A Review of Recent Federal Legislative and Policy Initiatives to Enhance the Development and Evaluation of High Value Drugs in the United States

George A. Neyarapally

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A REVIEW OF RECENT FEDERAL LEGISLATIVE AND POLICY INITIATIVES TO ENHANCE THE DEVELOPMENT AND EVALUATION OF HIGH VALUE DRUGS IN THE UNITED STATES

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INTRODUCTION: THE NEED TO ENHANCE THE DEVELOPMENT AND EVALUATION OF HIGH VALUE DRUGS

The current rate of growth of health care costs in the United States is unsustainable. Annual health care costs in the United States far exceed annual health care costs in all other countries despite not providing comparatively high value to patients based on important health metrics such as in-hospital case-fatality mortality (the ratio of death occurring in patients presenting to a hospital with certain conditions, such as acute myocardial infarction) and health care quality (in 2010, the United States ranked second lowest on health care effectiveness and patient-centeredness out of seven industrialized countries). Health care currently accounts for about eighteen percent of Gross Domestic Product ("GDP"), costing approxi-
mately $2.7 trillion, and will likely increase in future years. In fact, federal health spending alone may surpass twelve percent of GDP by 2050. Congress recently failed to avoid the fiscal cliff, the draconian budget sequester, which will non-strategically decrease the funding of federal agencies across the board. Thus, Congress must soon complete the seemingly Herculean task of working together to comprehensively address the rising national deficit and debt. Specifically, as the Medicare and Medicaid health care program costs will continue to rise rapidly in the upcoming years, members of Congress are seeking ways to decrease health care costs, including the cost of drugs, while improving health care quality and patient health outcomes. Despite these staggering numbers, in 2005, the United States only spent six cents of every health care dollar on biomedical research and only one-tenth of a cent of every dollar on the long term evaluation of which drugs work best at the lower cost (identification of high value drugs).

Furthermore, there is a need for a continuously learning health care system because health care is increasing in complexity and uncertainty in light of the many new drugs, diagnostics, and other medical interventions that are approved every year. Specifically, this system would enable the generation and rapid use of evidence on health care interventions, including drugs; in such a system, "research influences practice and practice influences research." Additionally, the increased knowledge about the human genome has spurred the growing field of pharmacogenomics –

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4. William A. Mceachern, Macroeconomics: A Contemporary Introduction, 103, 105-6 (1997) (The annual national budget deficit is the amount by which federal expenditures in a given year exceed federal revenues. National debt is the accumulation of national deficits over time).

5. Hamilton Moses et al., Financial Anatomy of Biomedical Research, 294 JAMA 1333 (2005). See also, Hamilton Moses & E. Ray Dorsey, Biomedical Research in the Age of Austerity, 308 JAMA 2341 (2012) (The sequester, will significantly decrease funding for science and health agencies. For example, the NIH budget will decrease by about eight percent and the CDC and National Science Foundation will lose hundreds of millions in funding).

6. Institute of Medicine, Best Care at Lower Cost: The Path to Continuously Learning Health Care in America, S-5, 2-11 (2012).

7. Sarah M. Greene, Robert J. Reid, & Eric B. Larson, Implementing the Learning Health System: From Concept to Action, 157 ANN. INTERN. MED. 207, 208 (2012). See also Maureen Bisognano & Charles Kenney, Pursuing the Triple Aim: Seven Innovators Show the Way to Better Care, Better Health, and Lower Costs (2012) (This system pertains to the first part of the health reform triple aim, the provision of better (safer, more effective, and patient-centered) health care (the other two reform aims include better population health and lower per capita health care costs)).
study of how genetic differences impact drug effects – with important implications for personalized medicine and the development and prediction of real world drug safety and effectiveness. It is very difficult for prescribers to keep up with all of the new drugs, interventions, and emerging pharmacogenomic and biomedical information. Also, often clinical guidelines that apply to specific patients are not readily available; in fact, some studies estimate that only ten to twenty percent of clinical decisions are evidence-based. As new interventions are contributing to the complexity of care, so is the aging population. The first baby boomers entered the ranks of the elderly in 2011, and by 2020, approximately 157 million people will have at least one chronic condition. This will add further complexity to health care treatment regimens because elderly patients often suffer from multiple chronic conditions and hence take several medications, which “probably are the single most important health care technology in preventing illness, disability, and death” in this population. Often, evidence on the real world effectiveness of the many newly approved drugs each year in these chronically ill populations is lacking. Furthermore, with respect to drug safety, medication errors, an important subset of medical errors, are more likely to occur in patients taking multiple medications (who are not typically studied in clinical trials) and will likely increase as the elderly population increases. Also, recent Centers for Disease Control and Prevention (“CDC”) evaluation of the National Electronic Injury Surveillance

8. Institute of Medicine Report, supra note 6, at S-5, 2-11; Francis S. Collins, The Language of Life: DNA and the Revolution in Personalized Medicine, 238-43 (2010); Department of Health & Human Services: Secretary’s Advisory Committee on Genetics, Health and Society, Realizing the Potential of Pharmacogenomics: Opportunities and Challenges 1 (May 2008), available at http://oba.od.nih.gov/oba/sacghs/reports/sacghs_pgx_report.pdf (Pharmacogenomics has significantly contributed to the evaluation of which drugs work in which patients and which patients may be at risk for serious adverse reactions based on genetic mutations such as single nucleotide polymorphisms (SNPs)). See Talitha I. Verhoef, et al., Cost-effectiveness of pharmacogenetics in anticoagulation: international differences in healthcare systems and costs, 13 Pharmacogenomics 1405, 1412 (2012). FDA has made several drug label changes based on pharmacogenomic information and drug safety and effectiveness, e.g., Warfarin, an anti-thrombotic drug commonly used to prevent serious cardiovascular events such as stroke, and therapeutic dosing based on the activity of certain metabolic enzymes; Abacavir, a HIV drug, and serious hypersensitivity reactions based on the "presence of genetic variants on chromosome 6"; and clopidogrel, an anti-platelet drug used to prevent serious CV events, effectiveness based on the activity of metabolic enzyme need to active this pro-drug). Although these label changes are important, ongoing trials are needed to evaluate the cost-effectiveness of these genetic tests in light of their costs and impact on patient outcomes.

9. Institute of Medicine Report, supra note 6, at 3-3. In addition, although clinical practice guidelines have increased significantly in recent years, the scientific evidence underlying these guidelines has been quite variable and underutilized by physicians due to lack of awareness. Ronen Avraham, Clinical Practice Guidelines: The Warped Incentives in the US Healthcare System, 37 AM.J.L. & MED. 7, 16-18 (2011).


System ("NEISS") recently found that commonly used drugs such as antithrombotics (e.g., warfarin) are responsible for a significant number of adverse drug events in elderly patients. Thus, considerations of medication errors and drug safety in the elderly are important in the context of the evaluation of the value of drugs (i.e., comparative effectiveness and safety) in this growing population.

Despite the fact that drugs account for only about ten percent of health care costs, the cost of prescription drugs in the United States has increased significantly in recent years, and increased from $40 billion in 1990 to $250 billion in 2009. Furthermore, although the global market for drugs is increasing between three percent and six percent annually, most of this occurs not in the United States but rather in developing countries. Pharmaceutical companies are faced with increasing challenges as many blockbuster drugs are now coming off patent, resulting in major losses in profit. For example, Lipitor, a HMG coenzyme reductase inhibitor (a "statin" drug, which lowers cholesterol levels) drug indicated for the treatment of hyperlipidemia, which netted Pfizer almost $12 billion per year, recently went off patent. Thus, while the cost of health care and drugs is increasing at an unsustainable rate, pharmaceutical companies are facing great challenges in maintaining profits in the United States and will lose over $100 billion in profits as a result of generic market entrants that will compete with branded blockbusters.

Also, the efficiency of pharmaceutical company funded research has significantly decreased, spawning the new term "Eroom's law," which is the opposite of Moore’s law, a prediction by Intel founder Gordon Moore of the doubling of the "number of components that could be packed on a [micro] chip . . . doubling of . . . memory capacity and processing speed, a halving of size and cost" which has held true in recent decades. Eroom’s law describes a phenomenon that, contrary to Moore’s law, describes the halving of new drug approvals per $1 billion in Research and Development ("R&D") approximately every nine years. Furthermore, in light of

15. Id.
16. President's Council of Advisors on Science and Technology ("PCAST"), Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation, 9 (Sept. 2012).
the sluggish economic recovery, funding from venture capitalists to support smaller biotechnology companies is harder to obtain.\textsuperscript{20} Despite these challenges, it is true that the Food and Drug Administration ("FDA") approvals of new molecular entities ("NMEs") were much higher than in 2011 and 2012 (twenty-four and thirty-three respectively) than in recent years and included high value drugs, attributable in part to the increased investment by pharmaceutical companies in specialty and orphan drugs (see Part I. Sect. E of this paper).\textsuperscript{21} Thus, the industry has responded to the "Eroom" dilemma by shifting their focus to high cost specialty and orphan drugs that address unmet medical needs in relatively small patient populations compared to investing in drugs designed to treat the most prevalent chronic conditions in the United States.\textsuperscript{22} It remains to be seen if this trend to develop high cost, narrowly focused drugs will continue into the future.

Considering the impending budget sequestration, increasing national debt (and associated decreases in funds available for federal expenditures, including health care entitlements such as Medicare and Medicaid), and rising cost of healthcare (e.g., medical technologies, services, drugs); increasing health care complexity; and pharmaceutical and biotechnology company monetary challenges; it is imperative to evaluate recent (from 2007-2012) federal legislative and policy initiatives to enhance the development and evaluation of high value drugs. For purposes of this paper, high value drugs\textsuperscript{23} ("HVDs") are defined as drugs that (1) provide good benefit for their cost; (2) are comparatively/incrementally more effective and/or safe relative to the standard of care, thus addressing unmet medical needs (as stated by FDA, a "medical need not addressed adequately by an existing therapy"\textsuperscript{24}); and (3) improve health outcomes and metrics important to patients. Part I will discuss recent federal legislative and policy initiatives (with some brief mention of pharmaceutical company and payer efforts) to maximize the development and approval (premarket stage) of high value drugs. Part II will review recent federal legislative and policy initiatives pertaining to the evaluation (postmarket stage) of high value therapeutics for patients. Part III will discuss potential future federal legis-

\textsuperscript{20} Id.
\textsuperscript{22} Janet Woodcock, THE FUTURE OF ORPHAN DRUG DEVELOPMENT, 92 CLINICAL PHARMACOLOGY & THERAPEUTICS 146, 146 (2012). See also Formulary Staff, New nonprofit represents specialty pharmacy, 48 FORMULARY 39, 39 (2013).
\textsuperscript{23} Institute of Medicine Report, supra note 6, at 8-5 (The Institute of Medicine points out that better metrics are needed to evaluate value with existing data and defines value as "the level of benefit achieved at a given cost").
\textsuperscript{24} FDA, Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review 6 (Jan. 2006).
lative and policy efforts that may further enhance the development of HVDs and evaluation and use of these drugs. This paper does not primarily focus on: efforts to improve the value of drugs by improving product quality (e.g., anti-counterfeiting efforts, good manufacturing practice ("GMP") drug quality-related efforts to minimize substandard and falsified drugs\(^2\)) and decreasing health care fraud (knowingly or recklessly misrepresenting material facts for pecuniary gain), which accounts for significant drug-related costs in the health care system and results in the use of drugs that may not be valuable for patients (e.g., illegal off-label promotion of drugs that are not effective in treating conditions for which they purportedly work)\(^2\); efforts to increase use of generic small molecule drugs, although these efforts have significantly increased access to cost-effective, valuable therapies\(^7\); health care delivery system innovations, which may systematically enhance the impact of high value drugs by improving the underlying infrastructure (e.g., the use of electronic health records to evaluate use of high value drugs in the real world)\(^2\), global payments to reward achievement of good clinical outcomes) and efforts to enhance the communication, translation, and dissemination of evaluations of drug value, although this is also critical so patients and healthcare providers can make informed, evidence-based decisions.\(^9\)

**PART I: RECENT FEDERAL LEGISLATIVE AND POLICY INITIATIVES TO MAXIMIZE THE DEVELOPMENT**


26. TERRY L. LEAP, PHANTOM BILLING, FAKE PRESCRIPTIONS, AND THE HIGH COST OF MEDICINE: HEALTH CARE FRAUD AND WHAT TO DO ABOUT IT 3 (2011) (In 2009, fraudulent Medicare and Medicaid payments alone were approximately $54 billion).

27. Generic competition under the Hatch-Waxman Act of 1984 has served as the primary “driver of declining prices for several highly prescribed drug classes.” As many of these drugs are HVDs, this has significantly increased patient access to HVDs by making these drugs affordable. See Henry Grabowski et al., Evolving Brand-Name and Generic Drug Competition May Warrant a Revision of the Hatch-Waxman Act, 11 HEALTH AFF. 2157, 2163 (2011).

28. See American College of Cardiology Annual Scientific Session & Expo 2012: Formulary decision process at Mayo Clinic leads to abandoning 80-mg dose of simvastatin, 47 FORMULARY 340 (2012) (Recently the Mayo Clinic used electronic health records ("EHRs") to evaluate the use of simvastatin 80 mg, after a FDA drug safety communication discussed the increased risk associated with muscle damage at this dose. As many patients were taking this high risk dose of the drug (based on a review of EHRs), the clinic’s taskforce leveraged this knowledge to communicate with physicians and patients about this safety issue and inform their clinical decision-making about the appropriate therapy).

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(PREMARKET STAGE) OF HIGH VALUE DRUGS

A. Background

There are important, recent legislative and policy initiatives undertaken by the federal government to maximize the development of high value drugs ("HVDs"). This section will evaluate these initiatives and their potential impact on the development of HVDs. In the context of drug development enhancements, the recent report by the President’s Council of Advisors on Science and Technology ("PCAST") pointed out specific challenges including the high failure rate of drugs throughout the approval process, regulatory uncertainty, high expenses, long time to market, amongst other challenges.\(^3\)

To support the United States' economic competitiveness and innovation, in addition to enhancing public health outcomes, PCAST set an ambitious goal to "double the annual output of new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety through industry, academia and government working together."\(^3\) Jack Scannell and colleagues point out the following policy challenges in drug development that may impede PCAST's ambitious goal: (1) as more drugs have been approved, it is more difficult to obtain approval and reimbursement for high value drugs (e.g., producers of a new drug for acid reflex must attempt to provide added value to the current H2 blockers and proton pump inhibitors ("PPIs") if they wish their drugs to be reimbursed)\(^3\); (2) the low hanging fruit problem of development of drugs with easily identified targets (which may not provide additional value compared to currently available drugs); (3) the cautious regulator problem; and (4) the "throw money at it" tendency, which involves the commitment of significant resources without understanding factors that affect return on investment.\(^3\) These policy challenges must be addressed to improve drug development in the United States; the initiatives discussed below will address some of these challenges.

