] [endpoints] do not automatically translate into benefits to health.”<sup>213</sup> As a result,

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experience information, and observational data” based on “routine clinical use or ‘real world evidence’”).

<sup>206</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3054, § 510, 130 Stat. 1033, 1126–27 (codified as amended in scattered sections of 21 U.S.C. 360).

<sup>207</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3058, § 515, 130 Stat. 1033, 1128–29 (codified as amended in scattered sections of 21 U.S.C. 360).

<sup>208</sup> Barlas, *supra* note 8; *see also* Gaybay, *supra* note 8 (last viewed Oct. 21, 2019) (stating that healthcare professionals are concerned that Title III will weaken the merits of clinical trial data).

<sup>209</sup> Goble, *supra* note 1, at 678.

<sup>210</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3011(b)(2)(A), § 507, 130 Stat. 1033, 1087 (2016) (codified as amended at 21 U.S.C. 357).

<sup>211</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3011(e)(5), § 507, 130 Stat. 1033, 1089 (2016) (codified as amended at 21 U.S.C. 357). The Act defines a biomarker as “a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention.” *Id.* The Act notes that surrogate endpoints are a type of biomarker. *Id.*

<sup>212</sup> *Infra* note 219. A surrogate endpoint is “a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of a clinical benefit.” 21st Century Cures Act, Pub. L. No. 114-255, sec. 3011(e)(9), § 507, 130 Stat. 1033, 1089 (2016) (codified as amended at 21 U.S.C. 357). Surrogate endpoints are attractive “proxies for hard clinical trial outcomes” because they “enable smaller, faster, and thus cheaper clinical trials.” David Menkes, *Surrogate Outcomes in Clinical Trials: A Cautionary Tale*, 173 J. AM. MED. ASS. INTERNAL MED. 611, 611 (2013).

<sup>213</sup> Menkes, *supra* note 212. From 2008 to 2012, the FDA approved thirty-six of fifty-four new cancer drugs “on the basis of surrogate markers.” Kaplan, *supra* note 22. Most of the surrogate markers measured a drug's ability to shrink tumors. *Id.* However, a study revealed that 50% of the drugs provided “no evidence of improved life expectancy.” *Id.* Because 36% of the

some experts are concerned that Title III's endorsement of drug development tools will cause the FDA to "mov[e] away from requiring drug manufacturers to prove that a drug actually benefits a patient."<sup>214</sup>

In the past, the FDA admitted that surrogate endpoints do not provide "reliable evidence" due to their inconsistent results.<sup>215</sup> One study reported that "65% of potential drug targets or biomarkers have inconsistencies when attempting to reproduce findings."<sup>216</sup> Moreover, some surrogate endpoints "have proven to be poor or misleading" once the drug entered the market.<sup>217</sup> Correspondingly, another study exposed the potential harms of surrogate endpoints, and it referenced fourteen instances where surrogate drug approvals injured patients.<sup>218</sup>

Recently, surrogate endpoints have become "commonplace," and they were "the primary endpoint in clinical trials for 45% of new drugs approved between 2010 and 2012."<sup>219</sup> However, many healthcare professionals believe that clinical trials should only use surrogate markers in a limited number of circumstances<sup>220</sup> because "growing evidence" suggests that a researcher's sole "rel[iance] on surrogate trials . . . is, in most circumstances, fundamentally flawed."<sup>221</sup>

## 2. Permitting Use of "Real-world" Evidence

Like surrogate endpoints in Subtitle B, real-world evidence is another "contentious" provision.<sup>222</sup> Title III, Subtitle C § 3022 permits pharmaceutical manufacturers to "submit real-world evidence . . . instead of randomized control trial . . . data to seek new indications for existing medications."<sup>223</sup>

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drugs lacked any survival data, it was possible that the study underreported the percentage of drugs that produced no discernable health benefit. *Id.* Not only did many of the drugs fail to demonstrate a health benefit, but two of the drugs "actually made [a patient's] quality of life worse." *Id.* Yet, one of the drugs that "reduce[d] quality of life and d[id] not increase life expectancy [was] sold for approximately \$170,000 per person per year." *Id.*

<sup>214</sup> Barlas, *supra* note 8.

<sup>215</sup> Goble, *supra* note 1, at 678. In an oncology meta-analysis, a study reported "that the correlation between surrogate markers and overall survival was low in 52% of the studies, medium in 25%, and high in only 23%." *Id.*

<sup>216</sup> *Id.*

<sup>217</sup> *Id.* The FDA approved cyclic adenosine, a heart drug, based on surrogate markers. Subsequently, studies discovered that the drug increased mortality up to 28%. Similarly, three other surrogate-approved drugs were "later found to increase mortality." Menkes, *supra* note 212.

<sup>218</sup> Goble, *supra* note 1, at 678.

