

2019

Drug Prices, Dying Patients, and the Pharmaceutical Marketplace: A New Conditional Approval Pathway for Critical Unmet Medical Needs

Robert A. Bohrer
California Western School of Law, rab@cwsl.edu

Follow this and additional works at: <https://scholarlycommons.law.cwsl.edu/fs>



Part of the [Food and Drug Law Commons](#), and the [Pharmacy Administration, Policy and Regulation Commons](#)

Recommended Citation

Robert A. Bohrer, *Drug Prices, Dying Patients, and the Pharmaceutical Marketplace: A New Conditional Approval Pathway for Critical Unmet Medical Needs*, 12 *Drexel L. Rev.* 1 (2019).
Available at: <https://scholarlycommons.law.cwsl.edu/fs/329>

This Article is brought to you for free and open access by CWSL Scholarly Commons. It has been accepted for inclusion in Faculty Scholarship by an authorized administrator of CWSL Scholarly Commons. For more information, please contact alm@cwsl.edu.

DRUG PRICES, DYING PATIENTS, AND THE PHARMACEUTICAL MARKETPLACE: A NEW CONDITIONAL APPROVAL PATHWAY FOR CRITICAL UNMET MEDICAL NEEDS

By Robert A. Bohrer J.D., LL.M.*

ABSTRACT

Prescription drugs have been a major topic in the news for much of the past year. There are two issues which appear often: first, the very high prices of new drugs, particularly the “specialty” drugs developed for serious diseases; and second, the time required for FDA approval in relation to the perceived need for earlier access to new therapies for critically ill patients. Much less in the news, but lurking behind both issues, is the need for better information for physicians and patients to use in making decisions about prescribing and taking drugs, and for insurance companies and the government to use to structure their pharmaceutical benefits plans. This Article proposes an approach to accelerated access and drug prices that would generate this much-needed information for doctors, patients, the government, and private insurers. The new form of conditional approval proposed here would be similar to the parallel track program developed by the FDA in the 1990s, during the HIV crisis. I argue that, like parallel track, the FDA could implement the conditional approval proposed here under its existing authority, that this approach would allow critically ill patients wide access to desperately needed drugs, and would also control prices for drugs that have not demonstrated clinical benefit until sufficient information is available about their real safety and efficacy.

* Professor of Law, California Western School of Law, B.A. Haverford College, J.D. U. of Illinois, LL.M. Harvard Law School. I have benefitted from discussions with numerous colleagues and from diligent work by a number of research assistants. I wish to particularly thank for their comments the FDA scholars who have made the ASLME Annual Health Law Professors Conference my academic home. Finally, I wish to acknowledge the invaluable support of my editor-in-chief, Karen Bohrer.

TABLE OF CONTENTS

INTRODUCTION: DRUG PRICING, ACCELERATED ACCESS, AND INFORMATION ABOUT DRUG EFFECTIVENESS.....	2
II. THE FDA’S APPROVAL PROCESS FOR NEW DRUGS	6
III. CURRENT APPROACHES TO PRE-APPROVAL ACCESS AND ACCELERATED APPROVAL FOR DRUGS FOR CRITICALLY ILL PATIENTS	12
A. <i>Right to Try</i>	13
B. <i>Accelerated Access to Experimental Drugs</i>	15
1. <i>FDA provisions for access prior to approval</i>	15
2. <i>Accelerated approval</i>	17
C. <i>Breakthrough Drugs</i>	20
IV. THE FDA’S ROLE IN PROVIDING INFORMATION TO THE PHARMACEUTICAL MARKET.....	25
V. IS THE FDA’S PROCESS REALLY NECESSARY OR COULD A FREE MARKET WORK AS WELL?	28
VI. CONDITIONAL APPROVAL COULD ACCELERATE ACCESS, REDUCE PRICES, AND MORE QUICKLY PROVIDE THE INFORMATION THAT DOCTORS, PATIENTS, AND PROVIDERS NEED.....	37
A. <i>The New Conditional Approval</i>	40
B. <i>Pricing Conditionally Approved Drugs</i>	42
CONCLUSION.....	44

INTRODUCTION: DRUG PRICING, ACCELERATED ACCESS, AND
INFORMATION ABOUT DRUG EFFECTIVENESS

Prescription drugs have been a major topic in the news for much of the past year. There are two issues which appear quite often: the exceptionally high prices of new drugs,¹ particularly the “specialty” drugs developed for serious diseases, and the time required for FDA approval in relation to the perceived

1. See, e.g., Paige Winfield Cunningham, *The Health 202: The Trump Administration is Taking on Middlemen that Inflate Drug Prices*, WASH. POST (Feb. 1, 2019), https://www.washingtonpost.com/news/powerpost/paloma/the-health-202/2019/02/01/the-health-202-02012019-health202/5c5303da1b326b29c3778d32/?utm_term=.baf783fa1725; Stephanie Armour, *Trump’s Plan to Lower Drug Prices: A Q&A*, WALL ST. J. (May 11, 2018, 6:21 PM), <https://www.wsj.com/articles/trumps-plan-to-lower-drug-prices-a-q-a-1526077290>.

need for earlier access to new therapies for critically ill patients.² Much less in the news, but lurking behind both issues, is the need for more accessible and useful information for physicians prescribing drugs, patients, and insurance companies and the government structuring pharmaceutical benefit plans that reimburse patients for some portion of the cost of drugs. This Article proposes an approach to both accelerated access and drug prices that would provide the information that doctors, patients, the government, and private insurance companies need to appropriately make decisions about drug prescriptions, access, and coverage.