B. The FDA Safety and Innovation Act: Legislative Initiatives

In July 2012, President Obama signed into law the omnibus FDA bill, the FDA Safety and Innovation Act (FDASIA), which includes new user fee authorizations and re-authorizations for prescription drugs (PDUFA),

\(^{31}\) PCAST, supra note 16.
\(^{32}\) Scannell, et al., supra note 17, at 194.
\(^{33}\) Id.
medical devices (MDUFA), generic drugs (GDUFA), and biosimilars ("BSUFA") and will enable FDA to collect up to $6 billion in the next five years. This law, which is organized into eleven titles, includes several provisions designed to stimulate the development of high value drugs. Titles III and IV provide for user fees to speed up the approval of small molecule generic drugs (Title III) and biosimilars (Title IV). After the advent of the Drug Price Competition and Patent Restoration Act (Hatch-Waxman Act) of 1984, the development and approval of generic drugs has significantly decreased the price of high value drugs once brand drugs go off patent, historically resulting in savings of $8 billion to $10 billion annually which has increased in recent years to just under $200 billion per year. However, in recent years, FDA has accumulated a significant backlog of generic drug applications due to understaffing. The funds from the Generic Drug User Fee Act and provisions will increase staffing and support efforts to expedite the review of generic drugs, enhance the post-market safety evaluation of such drugs, and ensure product quality. Funding for this authorization was tenuous in light of the recent continuing resolution passage to fund the federal government with the same level of funding as the prior fiscal year; but, at the last minute Congress passed a bill that enabled FDA to begin collecting user fees on October 1, 2012, and thus FDA can move forward with this new user fee program. The program will significantly reduce review times from thirty months to ten months. This provision of FDASIA will expedite the approval of generic drugs, enabling earlier access to drugs that improve health outcomes at a much lower cost. However, as a significant percent of the market use already uses generic drugs once they are available, this will have a modest, albeit important, effect on the approval and use of such drugs by speeding access to them by just under two years.

Congress recently authorized a new abbreviated approval pathway for medical devices (MDUFA), generic drugs (GDUFA), and biosimilars ("BSUFA") and will enable FDA to collect up to $6 billion in the next five years. This law, which is organized into eleven titles, includes several provisions designed to stimulate the development of high value drugs. Titles III and IV provide for user fees to speed up the approval of small molecule generic drugs (Title III) and biosimilars (Title IV). After the advent of the Drug Price Competition and Patent Restoration Act (Hatch-Waxman Act) of 1984, the development and approval of generic drugs has significantly decreased the price of high value drugs once brand drugs go off patent, historically resulting in savings of $8 billion to $10 billion annually which has increased in recent years to just under $200 billion per year. However, in recent years, FDA has accumulated a significant backlog of generic drug applications due to understaffing. The funds from the Generic Drug User Fee Act and provisions will increase staffing and support efforts to expedite the review of generic drugs, enhance the post-market safety evaluation of such drugs, and ensure product quality. Funding for this authorization was tenuous in light of the recent continuing resolution passage to fund the federal government with the same level of funding as the prior fiscal year; but, at the last minute Congress passed a bill that enabled FDA to begin collecting user fees on October 1, 2012, and thus FDA can move forward with this new user fee program. The program will significantly reduce review times from thirty months to ten months. This provision of FDASIA will expedite the approval of generic drugs, enabling earlier access to drugs that improve health outcomes at a much lower cost. However, as a significant percent of the market use already uses generic drugs once they are available, this will have a modest, albeit important, effect on the approval and use of such drugs by speeding access to them by just under two years.

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Congress recently authorized a new abbreviated approval pathway for

35. See Congressional Budget Office, How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry (Jul. 1998). These savings are now much greater in light of the patent expiration of several blockbuster drugs in recent years (e.g., Lipitor). See also The Generic Pharmaceutical Association, Savings: $1 Trillion Over 10 Years; Generic Drug Savings in the U.S. (2012), available at www.gphainline.org/media/cms/IMSStudyAug2012WEB.pdf (last visited Mar. 06, 2013).
36. FDASIA, Pub. L. No. 112-144 (2012) at Title III; Margaret A. Hamburg, Remarks at the Annual Conference of the Food and Drug Law Institute, FOOD & DRUG L.J. 123, 126 (2012).
37. FDA User Fee Corrections Act of 2012, H.R. 6433 (approved by the House and Senate July 2012).
38. Government Accountability Office, Savings from Generic Drug Use, GAO-12-371R at 2 (Jan. 31, 2012) (seventy-eight percent of drugs that are dispensed in retail pharmacies are generics, and this percentage may increase in upcoming years in light of the expiration of blockbuster drug patents).
biosimilar drugs, defined as “highly similar” to their reference biologic products, in the Patient Protection and Affordable Care Act (“ACA”). In 2012, FDA published guidance documents on the approval of biosimilars. Title IV of FDASIA provides for biosimilar drug user fees. This provision can significant expedite and enhance the approval of affordable high value biologic therapies in the future. This is important as many of these biologic drugs are extremely expensive; for example, Cerezyme, a drug used to treat Gaucher disease, costs approximately $200,000 per year. In addition in 2012 biologic drugs accounted for a majority of clinical and hospital drug expenditures. Thus, the expedited approval of biosimilars could stimulate the development and approval of beneficial biologic drugs at a lower cost, increasing the value of these drugs.

Importantly, more pharmaceutical and biotechnology companies are seeking to develop these therapies because they provide high value and are much more profitable than small molecule drugs, which are subject to more competition (i.e., generics). However, the development of biologic drugs, which are much more complex (i.e., protein folding) than small molecule drugs, is much more expensive and involves a complex manufacturing process. Thus, due to these high barriers to entry, the market for biosimilars is anticipated to be much smaller than that of small molecule generic drugs. The market for biosimilars may increase in future years with advancements in analytical technology and it is estimated that it will be approximately $2 billion to $2.5 billion annually by 2015 (the Congressional Budget Office scored approximately $7 billion in savings over a ten-year timeframe from the use of biosimilars.). Thus, biosimilars will

44. IMS Health, Shaping the biosimilars opportunity: a global perspective on the evolving biosimilars landscape 1 (Dec. 2011). This is relatively small compared to the global biopharmaceutical market, estimated to be $856 billion in 2010) and spending on prescription drugs in the U.S., which was approximately $250 billion in 2009 (see CMS, Office of the Actuary, National Health Statistics Group (2011) available at: http://www.cms.gov/NationalHealthExpendData/downloads/tables.pdf; JOHN E. MCDONOUGH, INSIDE NATIONAL HEALTH REFORM 230 (2011)). In addition, the “complex patent litigation procedures” for biosimilars may limit the utility of the market exclusivity associated with interchangeable biosimilar products. See Kenneth J. Szetzo & Marian Wolanski, Initial Steps in the Regulation of Generic Biological Drugs: A
likely enhance approval of cost-effective valuable drugs in the longer term but in the near term will likely not have the same impact on prices and value as small molecule generics. Furthermore, unique comparative safety issues associated with complex biologic drugs (in contrast to small molecule drugs), such as immunogenicity, may make clinicians less likely to prescribe biosimilars in the future, even if required clinical studies are completed; for example, a small manufacturing process change in the production of the biologic Eprex (a red blood cell production stimulator) resulted in patients experience a severe, immunogenicity-related condition, pure red cell aplasia.

In addition to the above user fee programs, FDASIA includes provisions to stimulate the development of drugs that address unmet medical needs. The law enhances patient access under accelerated approval and creates a “breakthrough therapy” designation for drugs. During the inception of the expedited development and accelerated approval programs in the 1980s, the focus was on important unmet medical needs such as HIV/AIDS and cancer. The accelerated approval program facilitates increased communication between FDA and drug sponsors early on to “seek agreement on the design of necessary preclinical and clinical studies needed to gain marketing approval.” This communication expedites the rapid development and review of these products that address unmet medical needs.

In 1997 Congress codified this program as the “Fast Track” program in the FDA Modernization Act (“FDAMA”). In the 2006 FDA guidance on the fast track program, FDA defined “unmet medical need” with respect to serious conditions as follows: (1) no available therapy; (2) available therapies but: (i) superior effect on serious outcomes, (ii) effect on serious outcomes not affected by other therapies, (iii) ability to provide benefit while avoiding serious toxicity, or (iv) ability to provide benefit while avoiding serious toxicity, or (iv) ability to provide benefit for

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47. FDASIA, Pub. L. 112-144 (2012), at Title IX, §§ 901 & 902.
49. Id.
51. FDA Modernization Act (“FDAMA”), Pub. L. 105-115 (2007), Sec.112.
patients who can’t tolerate alternative therapies; and (3) the only available therapy was approved under accelerated approval.\(^5\) It is important to bear this unmet medical need definition in mind when evaluating the new FDASIA provisions pertaining to accelerated approval. One critical aspect of this program has been the early and informative feedback from FDA to the drug sponsors and strong collaborations between the two.\(^5\) Also, the accelerated approval process has enabled FDA to approve drugs for these serious conditions to address unmet medical needs based on “surrogate” outcomes (e.g., clinical laboratory values); this is essential as it enables approval of drugs without long clinical trials, although it underscores the need to evaluate health outcomes in the post-market setting (i.e., Phase IV studies) to ensure the drugs are safe and effective. Overall, drugs approved under the expedited development program have been made available significantly faster than drugs not approved under the program and the “total regulatory phase” was 3.3 years less during the period between 1988 and 1993 for drugs in the program compared to drugs not approved under the program.\(^5\) In addition, the “five original drugs” approved under the accelerated approval program were approved more quickly, including a FDA review phase with a mean of 8.3 months.\(^5\) Thus, the program has successfully accelerated the development and approval of high value drugs.

In Section 901 of FDASIA, the law stipulates that after the initial establishment of the accelerated access program, advancements in science, such as genomics and molecular biology, along with innovative clinical trial designs and other aspects of drug development, have enabled the creation of targeted, novel, and innovative therapies.\(^5\) In light of these developments, the law describes Congress’ interest in ensuring that the FDA take steps to increase access to these innovative drugs, thus addressing unmet medical needs for serious or life threatening diseases or conditions. Society’s focus on enhancing patient access to drugs that address unmet medical needs is illustrated, by the recent efforts of the FDA before FDASIA enactment to enhance access to HVDs. For example, in 2009, the FDA enhanced previous expanded access efforts by promulgating a fi-

\(^{52}\) FDA Guidance: Fast Track Drug Development Programs, supra note 50, at 6.


\(^{54}\) Id. at 513.

\(^{55}\) Id. at 516.

\(^{56}\) FDASIA, supra note 47, at § 901. The law will also enable FDA to use more flexibility when evaluating endpoints for drugs under accelerated approval. See, Cheryl Thompson, Rare-disease drugs to receive consideration on par with serious-disease drugs, 69 AM. J. HEALTH SYS. PHARM. 1936, 1937 (2012).
nal rule on expanded access to investigational drugs for individual patients and intermediate size patient populations. This increased access to HVDs for a small, but important group of patients with unmet medical needs. This afforded access to approximately 3,000 patients, thus increasing overall access to patients with serious or life-threatening conditions to approximately 56,000 patients.58

Section 901 of FDASIA requires the FDA to consider the application of the accelerated approval program to a “broad range” of serious or life-threatening conditions and the FDA has indicated its intention to expand accelerated approval in light of this section of the law.59 In addition, the FDA will develop a guidance on surrogate endpoints which will inform industry of FDA’s latest thinking on this issue and help companies to understand when they can pursue this approach.60 This increased certainty may increase industry’s investment in the HVDs that may be approved via this streamlined “surrogate” based approach. In Section 902, Congress created a “breakthrough therapy” designation.61 This section is designed to decrease the time of development of HVDs. Drugs are designated as breakthrough therapies if they are to be used for treatment of a serious or life-threatening condition and “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.”62 Thus, the new provision focuses on enhancing the development of drugs with a comparatively high value, when compared to currently available drugs with the same indication. The law authorizes the FDA to take specific actions to expedite the development of breakthrough drugs, including: (1) holding meetings with the sponsor throughout drug development; (2) providing advice on the necessary clinical and non-clinical data for the development program; (3) involving senior managers; (4) establishing a cross-disciplinary review team leader; and (5) taking steps to ensure the clinical trial process is efficient.63 The FDA will now “issue initial instructions to industry about how it will identify a breakthrough drug”64 and is required to publish a draft guidance on implementation of the breakthrough therapy

58. Id. at 40930.
60. Id. at 1921.
61. FDASIA, supra note 47, at § 902, Breakthrough Therapies.
62. Id.
63. Id.
64. Norman, supra note 59, at 1920.
provisions. Although the impact of these provisions remain to be seen, the national disease specific organizations, who represent patients, have significant expertise on the rare diseases that might be addressed by breakthrough therapies. They will provide important stakeholder input on this approach, staunchly support this provision, and think it will enhance the development and approval of important HVDs. However, it is possible that the FDA may have worked with sponsors to accelerate these therapies on their own initiative and now the agency may instead be bogged down in reviews required of drugs meeting the criteria instead of collaborating directly with sponsors via the current process. The FDA’s required guidance on the breakthrough therapy provision, which must be completed by 2014, may alleviate this problem by informing the industry of how this provision may be applied by the FDA.

In addition, FDASIA includes a provision to extend the patent exclusivity period for new qualified infectious disease products to stimulate the development of much needed new antibiotics. The lack of antibiotics is a significant unmet medical need. Most of the 2 million hospital-acquired infections that occur annually are caused by pathogens resistant to bacteria, causing significant morbidity and mortality and costing over $30 billion each year. It is similar to the Hatch-Waxman Act of 1984, which patients with serious diseases supported, because it incentivized pharmaceutical companies to develop drugs to treat conditions for which there was not any available therapeutic by extending patent terms. It is also similar to FDAMA and the Best Pharmaceuticals for Children Act (“BPCA”), which provided for additional market exclusivity in exchange for the conduct and completion of studies to provide evidence on the safety and effectiveness of drugs in children, patients are counting on the current market exclusivity provisions to enhance the development of access to

65. FDASIA, supra note 47, at § 902.
66. Norman, supra note 59, at 1919. See also, Wechsler, supra note 34.
68. FDASIA, supra note 47, at § 902.
69. FDASIA, supra note 47, at § 505E. [355f], Extension of patent exclusivity for new qualified infectious disease products.
high value therapies. As BPCA continues to significantly increase the development of drugs to treat children, this provision may also enhance the development of high value antibiotics by addressing the market failure attributable to the low profitability of these drugs.