<sup>219</sup> *Id.*

<sup>220</sup> Some experts purport that "surrogate endpoints in clinical studies may be advantageous when clinical outcomes are difficult to collect or take an unreasonable time to capture." *Id.*

<sup>221</sup> Menkes, *supra* note 212, at 612.

<sup>222</sup> Goble, *supra* note 1, at 679.

<sup>223</sup> *Id.*; see Vernessa T. Pollard et. al., *FDA Issues Real-World Evidence Framework for Drugs and Biologics*, MCDERMOTT WILL & EMERY (Dec. 12, 2018), <https://www.mwe.com/insights/fda-issues-real-world-evidence-framework-for-drugs-and-biologics/> (explaining that Title III, Subtitle C § 3022 "added §505F (21 USC 355g) to the Federal Food, Drug and Cosmetic Act (FDCA), requiring [the] FDA to establish a program to evaluate the potential use of evidence from clinical experience to help (1) support the approval of a new indication for a drug already approved under section 505(c) (21 USC § 355(c)) of the FDCA or (2) support or satisfy drug post-approval study requirements").

Title III describes real-world evidence as any “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.”<sup>224</sup> The provisions specifically accept real-world evidence that “includ[es] ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities.”<sup>225</sup>

Experts have raised concerns about clinical trials using real-world evidence due to “the relatively large number of assumptions necessary to analyze nonrandomized observational data.”<sup>226</sup> The main disadvantage of real-world evidence is that it is subject to selection bias.<sup>227</sup> Moreover, real-world evidence often will produce “information gaps” that decrease its quality and usefulness as clinical trial data.<sup>228</sup> As a matter of fact, real-world evidence can overestimate a drug’s benefits where the principal researcher does not implement controls against spurious correlations.<sup>229</sup>

## B. Increasing Device Development Laxity

### 1. Exempting Certain Class I and II Devices

Title III, Subtitle F § 3054 requires the FDA to establish a list of Class I devices that “no longer” need PMN review within “120 calendar days” of the Act’s passage and “at least once every 5 years thereafter.”<sup>230</sup> Similarly, the provision requires the FDA to establish a list of Class II devices that “no longer” need PMN review within “90 days” of the Act’s passage and “at least once every 5 years thereafter.”<sup>231</sup> As a result, the FDA exempted “more than 70 Class I device types and more than 1,000 Class II device types” from PMN review as of 2017.<sup>232</sup>

Some experts warn that the exemption initiative may increase patient harms because it lowers the approval standards of products that “[a]lready . . . [had] lax regulation.”<sup>233</sup> Regulators and stakeholders must understand that § 3054

<sup>224</sup> 21st Century Cures Act, Pub. L. No. 114-255, § 3022(b), § 505 F, 130 Stat 1033, 1096 (2016) (codified as amended at 21 U.S.C. 355(g)).

<sup>225</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3022(c)(2)(A), § 505 F, 130 Stat 1033, 1096 (2016) (codified as amended at 21 U.S.C.). Some experts believe that clinical trials are the “gold standard” for medical research, and an alternative standard could be “a step in the wrong direction.” Barlas, *supra* note 8 (quoting Sanket Dhruva, “a cardiologist and . . . researcher at the Yale School of Medicine”).

<sup>226</sup> Goble, *supra* note 1, at 679.

<sup>227</sup> *Id.* Selection bias occurs where the principal researcher selects study participants that are not representative of the target population, leading to bias and unreliable data. Wayne W. LaMorfe, *Selection Bias*, B.U. PUB. HEALTH, [http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713\\_Bias/EP713\\_Bias2.html](http://sphweb.bumc.bu.edu/otlt/MPH-Modules/EP/EP713_Bias/EP713_Bias2.html) (last updated June 19, 2020).

<sup>228</sup> Goble, *supra* note 1, at 679.

<sup>229</sup> *Id.*

<sup>230</sup> 21st Century Cures Act, Pub. L. No. 114–255, sec. 3054(a)(2), § 510(l), 130 Stat. 1033, 1126 (2016) (codified as amended at 21 U.S.C. 360(m)).

<sup>231</sup> 21st Century Cures Act, Pub. L. No. 114–255, sec. 3054(b)(1)(A)-(b)(1)(A)(ii), § 510(l), 130 Stat. 1033, 1126 (2016) (codified as amended at 21 U.S.C. 360(m)).

<sup>232</sup> Gottlieb, *supra* note 58.

<sup>233</sup> Rachel Solnick, *The 21st Century Cures Act: Big Pharma Handout or Drug Development Boon?*, EM RESIDENT (Feb. 1, 2017), <https://www.emra.org/emresident/article/the-21st-century-cures-act-big-pharma-handout-or-drug-development-boon/>. According to former United States

may lead to patient harms because it increases the number of commercially available devices that lack evidence of their safety and effectiveness.