Section 908 of FDASIA contains provisions for a priority review voucher program to stimulate investment in the development of therapies for the treatment of rare pediatric diseases, an important unmet medical need. This program is modeled on the priority review voucher program from the FDA Amendments Act ("FDAAA") of 2007, which was created to stimulate investment in tropical neglected diseases. Upon a drug sponsor's successful development of a drug indicated to treat a rare pediatric disease, the law provides for FDA to grant priority review of another drug product (e.g., a product that the sponsor anticipate will be highly profitable, such as one to treat a highly prevalent, chronic disease). Although in theory this voucher is valuable because it could enable a sponsor to get a highly profitable drug on the market faster, providing for earlier profit accrual, the priority review voucher program has not been very successful and has only resulted in the approval of one drug to treat a neglected disease. One reason this may not have attracted much industry interest is because it requires investment in costly clinical trials for these rare diseases, which are risky in light of the high cost and failure rates of trials. In addition, the recent Canadian experience with priority approvals indicates that drugs approved under an accelerated paradigm may be asso-

73. Rib-X Pharmaceuticals, Rib-X Pharmaceuticals Receives Qualified Infectious Disease Product (QIDP) Designation from the FDA for Delafloxacin, (Sept. 17, 2012), available at http://www.reuters.com/article/2012/09/17/idUS82683+17-Sep-2012+BW20120917 (FDA designated delafloxacin, develop by Rib-X Pharmaceuticals as one of the first QIDPs soon after the passage of FDASIA). See also FDA, CDER, & HHS, Public Hearing, Establishing a List of Qualifying Pathogens That Have the Potential to Pose a Serious Threat to Public Health (Dec. 18, 2012), transcript available at http://www.fda.gov/downloads/Drugs/NewsEvents/UCM338748.pdf (During this meeting, drug sponsors, including the company Rib-X, whose product received the first QIDP designation, emphasized the importance of the extended market exclusivity in stimulating investment in this area, especially for small companies with limited resources and no or few successful products on the market).
74. FDASIA, supra note 47, at § 908; Industry Gains Incentives for Drugs for Children. 2 CANCER DISCOVERY 758 (2012).
76. Brenda Sandburg, FDA Awards First-Ever Priority Review Voucher to Novartis for Coartem Approval, THE PINK SHEET 005 (Apr. 8, 2009); Tatum Anderson. Novartis under fire for accepting new reward for old drug, 373 LANCET 1414 (2009). See also, Michael McCaughan, The End of the Priority Review Voucher (Revisited), THE RPM REPORT (2012) (indicating that Novartis is still the first and only company to receive a priority review voucher for developing a drug to treat neglected diseases (as of February 2012)).
associated with increased safety issues.78

FDASIA requires FDA to “solicit views of patients during the medical product development process” by creating a process for a patient representative to attend drug development meetings between drug sponsors and FDA and identifying patients with minimal conflicts of interest.79 This statutory requirement will enhance patient input in the drug development process and in turn increase the focus drug development discussions on patient, in addition to regulatory and prescriber-based consideration. Further, in the PDUFA V goals letter, which lists the PDUFA funding reauthorization commitments, FDA also highlights important regulatory science and policy-related initiatives by FDA that will enhance the development of HVDs.80 With respect to patient-reported outcomes (“PROs”), the FDA will hire new staff with relevant clinical and statistical expertise, provide consultations on and promote best practices for the development of PROs, and integrate the new staff into new drug divisions.81 This will, in turn, improve HVD development by providing for a “greater understanding of challenges that arise during development of outcomes assessment tools, potential strategies to overcome these challenges, and greater consistency in FDA’s approach to the review, qualification, and usage of these tools as part of the drug development process.”82 The PRO provisions are especially important in light of the developing evidence base supporting the positive effect of shared decision-making (with patients and healthcare professionals) on the improvement of patient health outcomes in a complex medical care environment.83 Obtaining patient input and focusing on outcomes important to patients when developing medical interventions, including drugs, may lead to the approval of drugs which significantly improve patient quality of life and other important patient-focused measures and hence provide significant value. The Institute of Medicine (“IOM”) recently asserted, “a learning health care system is anchored on patient needs and perspectives.”84 FDA’s PRO-related efforts will be consistent with this approach and support the development of HVDs in such a

79. FDASIA, supra note 47, at § 1137.
81. Id. at 21.
82. Id. at 22.
83. Annette O’Connor et al., Toward the Tipping Point: Decision Aids and Informed Patient Choice, 26 HEALTH AFF. 716, 716-725 (2007).
84. Institute of Medicine Report, supra note 6, at 5-5.
system. Furthermore, the clinical trial-related PRO methods development can enhance the rapid testing and approval of HVDs. In addition, under PDUFA V, FDA will be advancing the development of biomarkers. This is critical to the development of high value drugs for certain conditions such as cancer, which is a disease of genetic progression. Targeted drugs have been developed based on biomarkers that can predict drug effectiveness and safety in the real world, such as effects on molecular targets and inductions of certain enzymes that may increase drug toxicity.85

C. The Patient Protection and Affordable Care Act (ACA):
Legislative Initiatives

There are some key legislative initiatives in the ACA, in addition to the biosimilars pathway mentioned above, that may enhance the development and approval of high value drugs. One key legislative initiative in ACA is the Cures Acceleration Network (“CAN”), which was created to support translational research86 that may accelerate the development of high value drugs and other medical products.87 Specifically, this may address the fact that “95% of drugs fail in [increasingly expensive] clinical trials, with 82% [of the drugs] dying in Phase II alone.”88 This low rate of success has stymied the development of cures, and as a result, in recent years less HVDs have been developed to address unmet medical needs and cure diseases.89 The genesis of this provision stems from Senator Joseph Lieberman’s proposal during the Democratic presidential primary to support the development of cures by funding a $150 billion federal initiative to support the development of disease cures.90 In 2005, Senator Lieberman introduced the American Center for Cures Act91 which emphasized the importance of funding translational research,92 especially in light of the in-

87. Id.
88. Id.
89. Id. (Senator Lieberman defined translational research as “investigation in which knowledge obtained from fundamental research such as with genes, cells, or animals, is transformed through early and late state development prototyping and testing into diagnostic or therapeutic interventions that can be applied to the treatment or prevention of disease or frailty.”)
90. OLSON & CLAIBORNE, supra note 88, at 3.
92. Id. (Senator Lieberman defined translational research as “investigation in which knowledge obtained from fundamental research such as with genes, cells, or animals, is transformed through early and late state development prototyping and testing into diagnostic or therapeutic interventions that can be applied to the treatment or prevention of disease or frailty.”)
creasing complexity of chronic diseases, which at the time accounted for billions of dollars spent in the United States on health care each year (this amount will increase due to the aging population). Specifically, the bill would have created an American Center for Cures within the National Institute of Health ("NIH") whose mission would be to "increase the capacity of the National Institute of Health to promote translational research" to "speed the development of effective therapies, diagnostics, and cures essential to human health and well being."\footnote{Id.} This Center would have implemented a strategy for translational research, including prioritization and funding of innovative multi-disciplinary projects guided by "Grand Challenges" to direct the research community in undertaking projects that "transform the healthcare environment," such as nanotechnology, stem cell research, infrastructure to facilitate studying the human genome, development of rapid vaccine manufacturing capacity, a fast track clinical trial infrastructure, antibiotic resistance, and other projects.\footnote{Cures Act, supra note 91.} Also, the Center would have facilitated the development of HVDs by providing funding to develop drugs to treat conditions without a large, continuous market, such as antibiotics (there is an unmet need for new antibiotics in light of increasing resistance to existing agents and the emergence of superbugs) and vaccines (the current technology was based solely on egg-based production\footnote{The flu vaccine shortage in 2004 was caused in part by our continued reliance at the time on the old intensive egg-based vaccine production process. See \textsc{Tim Brookes}, \textsc{Chapter 3: Making Flu Vaccine}, in \textsc{Influenza and the 2004 Flu Vaccine Shortage}, 15-22 (2005).}, which limits rapid production and there is still a great need for a HIV vaccine). The Center also was tasked with supporting infrastructure development that individual corporations did not support on their own, such as human genomics research infrastructure. Importantly, the bill authorized $5 billion a year to "support research and development of breakthrough biomedical discoveries via grants, contracts, and cooperative agreements to public and private sector organization."\footnote{Cures Act, supra note 91.} Half of the funds would be allocated to the Health Advanced Projects Research Agency, modeled after the Defense Advance Research Projects Agency ("DARPA"), which has successfully funded innovative high risk projects in the defense technology arena that are too risky for companies to pursue. The bill would have also created a Center for Cures Council composed of the directors of the key federal health agencies, including NIH, CDC, FDA, the Agency for Healthcare Research & Quality ("AHRQ"), other organizations such as the Institute of Medicine, small businesses, and the bi-
opharmaceutical industry. These leaders with significant expertise from these technical agencies, institutes and industry would make recommendations to the Cures Director on research priorities.

The bill also would have set up Federally Funded Research and Development Centers ("FFRDCs") to carry out Center activities in consultation with representatives from private industry, institutions of higher education, other federal agencies, and other organizations.97 FFRDCs are hybrid organizations that address needs of the United States via private companies whose strengths lie in “their flexibility to assemble teams of technical experts on a project basis” and they are designed to “translate research into projects.”98 Thus, this was an important aspect of the Cures Act as it would enable multi-disciplinary teams to successfully fund risky, translational research to develop cures. In addition, the Cures Act also would have created the Health Advanced Research Projects Agency (“HARPA”), modeled after DARPA. This agency would have consisted of several portfolio managers and would be flexible, non-hierarchical, and have substantial freedom and incentives to fund high-risk projects that may translate research into cures. Further, the staff would rotate in and out every three to five years, thus continuing the cycle of funding innovative managers and researchers. These innovative entities would have the flexibility and ability to fund high-risk projects that could develop HVDs (in contrast to NIH, generally, which is subject to significant funding rules and restrictions). Other provisions would have included support of centralized institutional review boards (“CIRBs”) to expedite the review process99, provisions for funding small businesses to stimulate investments in translational research, assistance in the regulatory product development process for small companies, database creation of translational research, patent incentive provisions, and a Center for Excellence in Clinical Bioinformatics to support the development of tools and methods.100 Overall, the comprehensive bill authorized a significant amount, $50 billion in ten years101, and supported numerous approaches to stimulate translational research and ultimately, the development of cures for serious conditions. In

97. Id.
99. The Centralized IRB proposal is a critical one because one of the main challenges in conducting trials of potentially high value drugs is the fact that multi-site studies currently require increased time and effort, in addition to reduced protection of patients, due to the current regulations requiring cumbersome multi-site IRB reviews for these studies. See Jerry Menikoff, The Paradoxical Problem with Multiple-IRB review, 363 NEW ENG. J. MED. 1591, 1592-3 (2010).
100. Cures Act, supra note 91.
101. Id.
2008, Senator Lieberman reintroduced this bill in the 2008 Congress under the new name, the Accelerating Cures Act. This bill would have also created a FFRDC, although for clinical effectiveness research, and the HARPA, similar to the 2005 bill, to support translational research. The bill also included the CIRB provisions to streamline research, and support for the training of translational researchers and small businesses.

Senator Arlen Specter introduced a bill in 2009 to create an extra-NIH entity that would significantly increase authorization for NIH funding and authorize $1 billion in funds for the new Cures Acceleration Network. In the Patient Protection and Affordable Care Act, with the support of Senator Arlen Specter, who was interested in Lieberman’s concepts and saving the biotech industry, Congress created the CAN within NIH. The ACA authorized $500 million in 2010 for CAN to provide grants and awards, including some percentage of DARPA-type funding for high risk projects (Cures Acceleration Flexible Research Awards), building on Senator Lieberman’s model. In the Consolidated Appropriations Act of 2012, Congress moved the CAN into the newly created National Center for Advancing Translational Sciences (“NCATS”). NCATS is important because it is the first NIH Center to comprehensively focus on the “science and technology of drug development.” Specifically, CAN created three grant programs, the Cures Acceleration Partnership, Cures Acceleration Grant, and Cures Acceleration Flexible Research Programs. CAN’s functions are to “conduct and support revolutionary advances in basic research” to translate this research into cures, “award grants to accelerate the development of high need cures,” “facilitate review by FDA for high need cures funded by FDA” to make sure CAN considers FDA approval requirements, and appropriate FDA technical assistance is provided. The CAN is authorized to use “other transactional authority (‘OTA’),” which decreases restrictions on funding that may be caused by federal regulations. In particular, the OTA may alleviate restrictions caused by the Bayh-Dole Act (which can be restrictive to companies), and NIH requirements, facilitating the funding of translational projects. This authority and the focus on collaboration and communication with industry

103. Id. at 11, 20.
104. Id. at 28.
105. Cures Acceleration Network Act, S.914 (111th Congress).
107. PCAST, supra note 16, at 52.
108. OLSON & CLAIBORNE, supra note 88, at 6.
109. Id. at 35.
110. Id. at 7.
via public-private partnerships are effective methods to stimulate translational research (e.g., newer animal models, stem cell biology techniques, development of platform technologies to “reveal molecular signatures of disease progression and drug responses”)\(^{111}\) that may result in the development of HVDs. However, the FY 2012 budget for the CAN was only $10 million, a mere 0.2 percent of the annual funding Senator Lieberman authorized for the Cures Center in his seminal 2005 bill, and one percent of the funds Sen. Specter subsequently authorized in his bill. Thus, although CAN efforts address translational research – an important aspect of the development of HVDs – the funding is likely insufficient to significantly address this need even though parts of the funding require matching dollars from recipients.\(^{112}\) By contrast, the Biomedical Advanced Research and Development Authority – authorized under the Pandemic and All-Hazards Preparedness Act of 2006\(^{113}\) and designed to increase the development of medical countermeasures, including drugs, for terrorist events (e.g., a biological attack) – has a current budget of $1.6 billion.\(^{114}\) The PCAST points out that CAN will only address a small aspect of the HVD development problem due to low appropriated funding ($10 million).\(^{115}\) Also, CAN does not have the ability to leverage FFRDCs, which, as mentioned, provide significant flexibility in developing innovative products. This will decrease CAN’s effectiveness in contrast to prior comprehensive legislative proposals, which authorized significantly more funding. Finally, CAN does not constitute a comprehensive approach to address multiple HVD development challenges. Senator Lieberman’s broad approach, which would mandate that one Center holistically address translational research, clinical trials, genomics infrastructure, market failures with antibiotic and vaccine development issues, flexible approaches, and many other translation research and drug development issues, may have accelerated multi-disciplinary, collaborative, and focused solutions to related problems.\(^{116}\) However, NCATS as a whole addresses some aspects of this broader approach (albeit without the $5 billion per year funding envisioned by Senator Lieberman’s 2005 bill), and FDASIA provisions address others (e.g., the extension of market exclusivity for high value anti-

\(^{111}\) *Id.* at 17.

\(^{112}\) *See id.* at 25 (CAN requires recipients of the Cures Acceleration Partnership Awards to “contribute . . . $1 for every $3 awarded.”)


\(^{116}\) *See id.* at 51 (for example, the PCAST report points out that there is still a major unmet need to improve the clinical trials enterprise, which would enhance the development of HVDs).
biotics). In addition, FDA and NIH are collaborating on regulatory science initiatives which include translational efforts to link NIH's basic science-funded research with FDA's public health regulatory approval authorities. Thus, Congress' piecemeal approach and other federal policy initiatives may address some of the gaps Senator Lieberman's bill intended to fill, although not nearly as comprehensively.

D. CMS-FDA Policy Initiative to Expedite Access to Novel Medical Interventions

In 2010, the FDA announced that it was considering, along with the Centers for Medicaid and Medicare Services ("CMS"), "a process for overlapping evaluations of premarket, FDA-regulated medical products when the product sponsor and both agencies agree to such parallel review." The purpose of this voluntary, formal process would be to decrease the time between FDA approval and CMS national coverage determinations. Doing so would potentially decrease the time it would take high-value interventions (e.g., devices) to reach Medicare and Medicaid patients, a group that currently numbers approximately ninety-five million people, which will significantly increase in the future in light of the aging population and optional expansion of Medicaid under the ACA. As such, a significant portion of the United States' population could potentially have access to such high-value interventions earlier. The FDA ensures that products are safe and efficacious in the premarket setting, and CMS evaluates whether the medical items and services it may cover are reasonable and necessary.

Although parallel review could increase access to high value drugs by decreasing time from FDA approval to return on investment via approval by CMS, it is not currently likely to have a significant impact on drugs because most undergo local coverage determinations ("LCDs") versus national coverage determinations ("NCDs") versus national coverage determinations (the proposed parallel review programs would only apply to NCDs). After reviewing the pub-
lic comments, the FDA and CMS have started a voluntary pilot program focused on medical devices as many more of these products undergo NCDs than drugs.\footnote{FDA-CMS Parallel Review (Oct. 13, 2012), at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm255678.htm.}

\section*{E. Recent Pharmaceutical Companies’ Focus on Specialty Drugs}

Pharmaceutical companies are also focusing on HVDs by shifting their investments into specialty drugs (e.g., TNF alpha blockers for the treatment of rheumatoid arthritis), which are innovative and address unmet medical needs by targeting unique causes of serious diseases such as cancer and multiple sclerosis.\footnote{John A. Romley et al., Survey Results Show That Adults Are Willing to Pay Higher Insurance Premiums for Generous Coverage of Specialty Drugs, 31 HEALTH AFF. 683-90 (2012).} Annual pharmaceutical companies’ revenues from specialty drugs relative to total revenue increased from thirty-nine percent in 2001 to forty-five percent in 2006, illustrating the increasing market share of these drugs in recent years.\footnote{McKinsey & Company, Invention Reinvented: McKinsey Perspectives on Pharmaceutical R&D (2010), at http://www.mckinsey.com/-/media/mckinsey/dotcom/client_service/pharma%20and%20medical%20products/pdfs/rdemergingmarkets.ashx. See also Stacy Lawrence, Billion dollar babies-biotech drugs as blockbusters, 25 NATURE BIOTECHNOLOGY 380-382 (2007) (In fact, some estimates predict that biologic drugs will constitute four of the top five selling drugs by 2014).} However, these HVDs are very expensive – in 2008, the average spending for specialty drugs per patient was $11,746 – and access to these medications may thus be limited even though patients have shown a willingness to pay substantial out-of-pocket costs for these drugs when feasible.\footnote{Romley, supra note 123, at 684.}

\section*{PART II. RECENT FEDERAL LEGISLATIVE AND POLICY INITIATIVES PERTAINING TO THE EVALUATION (POSTMARKET STAGE) OF HIGH VALUE DRUGS FOR PATIENTS}

\subsection*{A. Introduction}

As mentioned earlier, there has been an increased focus on the valuation of drugs in light of the budgetary crossroads in the United States. Several recent legislative and policy initiatives seek to enhance the valuation of drugs, including drug comparative effectiveness and safety and pa-
tient-centered outcomes. To facilitate efficacy evaluation, drugs are often studied in relatively small, healthy patient populations during the pre-approval phases (e.g., a Phase III clinical approval trial may include a few thousand patients), which may not produce generally reliable evidence on real world health outcomes. For example, trials may not include patients representative of those that will take the drug in the post-market real world setting and may not be adequately powered (i.e., small sample size) to evaluate drug safety, especially rare adverse events. Thus, there is a considerable amount of uncertainty regarding the effectiveness and safety of drugs used in the real world, and it is important to evaluate how effective and safe a drug is when actually used widely in the population. As noted previously, the recent IOM report on the learning health care system pointed out the lack of useful evidence on medical intervention-related outcomes of importance to the decisionmakers: patients and clinicians. Furthermore, the recently published IOM report addressing issues associated with studying the safety of approved drugs points out the considerable controversy surrounding the appropriate risk estimate threshold for evaluating the validity of observational pharmacoepidemiologic safety studies (drug safety studies) and the ability to make causal inferences based on these studies. In the judicial world, the scientific manual for judges discusses the risk estimate threshold of 2.0 – above which one may “believe” the findings from an observational study of an association – that may be used in drug tort liability cases, although this is not a legally-binding rule. Although further research is needed to determine risk estimate thresholds for specific drug and safety issues pairs, one researcher has leveraged the work of a NIH researcher in the 1960s and applied this to the

126. Patients in the real world may have many more chronic conditions and take multiple medications which may impact the effectiveness and safety of a drug in the real world. For example, although almost thirty percent of the population suffer from multiple chronic conditions, including a majority of elderly patients, in recent years, few randomized controlled trials, which are used to demonstrate drug efficacy and safety in the premarket setting, have included patients that have multiple co-morbidities, limiting the generalizability of clinical trial evidence on effectiveness and safety to the real world population. See Alejandro Jadad et al., Consideration of Multiple Chronic Diseases in Randomized Controlled Trials, 306 JAMA 2670, 2671 (2011); Sebastian Schneeweiss, Developments in Post-marketing Comparative Effectiveness Research, 82 CLINICAL PHARMACOLOGY & THERAPEUTICS 143 (2007); Tarek A. Hammad et al., Secondary Use of RCTs to Evaluate Drug Safety, 8 CLINICAL TRIALS 559, 561 (2011).

127. Additionally, off-label use is prevalent and may increase in the future due to efforts to accelerate approval of drugs indicated for narrow populations. See, Aaron Kesselheim, Off-Label Use and Promotion: Balancing Public Health Goals and Commercial Speech, 37 AM. J.L. & MED. 225, 227 (As there is often limited evidence on drug safety and effectiveness for off-label uses, which may lead to increased patient harms, it is important to evaluate these uses in the real world); Gerald Dal Pan, Monitoring the Safety of Medicines Used Off-Label, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 787-95 (2012).


129. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 381-86 (3d ed. 2011).
pharmacoepidemiology world. Such an approach may inform future efforts in this area to address uncertainty around observational studies so they can increase confidence in this form of evaluative evidence. Although it is appropriate for a regulatory agency such as FDA to consider whether a drug can work for the purpose of market approval, it is incumbent upon payers to evaluate how a drug does work in the real world. This enables evaluation of its value by patients; in other words, does it work for me and is it worth it? The Congressional Budget Office ("CBO") defined comparative effectiveness research ("CER") as a rigorous evaluation of the impact of different options that are available for treating a medical condition for a particular set of patients. Such a study may compare similar treatments like competing drugs, or it may analyze very different approaches such as a surgery and drug therapy. The analysis may focus only on the relative medical benefits and risks of each option, or it may also weigh both the costs and benefits of those options. Thus, according to this definition, pharmaceutical CER involves a valuation relative to other drugs. The Federal Coordinating Council on Comparative Effectiveness Research defined CER as the:

conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. The purpose of this research is to inform patients, providers, decision-makers . . . about which interventions are most effective for patients under specific circumstances . . . . Defined interventions compared may include medications, procedures, medical and assistive devices and technologies . . . . This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness research."

The Institute of Medicine defines CER as "the generation and synthesis of evidence that compares the benefits and harms of alternative meth-

132. Id.
ods to prevent, diagnose, treat, and monitor a clinical condition to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve health care at the individual and population levels."  This paper will adopt a definition of drug comparative effectiveness that reflects all of these definitions but eschews the cost aspect, because although this is an important aspect of effectiveness research, it is not the focus of relevant, recent federal legislative and policy initiatives: the generation and synthesis of evidence comparing the effectiveness and safety of two or more drugs in general and specific sub-populations to facilitate evidence-based decision-making by patients, health care professionals, and other decision-makers.

B. American Recovery and Reinvestment Act (ARRA) Funding for Federal Comparative Effectiveness Research

Historically, there has been significant congressional interest in learning about the effectiveness and safety of medical interventions in the real world. In 1987, Senator David Durenberger established the Patient Outcomes Research Teams ("PORTs") to evaluate outcomes of surgical interventions on important health conditions such as angina or chest pain due to coronary artery disease.  This in part stimulated the development of the Agency for Health Care Policy and Research ("AHCPR") in 1989, whose name was changed to the Agency for Health Care Research and Quality ("AHRQ") in 1999.  Importantly, because this outcomes research on medical interventions, including drugs, can create "winners" and "losers," it has been controversial and funding for AHCPR/AHRQ has nearly been eliminated by Congress multiple times since its inception, including recently.  In the 2003 Medicare Modernization Act, Congress established the Effective Health Care ("EHC") Program within AHRQ to "improve the quality, effectiveness, and efficiency" of the federal Medicare, Medicaid, and CHIP programs that now include a significant percentage of patients in the United States, with the number expected to grow in light of

136. JOHN E. WENNBERG, TRACKING MEDICINE: A RESEARCHER'S QUEST TO UNDERSTAND HEALTH CARE 89 (2010).
137. Id. at 89.
138. Id. at 99. In 1994, ACHPR's report on lower back pain, which found that first line surgery for this condition was not supported by good evidence, stimulated lower back surgeons to lobby Congress to eliminate the agency. See, Mike Mitka, Critics of US House Proposal to Ax AHRQ Says Idea is Penny-wise and Pound-foolish, 308 JAMA 849, 849-50 (2012) (Also, recently the House of Representatives recommended eliminating AHRQ).
the aging population and ACA-related Medicaid expansion. Under the EHC program, AHRQ collaborates with researchers to conduct reviews and synthesize evidence on medical interventions (via research reviews), including drugs, generate scientific evidence and tools (via original research and reports), and translate evidence for use by patients, health care professionals, and policy makers (via research summaries/guides).\textsuperscript{139} In addition, the National Institutes of Health ("NIH") has funded influential comparative effectiveness clinical trials, including on drugs, in the past.\textsuperscript{140} In 2009, Congress appropriated $1.1 billion for comparative effectiveness research, including $300 million allocated to the Agency for Healthcare Research and Quality, $400 million to NIH (this was transferred from AHRQ), and $300 million to the Office of the Secretary of Health and Human Services ("OS/HHS").\textsuperscript{141} Approximately forty-six percent of these funds have been allocated to evidence development and synthesis, forty-one percent to improve the infrastructure, enhance data and methods, seven percent for dissemination and translation, and five percent for prioritization and stakeholder engagement.\textsuperscript{142} One of the key comparative effectiveness research gaps is the development methodologies and infrastructure to leverage electronic health care data (administrative claims and electronic health record data), which include information on health outcomes in the real world setting. In light of the significant congressional funding supporting the adoption of electronic health records and resultant increase in adoption in the next few years\textsuperscript{143}, it is critical to maximize use of this population data for comparative effectiveness research. AHRQ used $25 million of the ARRA CER funds to support distributed research network ("DRN") pilot projects to leverage these data sources for the CER evaluation of medical intervention, including drug, outcomes in the real

\textsuperscript{139}. Medicare Prescription Drug Improvement and Modernization Act of 2003, P.L. 108-173, Sec. 1013. See also What Is the Effective Health Care Program, AGENCY FOR HEALTHCARE RESEARCH & QUALITY, at http://www.effectivehealthcare.ahrq.gov/index.cfm/what-is-the-effective-health-care-program/ (AHRQ's DEcIDE and CERTs programs fund investigators to conduct research on the clinical comparative effectiveness and safety of a variety of medical treatments, including drugs).

\textsuperscript{140}. For example, NIH funded the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial ("ALLHAT") trial that evaluates the effectiveness and safety of different anti-hypertensive medications. The trial found that older, less expensive thiazide diuretic drugs were as effective as newer, more costly (i.e., on patent) anti-hypertensive drugs. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, \textit{Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)}, 18 JAMA 2981-97 (2002).


\textsuperscript{142}. Joshua S. Benner et al., \textit{An Evaluation of Recent Federal Spending on Comparative Effectiveness Research: Priorities, Gaps, and Next Steps}, 29 HEALTH AFF. 1768, 1770 (2010).

\textsuperscript{143}. American Recovery and Reinvestment Act of 2009, Pub. L., 111-5., HITECH Act. The HITECH Act provided just under $30 billion in funding to support the adoption of interoperable electronic health records. CMS is currently funding stage two of this effort under the auspices of meaningful use.
world and is currently building off these distributed research network prototypes.\textsuperscript{144} Importantly, the DRN approaches eschew some important patient privacy problems by enabling health data holders to keep their data behind their own firewalls while transforming their data into a common format to facilitate comparative effectiveness studies using e-health data on patients across various health plans. HHS/Assistant Secretary for Planning and Evaluation ("ASPE") has also used some of the ARRA funds to fund data infrastructure projects, for example, a multi-payer claims database without patient identifiable information (to address privacy issues) that can inform large comparative effectiveness studies of real world patient outcomes in Medicare and privately insured populations.\textsuperscript{145} Despite these important and ongoing data development efforts funded by ARRA, there is a need for continued and increased funding of these projects and related methods development to ensure the increasingly available electronic health data can be used to evaluate the comparative effectiveness of drugs (and other interventions) and patient health outcomes.