## 2. Least Burdensome Device Review

Before Title III, the Food and Drug Administration Modernization Act (FDAMA) of 1997 required the FDA to “consider the least burdensome appropriate means necessary to demonstrate a reasonable assurance of device safety and effectiveness.”<sup>234</sup> Congress intended the least burdensome provisions to “eliminate[] unnecessary burdens that may delay the marketing of beneficial new products.”<sup>235</sup> Nevertheless, research sponsors alleged that the FDA failed to dutifully implement the least burdensome provisions into its approval process.<sup>236</sup> In response, Title III requires the FDA to more “accurately reflect Congress’ intent” regarding the FDAMA’s least burdensome provisions.<sup>237</sup>

Title III, Subtitle F § 3058 requires “each employee of the . . . [FDA] who is involved in the review of premarket submissions . . . [to] receive[] training” on “the meaning and implementation of the least burdensome requirements.”<sup>238</sup> Furthermore, it requires the FDA to periodically evaluate its use of the least burdensome principles to ensure that the agency is “[m]ore consistent[ly] and meaningful[ly] appl[ying]” them.<sup>239</sup>

Under Title III, the FDA has interpreted the least burdensome standard to require “the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.”<sup>240</sup> As a result, the FDA permits PMA devices to submit “[a]lternative sources of clinical data[,]” such as “peer-reviewed literature, outside the U.S. (OUS) data, real-world evidence (RWE), . . . well-documented case histories[,]” and nonclinical evidence.<sup>241</sup>

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Representative Mike Fitzpatrick of Pennsylvania, he “voted against the . . . [21st Century Cures Act] because it fail[ed] to protect patients against dangerous medical devices.” Llamas, *supra* note 27. See also *Congressman Mike Fitzpatrick: Medical device bill fails to protect patients*, BUCKS LOCAL NEWS (Dec. 1, 2016), [https://www.buckslocalnews.com/news/congressman-mike-fitzpatrick-medical-device-bill-fails-to-protect-patients/article\\_0ca589f0-55aa-5932-b584-b447257b9420.html](https://www.buckslocalnews.com/news/congressman-mike-fitzpatrick-medical-device-bill-fails-to-protect-patients/article_0ca589f0-55aa-5932-b584-b447257b9420.html).

<sup>234</sup> *The Least Burdensome Provisions: Concept and Principles: Guidance for Industry and Food and Drug Administration Staff*, FDA 5 (Feb. 5, 2019), <https://www.fda.gov/media/73188/download>.

<sup>235</sup> *Id.* at 4.

<sup>236</sup> See Sarah Faulkner, *How the 21st Century Cures Act will affect medical devices*, +MASS DEVICE (Dec. 8, 2016), <https://www.massdevice.com/21st-century-cures-act-will-affect-medical-devices/> (stating that “[t]he medical device industry has long held the position that . . . the [FDA] d[id] not comply with the requirement to determine the ‘least burdensome means’ of establishing substantial equivalence or effectiveness of a device”).

<sup>237</sup> *The Least Burdensome Provisions: Concept and Principles: Guidance for Industry and Food and Drug Administration Staff*, *supra* note 234, at 4.

<sup>238</sup> 21st Century Cures Act, Pub. L. No. 114-255, sec. 3058(a)(j)(1)(A), § 513 130 Stat. 1033, 1128 (2016) (codified as amended at 21 U.S.C. 360(c)).

<sup>239</sup> *Proposed FDA Work Plan for 21st Century Cures Act Innovation Account Activities*, FDA 11, <https://www.fda.gov/files/Proposed-FDA-Work-Plan-for-21st-Century-Cures-Act-Innovation-Account-Activities-as-Submitted-to-Science-Board.pdf> (last viewed Mar. 5, 2020).

<sup>240</sup> *The Least Burdensome Provisions*, *supra* note 234, at 4.

<sup>241</sup> *Id.* at 10–12.

Because Title III reduces the rigors of the FDA's most stringent review standards, it will allow high-risk devices to use weaker evidence to demonstrate their reasonable assurance of safety and effectiveness. It is essential that Title III does not convert PMA approvals into the equivalent of the less rigorous PMN pathway.

## VI. CONCLUSION

Congress passed the 21st Century Cures Act to increase the number of cures available to patients. However, Title III may deleteriously alter the evidentiary standards of drug and device approvals. For new drugs, Title III permits surrogate endpoints and real-world evidence in lieu of more rigorous scientific data. For new medical devices, Title III requires the FDA to exempt certain Class I and II devices from any kind of safety or efficacy evaluation. Moreover, Title III forces the FDA to use the least burdensome review standards across all device applications.

Although the 21st Century Cures Act may deliver benefits, potentially grave harms may offset its advantages. As a result, regulators and stakeholders must vigilantly monitor the Title III developments and safeguard the wellbeing of patients.