One of the key challenges of comparative effectiveness research is that most of the relevant studies, approximately eighty-five percent, are observational versus randomized studies.\textsuperscript{146} Traditional evidentiary hierarchies, which position randomized controlled trials higher than observational studies (with respect to quality of evidence), "attempt to replace judgment with an overly simplistic, pseudoquantitative, assessment of the quality of available evidence"\textsuperscript{147} and hence are not always useful in specific drug comparative effectiveness circumstances. Although observational studies reflect real world drug effectiveness and safety, in contrast pre-market randomized controlled trials, these studies are subject to more bias and confounding than randomized studies which may lead to misleading

\textsuperscript{144} Benner, supra note 142, at 1771; Jeff Brown et al., Enhanced Functionality for the Distributed Research Network Pilot, \textit{Effective Health Care Program Research Report Number 37}, at http://effectivehealthcare.ahrq.gov/ehc/products/215/1027/DEClDE37_DistribResearch_finalreport_20120403.pdf (The Distributed Research Network projects were funded initially to leverage existing intellectual and data resources for the conduct of rapid cycle comparative effectiveness research studies. Specifically, the projects focus on "standardized and re-usable information technology approaches for speeding the initiation and conduct of large-scale comparative effectiveness studies, including studies of treatments covered by Medicaid, Medicare, SCHIP, and other Federal payers." Users, such as payers like CMS, can then use the comparative effectiveness evidence from such studies, in conjunction with other evidence sources, to inform decisions about medical interventions, including drugs).


results.\textsuperscript{148} One significant form of confounding observational studies may suffer from is "confounding by indication" which "can occur when the underlying diagnosis [indication] or other clinical features that affect the use of a certain drug are also related to the outcome under study" and may threaten the validity of observational studies of effectiveness and safety.\textsuperscript{149} When new drugs are approved, they may be reserved for sicker patients, thus complicating the evaluation of the outcomes in patients on new drugs compared to other drugs used to treat the same condition (i.e., confounding by indication).

In addition, observational pharmacoepidemiologic CER studies which use secondary electronic health care data may suffer from unmeasured confounding; these studies lack information on relevant confounders, such as smoking, body mass index ("BMI"), over-the-counter ("OTC") use of aspirin, etc., it may be difficult to discern the comparative effectiveness of the COX-II inhibitors versus NSAIDs, as these unmeasured confounders may account for the observed difference in outcomes versus the actual drugs of interest.\textsuperscript{150} Thus, one critical aspect of CER is the development of methods to handle bias and confounding (in the instances in which confounding is not so great as to preclude the conduct of a useful observational study). Independent organizations and agencies have developed best practices for observational pharmacoepidemiologic studies, including the FDA (focused on drug safety)\textsuperscript{151} and the European Network of Centers on Pharmacoepidemiology and Pharmacoepidemiology,\textsuperscript{152} supported by the European Medicines Agency ("EMA"), FDA’s Eu-

\textsuperscript{148} Michael Lauer & Francis Collins, Using Science to Improve the Nation’s Health System: NIH’s commitment to Comparative Effectiveness Research, 303 JAMA 2182, 2183 (2010). One example that is often cited is the Women’s Health Initiative observational study, which initially found that postmenopausal hormone therapy was cardioprotective before a thorough evaluation of the study design highlighted the healthy user bias, that women who stayed on the drug were healthier than those who did not, biasing the results. See, J. E. Rossouw, et al., Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women’s Health Initiative randomized controlled trial, 288 JAMA 321, 321-33 (2002); Sean Tunis et al., Comparative effectiveness research: Policy context, methods development and research infrastructure, 29 STAT. IN MED. 1963, 1969 (2010).

\textsuperscript{149} Brian Strom, Pharmacoepidemiology 922 (2012). See also, Michael Barry, Helping Patients Make Better Personal Health Decisions: The Promise of Patient-Centered Outcomes Research, 306 JAMA 1258, 1259 (2011); Bruce M. Psaty & David S. Siscovick, Minimizing Bias Due to Confounding by Indication in Comparative Effectiveness Research: The Importance of Restriction, 304 JAMA 897, 897-8 (2010).

\textsuperscript{150} Schneeweiss, supra note 126.

\textsuperscript{151} FDA, Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (Feb. 2011). The FDA is also enhancing its epidemiology program and increasing access to data sources for the evaluation of postmarket drug safety. See Judy Staffa & Gerald Dal Pan, Regulatory innovation in postmarketing risk assessment and management, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 555, 555-7 (2012); Margaret A. Hamburg, The Growing Role of Epidemiology in Drug Safety Regulation, 22 EPIDEMIOLOGY 622, 622-624 (2011).

\textsuperscript{152} ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE, at http://www.encepp.eu/standards_and_guidances/index.shtml. ENCePP’s efforts to develop best practices
European counterpart, the International Society of Pharmacoepidemiology ("ISPE"), and the Good ReseArch for Comparative Effectiveness ("GRACE") group of experts. Recently, epidemiologists developed a preliminary evaluative framework and reviewed potential tools that may facilitate the consistent evaluation of observational pharmacoepidemiologic safety studies for regulatory decision-making; GRACE is developing a checklist for the evaluation of observational pharmacoepidemiologic CER studies for use by payers and others. The development of "specialized" methods for observational pharmacoepidemiologic CER research, such as high dimensional propensity scores and instrumental variables to handle confounders, are critical to these observational studies so it is possible to tease out the comparative impact of drug effectiveness and safety (i.e., value) in the real world and enhance confidence in this important evidence source. Furthermore, EMA has established a process via ENCePP to register observational studies, increasing the transparency of studies that may be used for regulatory decision-making.

A recent article posited that Clinicaltrials.gov could support observational pharmacoepidemiologic study registration in the United States. Currently, per the Food and Drug Administration Amendments Act ("FDAAA") requirements, companies are required to register Phase II to IV clinical trials and may register observational studies. Although required registration of observational pharmacoepidemiologic studies would and register observational pharmacoepidemiologic studies will increase transparency but will fail to guarantee quality, although this is not the intent of ENCePP; Sebastian Schneeweiss & Jerry Avorn, Postmarket- ing studies of drug safety: A European initiative could help bring more transparency and rigour to pharmacoepidemiology, 342 BMJ 344 (2011).


enhance transparency of these studies, this would not speak to their quality and in the clinical trials arena, the utility of required registration of trials has been limited due to a lack of compliance with timely posting of trial information and a lack of sufficient detail for syntheses such as individual patient-level meta-analyses.\textsuperscript{160} Efforts by the Patient Centered Outcomes Research Institute ("PCORI") and AHRQ to improve the standards for the conduct and analysis of observational PCORI studies will be needed to further evaluate how "nonrandomized approaches compare with or add to randomized controlled trials in diverse fields and settings."\textsuperscript{161} Despite these important efforts, it is possible that in many cases, trials will still be required because observational studies may not be able to adequately handle selection bias.\textsuperscript{162} However, pragmatic randomized trials, which are much less costly and more efficient than traditional randomized controlled trials, may alleviate some of the time and cost issues associated with traditional trials.\textsuperscript{163}

In addition, it is important to (1) establish an evidentiary framework for CER to facilitate appropriate and consistent research funding, use of appropriate study designs (e.g. randomized controlled trials, observational studies) for clinically meaningful CER questions, and synthesis of evidence for the evaluation of the relative safety and effectiveness of drugs and other medical interventions to discern their value; and (2) develop methods to combine evidence from multiple sources.\textsuperscript{164} Greater transparency is also needed around the evaluation of the quality of evidence of observational drug comparative effectiveness studies to inform decision-making and establishment of standards of when these studies are rigorous

\textsuperscript{160} See generally Michael R. Law et al., Despite Law, Fewer Than One In Eight Completed Studies Of Drugs And Biologics Are Reported On Time On ClinicalTrials.gov, 30 HEALTH AFF. 2338-2345; Hammad, supra note 126, at 564.


\textsuperscript{162} Joe V. Selby et al., Reviewing Hypothetical Migraine Studies Using Funding Criteria From the Patient Centered Outcomes Research Institute, 31 HEALTH AFF. 2193, 2196 (2012). James S. Floyd & Bruce M. Psaty, Observational Comparative Effectiveness Studies of Drug Therapies, 172 ARCH. INTERN. MED. 1412, 1413 (2012).

\textsuperscript{163} See Kalipso Chalkidou et al., The Role for Pragmatic Randomized Controlled Trials (pRCTs) in Comparative Effectiveness Research, 0 CLINICAL TRIALS 1 (2012). This article points out specific examples of traditional RCTs that involve findings from studying highly selective populations which do not generalize to real world patients. pRCTs balance the internal validity of trials with the external validity of observational studies, adding another important evidence source to evaluate high value drugs (and other interventions).

\textsuperscript{164} Tunis, supra note 148, at 1966, 70. See also, GRADE Working Group, Grading Quality of Evidence and Strength of Recommendations, 328 BMJ 1490 (2004) (The GRADE WG framework for the evaluation and synthesis of evidence for clinical guideline development may inform the development of such a framework).
and produce valid results.\textsuperscript{165} There is a recent collaborative initiative underway to enhance the transparency and evidence-based approach to evaluate observational CER evidence.\textsuperscript{166}

In addition to CER methods and data development, as stated earlier, approximately forty-six percent of the ARRA CER funds were allocated for evidence development and synthesis. To evaluate the impact, it first important to bear in mind that the total ARRA funds, $1.1 billion, are relatively small in comparison to the annual cost of health care which is now $2.8 trillion. Approximately half of the ARRA CER funding amounts to a mere $550 million for evidence development and synthesis\textsuperscript{167}, or approximately one dollar out of every $5,000 spent on health care. With respect to funding traditional clinical CER trials, these funds will likely not directly support CER trials due to their high cost; for example, the antihypertensive ALLHAT study involved more than 35,000 patients cost more than $100 million.\textsuperscript{168} In addition, years later, many clinicians have still not applied the main findings of the study, that older, less expensive thiazide diuretic drugs are as effective as newer, more expensive anti-hypertensive drugs. Due to the limited amount of resources available, in contrast to paying for traditional randomized controlled trials ("RCTs"), funds may be used to support alternate evidence development (e.g., observational studies) and synthesis activities. These activities include the development of methods for evidence synthesis, an important area in the evaluation of drug value as clinical guideline developers and others that impact medical practice often use systematic reviews, which synthesize comparative effectiveness evidence from different evidence sources (e.g., trials, observational studies), to identify research gaps and evidence on the impact of drugs and medical interventions on health outcomes.

Despite the importance of the ARRA funded comparative effectiveness initiatives to enhance the evaluation of the value of drugs and other medical interventions, there are some significant policy-related limitations to CER studies (in addition to the aforementioned scientific limitations). A recent article points out five important limitations: (1) economic incentives may limit the utility of CER as there are winners and losers and misaligned incentivizes – for example, a "loser" may be a pharmaceutical com-

\textsuperscript{165} Kesselheim \& Avorn, \textit{supra} note 158.
\textsuperscript{167} Benner, \textit{supra} note 142.
\textsuperscript{168} Harold Sox, \textit{The Patient-Centered Outcomes Research Institute Should Focus on High Impact Problems That Can Be Solved Quickly}. 31 HEALTH AFF. 2176, 2179 (2012).
pany that may seek to discredit evidence indicating the lack of superiority of their drug; (2) there is often uncertainty about the results due to a lack of evidentiary standards for different types of CER studies; (3) biases about CER, including confirmation, pro-intervention, and pro-technology biases; (4) the research does not address the needs of all stakeholders; and (5) the evidence is not linked to clinical decision support which would enable prescribers to rapidly use the evidence for decision making. These challenges must also be addressed to maximize the impact of CER, thus enhancing the evaluation of the value of drugs. Number (4) will be addressed by the activities of the institute created by ACA as mentioned in the following section.

C. Patient Protection and Affordable Care Act (ACA): the Patient Centered Outcomes Research Institute (PCORI)

As referenced above, the ACA established a public-private partnership, the Patient Centered Outcomes Research Institute ("PCORI"). PCORI is funded with $320 million in 2013 and $650 million per year for 2014 to 2019 by the United States Treasury, and a health insurance plan assessment fee and is tasked with supporting clinical CER that will "assist patients, clinicians, purchasers, policymakers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research evidence and synthesis." This definition is similar to the definitions of comparative effectiveness research ("CER") above, and emphasizes the importance of informed, evidence-based decision making by patients and clinicians. PCORI is focused on funding research that informs patient and clinician decision-making, consistent with the name of the organization. Pursuant to the mandate to develop a research agenda based on statutory criteria, PCORI developed the institute’s research agenda, which includes the following topic areas: (1) assessment of options for prevention, diagnosis, and treatment; (2) improving health care systems; (3) dissemination and communication of research; (4) addressing disparities; and (5) accelerating patient-centered outcomes re-

171. Id. See also PCORI, How are we funded?, PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE, at http://www.pcori.org/how-were-funded/.
search and methodology. 173 Importantly, the agenda focuses on “close coordination with other funders of CER, including NIH, AHRQ” and industry to ensure funding of complementary not duplicative work. 174

Similar to the ARRA CER work mentioned above, the methods employed by PCORI grantees and contractors will be critical as many of these studies will be either observational or randomized but not fully controlled (i.e., pragmatic). Thus, many of these studies of drugs and other medical interventions will be prone to some of the same types of confounding and bias and “for [such] research to be meaningful, its methodological foundation must be scientifically sound and patient centered.” 175 Importantly, the draft PCORI methodology report released in June 2012 highlights the importance of studying outcomes relevant to patients (e.g., the impact on symptoms and function versus surrogate measures) and research that is “inclusive of an individual’s preferences, autonomy, and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life.” 176 This is especially important because physicians may not understand what the patient prefers, and patient-centered outcomes are linked to improvement in the outcomes important to patients. Research in decision aids to improve shared decision making has born this out; for example, many patients with benign prostate hyperplasia (“BPH”) waiting for surgery were only able to adequately communicate their preference not to have surgery after the use of a decision aid. 177 A recent IOM Evidence Communication Innovation Collaboration highlighted that although patients want to “know the risks of each [treatment] option” and how each may impact their quality of life, many were not provided with the option to choose amongst the treatment options (i.e. drugs) even though they report a “better patient experience” when they are involved in care. 178 Similar to the CER definition discussion above, PCORI mentions that its research focuses on “how well the different treatment choices [e.g., drugs] can work, and for whom they


174. Id. at 1584.


177. WENNBERG, supra note 136, at 226.

work best and are safest.” in light of the significant uncertainty regarding post-market effectiveness and safety. The report recommends specific patient-centered outcomes research standards and highlights knowledge gaps pertaining to proposals and protocols, prioritization (including input from patients on topic generation), selection of data sources, research design, and analysis plan, research methods. This report and the subsequent updates to this report will increase confidence in this type of research because robust, scientific, and transparent methods will be developed and employed, thus increasing the potential use of the evidence generated for patient and clinician decision making. This report also points out the need, similar to the need mentioned above for CER, to transform electronic health record data so it is researchable for patient-centered outcomes research. With respect to drug patient-centered outcomes research (“PCOR”), the report includes a decision tree for the selection of study design, data sources, analytic strategy, and other considerations that will increase transparency and robustness of PCOR drug studies. Importantly, as many of the studies may be observational, the report highlights the research gap pertaining to methods of development for the evaluation of heterogeneity of treatment effect in observational studies, which will help to increase the availability of evidence on sub-populations of real world patients who may benefit from drugs.

Finally, as with CER, PCOR may leverage distributed research networks, such as the HMO Research Network, to study patient-centered outcomes of drugs and other medical interventions in large populations. Also, further research on and development of patient decision aids may enable the use of PCOR to optimize patient decision making regarding medical interventions, including drugs. In addition, FDA’s past guidance on patient reported outcomes and efforts to advance the development of patient-reported outcomes as mandated under PDUFA V will also enhance the evaluation of outcomes important to patients in clinical trials of drugs.

179. PCORI, supra note 176, at 15.
180. See PCORI report, supra note 176.
181. Id.
182. PCORI, supra note 176, at 51.
183. Navanthe, supra note 145, at 1255.
186. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, supra note 80, at 22.
D. Patient Protection and Affordable Care Act (ACA): Medication Therapy Management Legislative Initiative

The ACA included improvements to the Medication Therapy Management (“MTM”) Program created under the Medicare Modernization Act of 2003. This includes “a[] [required] annual comprehensive medication review” for qualified patients by pharmacists to review and evaluate medications annually. This will enhance pharmacists’ efforts to evaluate drugs at the individual patient level and identify high value drugs, increase adherence to these drugs which will increase their effectiveness, and identify “low value” drugs that may be duplicative or causing adverse events that may lead to decreased patient adherence or serious drug-drug interactions. In addition, this ACA section created an MTM program entitled “Medication Management Services in Treatment of Chronic Disease,” administered through CMS. The law authorized grants to pharmacists and other health care professionals to perform MTM for patients with chronic conditions, including the identification of medication-related problems. This funding in turn may further empower pharmacists by providing support for evaluating drug effectiveness and safety in individual patients with multiple chronic conditions, enhancing patient adherence (which can increase the value of drugs by increasing drug effectiveness), and identifying and preventing drug-related adverse events. The health care reform-related demonstration projects, such as patient-centered medical homes and accountable care organizations, funded by the Center for Medicare and Medicaid Innovation, will further facilitate pharmacists’ ability to evaluate risks associated with drugs in the real world, in addition to individual patient drug effectiveness, in patients with multiple chronic conditions on several medications. However, the ARRA funds appropriated to support

187. PPACA, Pub. L. 111-148 (2010), § 10328. See also, § 274, Medication Therapy Management Empowerment Act of 2011, 112th Congress (In addition, Senator Hagan previously introduced a bill (which she may introduce again) that would add to the PPACA Medication Therapy Management (“MTM”) provisions by expanding Part D MTM services coverage to Medicare patients with only one chronic condition, provide for pharmacists to be adequately reimbursed for such services, and expand coverage for these services to high risk patients, including dual eligibles and patients undergoing a transition of care).

188. Id.

189. Id. at § 3503.


191. See generally David Cutler & Wendy Everett, Thinking Outside the Pillbox – Medication Adherence as a Priority for Health Care Reform, 363 NEW ENG. J. MED. 1553 (2010) (Lack of patient adherence is a significant problem that can significantly decrease the utility of high value drugs. For example, eliminating the lack of patient adherence to anti-hypertensives could prevent 89,000 deaths each year).

192. Scott Steinke, ACO Survey Shows Areas for Improvement in Drug Management, 74 (44) THE PINK
the adoption of electronic health records ("EHRs") do not provide funds for pharmacies which is a shortcoming because most community pharmacies do not currently have access to electronic health records for evaluating drug therapies.193

E. Food and Drug Administration: FDA Amendments Act and FDASIA Legislative Initiatives

FDAAA conferred FDA with additional postmarket safety authorities to enhance postmarket drug safety and mandated the creation of a postmarket risk identification and analysis, or active surveillance, system.194 This statutory requirement spawned the Sentinel Initiative, which has successfully met the statutory requirements to access electronic health data (i.e., administrative claims and electronic medical record data) for the identification and analysis of safety issues.195 As one key aspect of the evaluation of the value of drugs in the postmarket setting is an evaluation of drug safety, the Sentinel Initiative is an important FDA initiative as it leverages the increasing availability of electronic health care data for signal detection and signal refinement.196 One of the Sentinel Pilot Projects, Mini-Sentinel, is using the same distributed network approach described earlier to identify and evaluate drug safety issues in the postmarket setting by enabling the active safety surveillance of drugs across disparate health care data sources. Importantly, these active drug safety surveillance efforts will complement, not replace, other evidence sources, including observational studies and clinical trials.197 Although evaluations of unintended, serious harms that may be associated with drugs in the real world setting do not suffer from the same extent of bias and confounding as drug CER studies, they are still prone to bias and confounding (e.g., confounding by drug indication)198 because they involve secondary use of data (e.g.,

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Sheet (2012), See also Marie Smith, et al., Why Pharmacists Belong in the Medical Home, 29 Health Aff. 906 (2010).


194. FDA Amendments Act of 2007, Pub. L. 110-85, Title IX.


196. Postmarket drug safety surveillance is especially important because the high prevalence of adverse drug reactions in the real world. Over two million patients are hospitalized and 100,000 die from adverse drug reactions each year. In addition, these reactions are the “fifth leading cause of death in the United States.” See Collins, supra note 8, at 233.


claims are created for reimbursement purposes, not research) and are non-randomized. Thus, the FDASIA-required report on Sentinel may help to increase confidence in the evidence from the future Sentinel system by describing methods and circumstances in which this evidence may inform regulatory decision making.\textsuperscript{199} The Mini-Sentinel Pilot Project already has access to data on more than 100 million patients, as permitted by law, although longitudinal data on most patients is more limited to one or two years due to the high churn rate of patients in health insurance plans.\textsuperscript{200} Furthermore, the industry funded Observational Medical Outcomes Partnership ("OMOP"), led by the foundation of NIH, in collaboration with FDA, is researching and developing active surveillance methods for comparative effectiveness and safety evaluations of drugs.\textsuperscript{201} Although Mini-Sentinel is an important effort, the President's Council of Advisors on Science and Technology ("PCAST") points out that Sentinel is underfunded and recommends that Congress "provide an initial line-item appropriation of $40 million per year to the FDA to expand post-marketing surveillance capability, such as the Sentinel System, to cover the American population in a rigorous, active surveillance and evaluation program to identify and evaluate the potential benefits and risks of medical products and the populations at highest risk of adverse events."\textsuperscript{202} Thus, this request is for significantly increased funding and the use of a future system to evaluate effectiveness, not just safety (currently per FDAAA, the FDA can only use Sentinel to identify and evaluate drug safety issues).\textsuperscript{203} Furthermore, the development of approaches to integrate active surveillance evidence with other postmarket safety evidence sources will be challenging but will enable informed regulatory decision making.\textsuperscript{204} Meta-analytic approaches to

\textsuperscript{199} PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, supra note 80.


\textsuperscript{201} About OMOP, OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP, available at http://omop.fnih.org/node/293 (OMOP's research and methods development have informed FDA's Sentinel Pilot Projects).

\textsuperscript{202} PCAST, supra note 16, at 70.


\textsuperscript{204} This need for a framework to weigh and integrate evidence also applies to CER evidence. See Robert
statistically combine data will also be critical in light of the increasing number of studies; under PDUFA V, FDA will be developing guidance on meta-analysis for regulatory decision making.\textsuperscript{205} Methods for linkage to emerging information from health information exchanges and across different data sources (e.g., claims, HER, HIE, personal health records) must also be further developed.

**PART III. SUMMARY AND REVIEW OF POTENTIAL FUTURE FEDERAL LEGISLATIVE AND POLICY INITIATIVES**

**A. Summary**

In summary, there are a number of new federal legislative and policy initiatives that enhance the development of and evaluation of high value drugs (HVDs). As discussed in the above sections, recent federal legislative and policy initiatives focus on: (1) incentivizing industry to invest in drug development, including in high risk areas such as translational research (2) enhancing methods to study drugs in the premarket setting (e.g., novel clinical trial designs and centralized IRBs), (3) increasing the use of surrogate outcomes with required postmarket studies to evaluate health outcome impact; (4) approaches to accelerate drug approval, including enhanced communication and collaboration between industry and FDA; (5) research infrastructure development; and other approaches. In the postmarket evaluative setting, important legislative and policy-related initiatives include: (1) development of observational CER/PCOR study analysis methods (e.g., to control for confounding) and methodological frameworks for selecting appropriate study designs; (2) developing practical randomized controlled trial designs; (3) the development of a research infrastructure that enables faster and cost-effective evaluations, such as the comparative effectiveness distributed research networks, Sentinel (including increased funds\textsuperscript{206}), and HHS/ASPE multi-payer claims database; (4) increased funds for the CER/PCOR research-related initiatives in light of low funding relative to total health care costs (this ratio has historically been low but must be increased); (5) the development of methods to take into account patient preferences to develop patient-centered health outcomes that will enable meaningful evaluations of drugs; and other efforts.

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\textsuperscript{205}. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, supra note 80, at 21.

\textsuperscript{206}. PCAST, supra note 16.

Although these initiatives will be important, in light of the impending debt crisis, it is important to evaluate potential future legislative and policy initiatives to complement current solutions, especially in light of the inability of these initiatives to fully address the scope of the policy problem and the relatively few dollars spent on these initiatives. As previously mentioned, although outside the scope of this paper, efforts to translate and disseminate CER/PCOR, such as academic detailing,207 and approaches to integrate evidence into prescriber workflow, such as via clinical decision support systems, will be critical to make sure that the appropriate high value drugs are used in the right patient at the right time.

B. Potential Future Legislative and Policy Initiatives for the Development of High Value Drugs

1. Improvement in the Clinical Trials Enterprise and Clinical Trial Inefficiencies

The PCAST report and Francis Collins, NIH Director, have proposed the development of clinical trial networks, which may leverage electronic health data systems, via a collaboration between industry, FDA, and the medical community.208 Further, these networks would ideally undergo more efficient institutional review board (“IRB”) review209 (as previously mentioned, multi-site studies require multiple IRB approval which may be time and cost prohibitive). This harkens back to Senator Lieberman’s proposal to support centralized IRB approval which would streamline clinical trials while still protecting trial participants. This type of collaborative work could be supported by the relatively new Reagan-Udall Foundation210 created by Congress and other organizations such as the NIH Foundation and perhaps appropriated funds and matching funds could be used, similar to NIH CAN’s approach to funding translational research. In addition to this PCAST proposal, FDA could consider leveraging large amounts of da-

207. See Michael Fisher & Jerry Avorn, Academic Detailing Can Play a Key Role in Assessing and Implementing Comparative Effectiveness Research Findings, 31 HEALTH AFF. 2206 (2012); See also, Mike Mitka, New Physician Education Initiatives Seek to Remove the Devil from the Detailing, 306 JAMA 1187 (2011) (AHRQ let a $11.7 million contract (from the ARRA funds) to enhance unbiased, evidence-based detailing of CER evidence to clinicians).

208. PCAST, supra note 16, at 54. Asher Mullard & Mark McClellan, An Audience with Mark McClellan, 11 NATURE REVS. DRUG DISCOVERY 668 (2012). Efforts to enhance clinical trials, including leveraging EHRs as adoption increases, are also consistent with FDA’s innovations in regulatory science to accelerate the development of innovative drugs. See Elliott M. Antman & Robert A. Harrington, Transforming Clinical Trials in Cardiovascular Disease: Mission Critical for Health and Economic Well-being, 308 JAMA 1743, 1744 (2012).

209. PCAST, supra note 16, at 54.

from clinical trials and observational studies, knowledge of human physiological systems, and high computing power and computer modeling during the drug approval process. For example, the validated Archimedes simulation modeling approach, based on mathematical equations representing biological systems, can model efficacy and safety in clinical trials and drug safety and effectiveness in the real world population before drug approval. One possible approach could involve a pilot initiative to identify and competitively select the top companies with validated simulation systems biology-based modeling capabilities (e.g., via a request for information) and run them simultaneously with the normal new drug application (“NDA”) clinical trial approval process (and postapproval). This would enable FDA to evaluate the consistency of these models and potential added value (including addressing aspects of uncertainty trials cannot, such as evaluating real world patient outcomes) of these models in real-time with actual drugs that are approved. FDA would learn if these simulation modeling approaches may improve clinical trial efficiency and the evaluation of drugs by adding more evidence that may complement, but likely not replace, clinical trials at the premarket and postmarket stages and potentially enhance postmarket surveillance by identifying potential safety issues prior to drug approval.

In addition, efforts by NIH and FDA, via the Clinical Trials Transformation Initiative, a public-private partnership, must continue to receive adequate funding to continue efforts to improve clinical trials, which will enhance the development of HVDs. New approaches to combine clinical trial data on drug efficacy, such as Bayesian statistical approaches, may also enhance the rapid development of HVDs and should continue to be improved upon.

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211. Institute of Medicine Report, supra note 6, at 10-19. Also, another initiative by NIH involves the repurposing of failed drugs that have already undergone clinical trial testing. This initiative has the potential to leverage existing clinical trial data on drugs that may be used for a different purpose. See Derrick Gingly, NIH Drug Repurposing Program Produces Surprise Overlaps, 74 THE PINK SHEET (Nov. 5, 2012).

212. What is the Archimedes Model?, ARCHIMEDES INCORPORATED, at http://archimedesmodel.com/archimedes-model. In fact, Archimedes has developed a global outcome (“GO”) score to evaluate the impact of medical interventions on the reduction in the risk of bad clinical outcomes, not simply discrete surrogate measures. See generally David M. Eddy et al., The Global Outcomes Score: A Quality Measure, Based on Health Outcomes, That Target Companies Current Care To A Target Level Of Care, 31 HEALTH AFF. 2441 (2012).


214. Institute of Medicine Report, supra note 6, at 10-19.

To enhance drug development, approval, and reimbursement, PCAST recommends the development of adaptive approval approaches which would involve "a series of approval stages that would iteratively expand the market for a drug based on the evidence generated about the drug's risks and benefits." Adaptive licensing requires "iterative phases of information" that are collected over time to evaluate medical product benefits and risks in the real world over time. Coverage with evidence development ("CED") for HVDs links reimbursement with future studies to further evaluate drugs in the real world setting via patient registries or studies. FDA precursors to this include accelerated approval, as mentioned, and Risk Evaluation and Mitigation Strategies ("REMS"), designed to manage serious risks associated with drugs while still making them available to patients with unmet medical needs. Under adaptive licensing, initially the high value drug would be restricted to a small population but then could be expanded to more patients in light of emerging evidence of effectiveness and safety based on pre-planned studies to continue studying the drug in the postmarket setting. Vemurafenib, a high value drug, was approved for metastatic melanoma based on a Phase II study, but as the adaptive licensing approach was not applied, continued studies on drug effectiveness and safety, including in subgroups who might respond better or worse, did not need to adhere to a pre-set timetable as to when additional data would be collected and reviewed. However, because most drugs are covered under Medicare Part D, CMS does not generally have the ability to use coverage with evidence development under this program. Thus, legislation that provides CMS with this CED authority more broadly could enhance the evaluation of HVDs (and rewarding value) by requiring CED programs for certain drugs that are approved quickly but whose value

215. Id.
217. Id. at 2.
218. Id. at 3. FDA REMS with Elements to Assure Safe Use (ETASU) to manage risk enable drugs to be approved that would otherwise not be approved due to serious safety risks (to ensure the benefits outweigh the risks). See FDA, Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, 1, 2-3 (2009).
219. Id.
220. Id. at 6.
221. Id.
may be more uncertain due to less rigorous approval studies.222

3. Securitization of Biomedical Research and Development (R&D)

A recent article proposed a policy solution to the dearth of R&D funding: the securitization of biomedical R&D in an effort to add another $30 billion in available funds for biomedical research and drug development.223 These funds could replace some of the significant losses in available R&D funds from pharmaceutical companies due to blockbuster drugs coming off patent in recent years. Investors could reduce their risk by investing in a number of diverse research projects and could reap benefits from long-term returns, which is not the case with less risky, shorter-term investments.224 One idea of how to apply this approach would be to pay professors for their research in exchange for royalties on any successes from their laboratories.225 Although the securitization approach may stimulate more drug development and translational research, it may be limited if the underlying, inefficient clinical trials paradigm remains unchanged.226 This may be comparable to the “E-room” phenomenon of throwing more money at a problem without understanding what produces a return on investment, although it is possible that due to a lack of prior commitments and baggage on the part of these investors, this model may be successful as they may be more likely to fund high-risk, high-impact projects.

222. Institute of Medicine Report, supra note 6, at 8-11. The IOM notes that one key strategy to rewarding value is the use of CED. Researchers have also pointed out that U.S. efforts to increase CER have not linked this to decision making, which may limit its value and conditional coverage policies are a better approach to reward innovation and inform evidence-based decision making. Specific considerations for condition approval may include: “Does current evidence suggest that the innovation is better than current practice?” “Is the collection of more information worthwhile?” and “Should we wait for more information?” See Kalipso Chalkidou et al., Evidence-Based Decision-Making: When Should We Wait for More Information? 27 HEATH AFF. 1642, 1644-1646, 1651 (2008). See also, CMS Draft Guidance for the Public, Industry, and CMS Staff Coverage with Evidence Development (Nov. 29, 2012) (In the context of coverage decisions, CMS recently published a revised draft guidance on CED that does not provide specific evidentiary thresholds for CED but does include factors CMS will consider when requiring CED. Evidentiary thresholds for requiring CED will vary depending on the particular product (e.g., drug, device) or service (e.g., imaging) of interest).


224. Id. at 736.

225. Id.

226. Id. at 737.
C. Potential Future Legislative and Policy Initiatives for the Evaluation of High Value Drugs

1. Consideration of Drug Cost-Effectiveness, Value, and Rationing Of Care

Despite the inclusion of costs in most definitions of high value (e.g., the aforementioned CBO CER definition), the recent legislative and policy initiatives by the United States government have not focused on cost-effectiveness. In the United Kingdom and many other countries, there are two entities involved in the approval of drugs (1) the regulator, the Medicines Health and Regulatory Agency, equivalent to the FDA in the United States, which reviews, approves, monitors drugs, and (2) an entity that values clinical and cost-effectiveness (value) of drugs and other medical interventions, which in the United Kingdom is the National Institutes for Health and Excellence ("NICE").227 The United States does not have an equivalent NICE-type agency that evaluates comparative clinical and cost-effectiveness for CMS.228 As a result, drugs may be approved that are not more clinically effective and safe relative to other drugs for the same condition (e.g., relative clinical value may not be greater) or may not be cost-effective (FDA does not consider costs, although payers do; thus, this is not a regulatory consideration before approval). With respect to clinical comparative and cost-effectiveness under the new PCORI, PCORI is prohibited from using the results of PCOR under the ACA to "mandate coverage, reimbursement, or other policies for any public or private payer."229 However, the ACA does not "bar CMS or any other public or private payer from using CER research to inform its own coverage decisions."230 Also, it does not specifically mention cost-effectiveness, which means this type of research is not prohibited. Although PCORI can fund cost-effectiveness research, it is focusing on clinical comparative effectiveness research and, unlike NICE, cannot make reimbursement recommendations based on cost per disability adjusted life year or other cost-effectiveness

227. Tim Kendall et al., If NICE was in the USA, 374 LANCET 272, 272-73 (2009). NICE evaluates cost-effectiveness based on costs of a drug per quality adjusted life years ("QALY"), which is a "measure of the patient's preferences for his/her health state or for the outcome of an intervention." BRIAN STROM, PHARMACOEPIDEMIOLOGY 682 (2012).
228. In addition, most comparative effectiveness studies do not also include formal cost-effectiveness studies, although information about both is necessary to full evaluate value. Michael Hochman & Danny McCormick, Characteristics of Published Comparative Effectiveness Studies of Medications, 303 JAMA 956, 956 (2010).
229. MCDONOUGH, supra note 44 at 222-3; Peter J. Neumann, What We Talk About When We Talk About Health Costs, 366 NEW ENG. J. MED. 585, 585 (2012).
230. Id.
metrics. NICE has increased the uptake of new high value drugs and patients now have a right to obtain NICE recommended drugs.\textsuperscript{231} Recently, NICE proposed to use value-based pricing, which would consider "important factors that patients and society value," thus increasing the focus on HVDs and other valuable treatments which may provide benefits important to patients.\textsuperscript{232} NICE also has the ability to assess emerging post-market evidence of a drug's value to inform the adjustment of drug pricing under the Pharmaceutical Price Regulation Scheme, thus directly linking price and the evaluation of value.\textsuperscript{233}

In the United States, although there is not an equivalent NICE, individual payers, such as private health insurance companies and self-insured companies, are increasingly employing value based insurance designs (designs which reduce cost sharing for drugs that provide high value) for the coverage of drugs.\textsuperscript{234} Although these companies often employ cost sharing and tiered formularies to reduce drug costs, this may reduce adherence to high value drugs such as generic statins, which are low cost but prevent costly and debilitating cardiovascular events.\textsuperscript{235} The creation via legislation of a NICE-type entity to evaluate the value of drugs (clinical comparative and cost-effectiveness) for coverage by CMS, the largest payer in the United States, would likely not be politically feasible currently due to resistance to government rationing of care, despite the fact that private insurance companies regularly ration and limit medical care, including drugs, via coverage decisions and tiered formularies, and drugs that are in short supply in the United States are rationed as needed.\textsuperscript{236} However, as

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\textsuperscript{232} Id. at 1291.

\textsuperscript{233} Adrian Towse, \textit{Value based pricing, research and development, and patient access schemes. Will the United Kingdom get it right or wrong?}, 70 BRITISH J. CLINICAL PHARMACOLOGY 360, 363 (2010). Of note, unlike the U.K. and Europe, the U.S. does not employ price controls, which is one reason why drug prices are so much higher in the U.S. HHS is prohibited from negotiating drug prices under Medicare Part D. See Medicare Modernization Act of 2003, PUB. L. 108-173, § 1860(D)(i), Noninterference clause.

\textsuperscript{234} ROSEMARY GIBSON & JANARDAN PRASAD SINGH, \textit{THE BATTLE OVER HEALTH CARE: WHAT OBAMA'S REFORMS MEAN FOR AMERICA'S FUTURE} 187 (2012) (Many policy experts support enabling Medicare to negotiate drug prices. Some experts propose providing publically determined subsidies in addition to price negotiation to transparently support drug company R&D in light of their decreased revenue that would result from lower negotiated prices).

\textsuperscript{235} James C. Robinson, \textit{Applying Value-Based Insurance Design to High-Cost Health Services}, 29 HEALTH AFF. 2009 (2010).

\textsuperscript{236} Philip M. Rosoff et al., \textit{Coping with Critical Drug Shortages: An Ethical Approach for Allocating Scarce Resources in Hospitals}, 172 ARCH. INTERN. MED. 1494 (2012). In fact, the ACA "explicitly rejects Britain's National Health Service Model, with its global budgeting and public acceptance of prioritization and consideration of costs." Faden supra note 231, at 1291.
the number of Medicare patients is projected to grow from forty-six million in 2010 to seventy-nine million in 2030, and the ratio of workers to retirees will decline, Medicare costs will increase by more than ninety percent.\textsuperscript{237} Further, the CBO stated that “projected increases in [Medicare] spending . . . would require tax increases of an unprecedented magnitude . . . under current policy, future generations will be worse off by higher taxation or lower benefits.”\textsuperscript{238}

Thus, similar to Massachusetts, which passed health reform under then-Governor Mitt Romney that insured virtually all state citizens and recently approved a law to lower health care costs, Congress will have to consider options to follow the ACA by significantly reducing health care costs, which may likely involve a form of rationing of health care services, including drugs.\textsuperscript{239} In a recent article, Daniel Callahan defined rationing as “an organized effort by public or private institutions (e.g., Medicare or a private insurer) to equitably limit the availability of some desired or needed medical treatments in the name of preserving the institution as a whole or equitably distributing a scarce resource.”\textsuperscript{239} Callahan emphasizes that rationing should be transparent and a societal policy versus being made on an individual case-by-case basis.\textsuperscript{240} As mentioned, in the United States, despite the rhetoric about government rationing and death panels, private insurance companies regularly ration health care, including drugs, via managed care approaches such as tiered formularies.\textsuperscript{241} If rationing is not done publically, it will be done “indirectly by pushing up copayment and deductibles to a painful, threatening level,” which is much less equitable and transparent.\textsuperscript{242} NICE uses quality adjusted life years (“QALYs”) and a cost-effectiveness threshold to ration medical treatments, including drugs, that cost above a certain dollar amount for a given amount of quality years of life conferred.\textsuperscript{243} Similar to the environmental regulations arena, alt-

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\textsuperscript{237.} Daniel Callahan, \textit{Must We Ration Health Care for the Elderly?}, J.L. MED. & ETHICS 10, 11 (2012).
\textsuperscript{239.} See, John Ayanian & Philip Van der Wees, \textit{Tackling Health Care Costs in Massachusetts}, 367 NEW ENG J. MED. 790, 790-3 (2012).
\textsuperscript{240.} Callahan, \textit{supra} note 237, at 12.
\textsuperscript{241.} Id.
\textsuperscript{243.} Callahan, \textit{supra} note 237, at 15.
\textsuperscript{244.} Although QALYs assign a value to the number of additional quality life years a medical intervention may confer, there are several problems with assigning value to a human life. These problems have been discussed in the environmental regulatory field, which often uses QALYs to evaluate environmental regulations focused on rare, serious environmental health risks. \textit{See generally} FRANK ACKERMAN & LISA HEINZERLING, PRICELESS: ON KNOWING THE PRICE OF EVERYTHING AND THE VALUE OF NOTHING (2004). \textit{See also} Peter Neumann, \textit{What’s Next for QALYs?} 305 JAMA 1806, 1806 (2011) (Also, QALYs “may not capture well how some individual value certain aspects of health.”).
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hough QALYs enable the encapsulation of value into a single number, they are subject to a number of controversial challenges, including: determining the appropriate value of a statistical life, how to incorporate life-years and quality adjusted life years approaches in an equitable manner (e.g., appropriate consideration of the elderly, who do not possess as many potential quality years of life), and how to appropriately quantify wealth-health considerations. Legislation could be passed that would create a federal agency to conduct cost-effectiveness research to determine the value of medical interventions (including drugs). Preferably, such agency would be more politically insulated, comparable to the Federal Reserve Board, that is not subject to the vagaries of the congressional appropriations process (Another option would be to mandate PCORI to conduct cost-effectiveness research, in addition to patient-centered outcomes research). Importantly, similar to NICE, this entity could obtain input from the public on the process of evaluating cost-effectiveness. States such as Oregon have passed laws in the past to provide for public, open rationing of care for poor patients (e.g., Medicaid) to ensure they had access to a basic package of health care services by surveying the public to ascertain the value of critical medical care services and then evaluating the list of services to determine their value by using a “net benefit value formula,” including data on expected health outcomes. Presently it is unlikely to be politically feasible to pursue the creation of a national cost-effectiveness center; however, one novel approach may be for payers and pharmacy benefit managers (“PBMs”) to integrate comparative effectiveness/patient-centered outcomes research evidence into the development of

245. See generally Jedediah Purdy, Climate Change and the Limits of the Possible, 18 DUKE ENVTL. L. & POL’Y F. 301 (2008). For a full discussion of the limitations of cost-benefit analyses, See generally RICHARD L. REVESZ & MICHAEL A. LIVERMORE, RETAKING RATIONALITY: HOW COST-BENEFIT ANALYSIS CAN BETTER PROTECT THE ENVIRONMENT AND OUR HEALTH (2008); U.S. EXPERT PANEL, COST-EFFECTIVENESS IN HEALTH AND MEDICINE (Marthe R. Gold et al. eds., 1996) (Despite these limitations, the panel recommended the use of QALYs to facilitate consideration of morbidity and mortality impact in one measure).


248. Faden, supra note 231, at 1290 (NICE is “viewed as a global leader in incorporating social values and public engagement into the development of health policy recommendations.”).

formularies and value-based purchasing insurance designs.\textsuperscript{250} This would enable prescription drug plans and PBMs to charge lower costs for higher value drugs and higher costs for lower value drugs (based on comparative effectiveness research evidence meeting agreed upon standards). Incentivizing patients to take medications that significantly improve their health can save the health care system money by reducing adverse outcomes and hospitalizations.\textsuperscript{251} In addition, the ACA created the Independent Payment Advisory Board ("IPAB"), vilified by Republicans during the presidential race, which will in the upcoming years recommend approaches to limit Medicare costs if they exceed projected annual target rates; however, unlike NICE, the IPAB is not an evaluative organization, but rather proposes ways to reduce costs (it does not evaluate drug and medical intervention clinical and cost-effectiveness) that are binding if Congress fails to sufficiently lower costs when Medicare costs increase at a rate above a specified threshold relative to general inflation. However, its existence may be short-lived due to opposition from Congress and health care stakeholders.\textsuperscript{252}

With respect to Medicare, the rising program costs are unsustainable and it is possible that some limitations on state-of-the-art technologies may be required, especially in the final months to years of life, which are the most expensive.\textsuperscript{253} Although access to information on the value of drugs is the \textit{sine qua non} (essential component) of an efficiently functioning market, prescribers and patients often lack comparative evidence of drugs' clinical value for some important reasons as mentioned in prior sections of this paper.\textsuperscript{254} Without this evidence of comparative clinical value, it is not

\begin{itemize}
  \item \textsuperscript{250} Michael E. Chernew et al., \textit{Comparative Effectiveness Research and Formulary Placement: The Case of Diabetes}, 19 J. MANAGED CARE 1, 2 (2013).
  \item \textsuperscript{251} Id.
  \item \textsuperscript{252} PPACA, § 3403, IPAB. Health Affairs, \textit{Health Policy Brief}, 4 (Dec. 15, 2011), at http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_59.pdf (Starting in 2013, a new entity will have authority to curb Medicare spending if growth exceeds targets). See Henry J. Aaron, \textit{The Independent Payment Advisory Board – Congress’s Good Deed}, 364 NEW ENG J. MED. 2377, 2379 (2011) (Republicans have introduced bills to eliminate this Board and former presidential candidate Romney purportedly would have repealed the entire health reform law, including the IPAB. Despite these limitations, the IPAB could play an important role if it survives as it can “mobilize the power of the country’s largest health care buyer” to promote change). Gibson & Singh, supra note 233, at 187. (The pharmaceutical industry has also fought against the IPAB because its actions might result in lower drug prices; Eli Lilly wrote “We think that the IPAB provision should be repealed. Should we have unelected, unaccountable bureaucrats making health care decisions rather than you and your physician?”). Emily Ethridge, \textit{New House Rules Would Amend Requirements on Medicare Board}, CQ NEWS (Dec. 31, 2012), at http://www.rollcall.com/news/new_house_rules_would_amend_requirements_on_medicare_board-220428-1.html (Republicans plan to limit the IPAB via House rules for the 113th Congress).
  \item \textsuperscript{253} Cynthia E. Boyd, \textit{Medicare: It’s Time to Talk About Changing It}, 19 ANNALS HEALTH L. 79, 80 (2010).
  \item \textsuperscript{254} Reinhardt supra note 247, at 111.
\end{itemize}
possible for a new semi-public entity to evaluate the cost-effectiveness of drugs, a key aspect of value. Although this paper does not focus on the communication of comparative effectiveness evidence, efforts to increase access to such evidence generated by PCORI and AHRQ, such as academic detailing, and to improve communication of evidence about drug harms and benefits more generally, may increase the use of HVDs.

2. Evaluation of Comparative Efficacy and Tolerability at the Time of Drug Approval

Physician Alec O'Connor proposes consideration of comparative efficacy and safety at the time of approval. Specifically, he points out that under the Code of Federal Regulations, a new drug is approved on the basis of substantial evidence, namely adequate and well-controlled investigations (with the exceptions discussed above created under the FDA Modernization Act of 1997). Dr. O'Connor points out that this means the law does not require a new drug to provide greater efficacy over placebo than another approved drug for the same condition, which could result in patients taking a newly approved drug that is less efficacious, potentially leading to worse health outcomes. Randall Stafford proposed changing the CFR to require sponsors to submit CER data to FDA. This could be very problematic if poor quality observational study evidence is submitted before an evidentiary framework for this type of research is firmly established, as this could potentially mislead prescribers about a drug's actual value. Instead, O'Connor focuses on clinical trials and proposes "strict FDA oversight of required active-comparator trials," which would ensure that the trials were adequately designed to evaluate the premarket comparative efficacy of treatments. This would require a change to the FDA regulations and may be infeasible as drug companies would likely be opposed to this approach. Opponents of this proposal have posited that (1) FDA already exercises authority to require comparative trials if patients may be at risk and (2) the size of the required trials would be too large; and (3) when drugs are very expensive relative to their marginal additive

255. Fisher & Avorn, supra note 207, at 194.
256. Lisa M. Schwartz & Steven Woloshin, Using a Drugs Fact Box to Communicate Drug Benefits and Harms, 150 ANNALS INTERN. MED 8 (2009).
258. Id.
benefit, payers will address this via formulary restrictions and other approaches. Although these points may be true in some circumstances, several me-too drugs that provide marginal, comparative benefit and tolerability to previously approved drugs in the same class, have been approved in recent years and many patients have been shifted to these much more costly patented drugs, possibly in part due to significant direct-to-consumer ("DTC") advertising, when cheaper generic drugs that provide the same relative clinical value have been available (e.g., esomeprazole [Nexium, the purple pill] and omeprazole [Prilosec]). Recently, the pharmaceutical industry requested FDA to allow drug companies to communicate the results of the CER studies, many of which are observational in nature, under the "competent and reliable" legal evidentiary standard for product communications. Also, FDA could change its interpretation of the "substantial clinical experience" standard (for communication of comparative claims) in the future to enable communication of CER results from PCORI and other entities. However, until the evidentiary standards for observational CER studies are well established, it is unlikely that FDA will allow drug sponsor communications about these studies due to the high potential for bias and confounding in these nonrandomized studies.


As mentioned above, guidelines and guidance documents have been created by several domestic and international government (e.g., FDA, AHRQ, EMA, ENCePP) and independent organizations and public-private partnerships (e.g., PCORI, ISPE, GRACE, ENCePP) for postmarket safety and CER/PCOR research. It is important for government, independent or-


262. Stephane Regnier, What is the value of 'me-too' drugs?, HEALTH CARE MGMT. SCI. 2013 (published online ahead of print, Feb. 26, 2013) (In the short term, me-too drugs may provide some cost savings but in the long term savings may be small, non-existent or negative). See also Joshua J. Gagne & Niteesh K. Choudhry, How Many "Me-Too" Drugs Is Too Many?, 305 JAMA 711, 711 (2011).

263. See Eleanor Perfetto, John E. Bailey, Kathleen R. Gans-Brangs, et al., Communication About Results of Comparative Effectiveness Studies: A Pharmaceutical Industry View, 31 HEALTH AFF. 2213, 2214, 2216 (2012) (Dr. Perfetto points out that payers currently use CER study evidence for coverage decisions such as formulary coverage that do not meet FDA's "substantial evidence" standard. However, this is different than FDA endorsing sponsors to discuss comparative effectiveness research results without widespread agreement on standards. As standards, which may include efforts by GRACE as previously mentioned become widely accepted, this FDA stance may change in the future).


organizations, such as academics, and industry to harmonize these documents to the greatest extent feasible so they may be best used for the evaluation of the quality of evidence to better ascertain the value of drugs in the postmarket setting.\footnote{266}

4. Leveraging Health Information Technology ("HIT") for the Evaluation of Drugs

In Section III, this paper discussed how HHS/ASPE and FDA initiatives are leveraging existing healthcare data to evaluate drugs in the real world. Government health agencies, clinicians, and HIT experts should also leverage aggregated data to evaluate patient adherence to medications, which will enable an evaluation of whether patients take their medications as prescribed and whether non-adherence is due to a lack of effectiveness or safety issues.\footnote{267} As mentioned, most pharmacists, especially those in the most accessible venue, community pharmacies, do not have access to patients’ EHRs.\footnote{268} Decisionmakers allocating future federal funding for EHRs and the medical and pharmacy communities should consider supporting new approaches that make clinical data available to pharmacies by integrating electronic pharmacy systems so that they can evaluate the value of drugs during medication therapy management.\footnote{269} In addition, if physicians have access to electronic health care data on all patients in their practice, they may identify patients who may be exposed to serious risks of

\footnote{266. Michael L. Johnson & Abhishek S. Chitnis, \textit{Comparative effectiveness research: guidelines for good practices are just the beginning, 11 EXPERT REV. 51, 54 (2011).}}

\footnote{267. PCAST, \textit{Report to the President: Realizing the Full Potential of Health Information Technology to Improve Healthcare for Americans: The Path Forward}, 17 (Dec. 2010); See also Lars Osterberg & Terrence Blaschke, \textit{Adherence to Medication}, 353 NEW ENG J. MED. 487, 487-97 (2005) (Lack of patient adherence is widespread problem and a recent study found that only sixty-six percent of patients were adherent to diabetes medications six months after initiation). See Aaron Mckethan et al., \textit{Seizing the Opportunity to Improve Medication Adherence}, HEALTH AFFAIRS BLOG (Aug. 28, 2012) at http://healthaffairs.org/blog/2012/08/28/seizing-the-opportunity-to-improve-medication-adherence/. See generally M. Christopher Roebuck et al, \textit{Medication Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending}, 30 HEALTH AFF. 91 (2011) (Furthermore, patients with chronic diseases who are more adherent have higher drug costs but better health outcomes and lower overall health care costs).}

\footnote{268. Diana Yap, \textit{Pharmacists can help with meaningful use}, AMERICAN PHARMACISTS ASSOCIATION (Dec. 1, 2012) at http://www.pharmacist.com/pharmacists-can-help-meaningful-use (Although currently most community pharmacists don’t have access to electronic health records, Walgreens recently announced an initiative to provide pharmacists with access to EHRs in most of its 8,000 pharmacies throughout the country. This disruptive innovation may drive the community pharmacy market to providing pharmacists with access to EHRs and may enable community pharmacists to collaborate with hospitals to ensure seamless transitions of care from the inpatient to outpatient setting.). See \textbf{PHARMACY E-HEALTH INFORMATION TECHNOLOGY COLLABORATIVE,} http://www.pharmacyhit.org/ (several pharmacist organizations have joined together under the auspices of the pharmacy e-health initiative to advocate CMS and other decision-makers to ensure that incentives for electronic health records and health information exchanges enable pharmacists to leverage this data for patient care).}
harm associated with drugs and take actions to mitigate this risk (e.g., high dose simvastatin and risk of muscle damage). Integrating drug adverse event reporting into EHRs, which the FDA supports, will enhance the evaluation of postmarket drug safety. Further, personal health records ("PHRs"), containing clinical information, claims, and lab data, and data directly from patients may significantly contribute to drug evaluation. Also, this may facilitate patients’ reporting outcomes to health care professionals (and enhance patients’ ability to manage their own care), and inform shared decision-making. Observational registries may also be increasingly leveraged for the conduct of "clinical registry trials," which will better reflect real world patient outcomes and enable trials for a larger number of patients at a lower cost.

5. Evaluation of Off-Label Drug Use

Off-label drug use is pervasive (about twenty percent of prescription drug use was estimated to be off-label in 2001) and may support innovation, such as information about new benefits, or increase patient harms, such as the use of drugs that do not work and/or cause harm in the non-indicated populations. Off-label drug use may be affected by a recent decision handed down by the United States Court of Appeals for the Second Circuit, which held that a drug sales representative had First Amendment free speech protection to discuss off-label drug use information with physicians. However, this was a "sui generis" case because it very fact-specific, involved truthful speech, and the court stated that FDA still has the right to regulate the marketing of drugs, including off-label marketing, when used as part of a broader evidence base to demon-

275. Randall S. Stafford, Off-Label Use of Drugs and Medical Devices: A Review of Policy Implications, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 920, 921 (2012); See also Dal Pan, supra note 127.
276. United States v. Caronia, 703 F.3d 149 (2d Cir. 2012). Marcia M. Boulil, Off-Label Marketing and the First Amendment, 368 NEW ENG. J. MED. 103 (2013); see also Andrew Pollack & Mosi Secret, Amgen Agrees to Pay $762 Million for Marketing Anemia Drug for Off-Label Use, N.Y. TIMES, Dec. 18, 2012, at B3 (furthermore, drug companies still promote the off-label drug use despite the lack of evidence on drug safety and efficacy. "Amgen pleaded guilty to illegally marketing the drug [Aranesp] and agreed to pay $762 million in criminal penalties and settlements of whistle-blower lawsuits.").
strate that a sales representative is marketing the drug for off-label use (in this case, the sole evidence was that of speech pertaining to off-label use). Thus, this may not have a significant impact on off-label use. In the United Kingdom, the National Institutes for Health and Clinical Excellence ("NICE") recently published product summaries of off-label use to summarize evidence on off-label use, although it indicated that it is not encouraging off-label prescribing. Because there is no equivalent to the NICE agency in the United States and this may be viewed as promoting off-label drug use, this may not be a viable option in the United States. One approach to address off-label use would be to require drug sponsors to discuss "possible future off-label use" when a drug is approved in exchange for a fast tracking of supplemental NDAs. Although this would require legislation, it would facilitate post-marketing surveillance of adverse effects in off-label populations, and it may prevent companies from seeking "approval for a second, but easier to approve, target." Although the FDA cannot regulate off-label drug use (only off-label promotion related to intended use), and thus does not have access to good evidence on such use, CMS's coverage with evidence development and PCORI funded research may enhance the evaluation of off-label use by studying the real world use of drugs and determining their value. France recently passed legislation that enables the creation of a temporary marketing authorization for drugs that are used off-label on the condition that companies monitor the drug's safety and efficacy. Although this approach may facilitate evaluation of off-label use, it may also increase off-label use regardless of whether or not permanent authorization is secured after the maximum three-year test period.

CONCLUSION

President Obama and Congress will need to take significant steps to strengthen the economy, of which the biopharmaceutical sector is a key

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279. Stafford, supra note 275, at 924.
280. Id.
281. Id.
part, and lower costs, of which health care (including drugs) costs, are increasingly the most significant part. These costs are rising more rapidly per year than the average increase in income over the past decade. The President has emphasized the importance of increasing investments in R&D more generally because, despite the importance of this research to American competitiveness, the percentage of federal funds spent on R&D as a percentage of GDP has “declined by 60% in 40 years,” according to a 2005 National Academies Report that was developed at the encouragement of the House and Senate. Considering the unprecedented economic crossroads in our country, the President needs rally public and congressional support to effectuate the policy initiatives referenced in this paper. In addition, the President will need to support the rapid evaluation, implementation and uptake of the ACA insurance and health care delivery-related reforms (e.g., Accountable Care Organizations and Patient-Centered Medical Homes), and develop new approaches to support high value health care (including drug therapy) that can improve patient health outcomes, decrease the approximately $750 billion per year in health care waste, and bend the cost curve of health care (including drugs).

284. Smith, supra note 273, at 1637.
285. THOMAS L. FRIEDMAN & MICHAEL MANDELBAUM, THAT USED TO BE US: HOW AMERICA FEEL BEHIND IN THE WORLD IT INVENTED AND HOW WE CAN COME BACK 231 (2011) (quoting Rising Above the Gathering Storm: Energizing and Employing America for a Brighter Future, a report done by the National Academy of Sciences, National Academy of Engineering, & the Institute of Medicine); Moses, supra note 5, at 1341. See also FAREED ZAKARIA, THE POST-AMERICAN WORLD 2 (2012) (increasing American competitiveness is all the more important in light of the “rise of the rest,” including India and China, whose GDP growth rates have remained at nine percent or greater almost every year for the past several years, in contrast to the slow U.S. GDP growth rate in recent years).