Both the high price and complex and lengthy process of getting new drugs to critically ill patients pose serious problems.³ It is vital to get drugs to desperate patients as quickly as possible without overwhelming them and the healthcare system. However, the solutions to these problems currently at the forefront of the debate—“Right to Try” laws⁴ and insuring that price rebates benefit patients rather than their insurers or their insurers’ pharmacy benefit managers (“PBMs”)⁵—fail to fully address either patients’ needs or the workings of the pharmaceutical marketplace. Now is the time to move forward with a new approach to accelerate access to new drugs for critically ill patients, while also tackling the soaring prices of the drugs they need.

2. See, e.g., *President Donald J. Trump to Sign Right to Try Legislation Fulfilling the Promise He Made to Expand Healthcare Options for Terminal Americans*, WHITE HOUSE (May 30, 2018), <https://www.whitehouse.gov/briefings-statements/president-donald-j-trump-sign-right-try-legislation-fulfilling-promise-made-expand-healthcare-options-terminal-americans/>; Kate Rawson, *Gottlieb Defends Accelerated Approval, Scorns Access Limits by Payors*, PINK SHEET (Oct. 23, 2017), <https://pink.pharmaintelligence.informa.com/PS121818/Gottlieb-Defends-Accelerated-Approval-Scorns-Access-Limits-By-Payors>; Steven M. Joffe & Holly Fernandez Lynch, *Federal Right-to-Try Legislation—Threatening the FDA’s Public Health Mission*, 378 NEW ENG. J. MED. 695, 695, 697 (2018).

3. See *supra* notes 1–2.

4. See discussion *infra* Section III.A.

5. See *Fraud and Abuse; Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Manager Service Fees*, 84 Fed. Reg. 2340, 2344 (Feb. 6, 2019) (to be codified at 42 C.F.R. pt. 1001).

While the Right to Try laws and FDA pre-approval access provisions—such as single-patient Investigational New Drug application (“INDs”), or accelerated approval and breakthrough drug approval—provide earlier access to critically needed drugs, it is at the cost of significant evidence about the actual effectiveness of those drugs.⁶ Any reasonable approach to drug pricing requires substantial knowledge of a drug’s effectiveness. If a fundamental characteristic of a functioning market is that the prices of goods are related to their value to the buyer, the pharmaceutical market cannot function well when a drug is approved before its value is established on the endpoints of real value to patients—what patients really care about is, for example, overall survival (in cancer) or the long-term ability to function in degenerative diseases like Parkinson’s or Muscular Dystrophy. Now is a time where real change is possible, as President Trump along with Democratic and Republican members of Congress have expressed concern about the high cost of drugs. This rare political consensus might make it possible to pursue a more effective method of accelerating access to drugs for critically ill patients and, at the same time, reduce the costs of those drugs.

One way to strike a better balance between accelerated access and limiting drug prices until their value is known would be a new form of “conditional approval,” with prices discounted until full approval is warranted. High prices and delays in getting drugs to desperate patients may appear to be separate problems, but both are rooted in the same fundamental information problem. Implementing the form of conditional approval proposed in this Article would be a major step towards providing the needed information and solving both the delay problem and the pricing problem.

6. U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE—QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY 3 (2016), <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf> [hereinafter EXPANDED ACCESS].

Part II of this Article provides a basic overview of the FDA's approval process for new drugs. Part III describes the FDA's current approaches to pre-approval access and accelerated approval for drugs for critically ill patients, which provide access to drugs on the basis of less than substantial evidence of actual patient clinical benefit. Part IV explains the FDA's role in providing information to the pharmaceutical market and discusses in further detail the kind of information generated by the FDA approval process. Part V considers whether the FDA's process is really necessary or if a free market could work as well. Data from the advisory committee process⁷ and literature on the weaknesses in industry-funded studies⁸ is used to demonstrate the value of the FDA's approval process in the marketplace for pharmaceuticals. Part VI provides the framework for a "conditional approval" pathway for allowing early access to drugs that could accelerate access, reduce prices, and more quickly provide the information that doctors, patients, and providers need. Part VII concludes that the conditional approval pathway proposed in this Article would better align the interests of patients and insurers with respect to desperately needed but essentially unproven therapeutics. Conditional approval would require only minimal legislative action to guarantee insurance coverage for conditionally-approved drugs at a relatively low pre-final approval price. In our current era of concern over the price of drugs, conditional approval may provide an attractive and politically viable step toward an overall solution to the problems of escalated pricing and time-consuming approval processes.

7. See *What is an FDA Advisory Committee?*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm222191.htm> (last updated Mar. 28, 2018) (defining FDA advisory committee).

8. See Joel Lexchin et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 *BRIT. MED. J.* 1167, 1169 (2003) (discussing studies that found drug-company-sponsored research is of a better quality than industry-funded research).

II. THE FDA'S APPROVAL PROCESS FOR NEW DRUGS

The Food, Drug, and Cosmetic Act (FDCA) defines a drug as a substance “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals . . . [or] intended to affect the structure or any function of the body of man.”⁹ To sell a new drug the manufacturer or sponsor of the drug needs to file an application and submit “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective.”¹⁰ In practice, “full reports of investigations” means the results of preclinical testing in the laboratory, both in vitro and in animals, as well as the results of human clinical trials.¹¹ Preclinical testing in the lab is completed first. Only upon successful completion of preclinical testing will the drug be ready to test in humans.

Traditionally, human testing has been divided into three stages, or “phases,” of experimental trials.¹² Often Phase 1 trials are designed only to get a preliminary assessment of the drug's safety.¹³ The subjects are usually healthy volunteers and therefore no evidence of how much effect in treating disease, or efficacy data, would be generated.¹⁴ However, in some cases, particularly cases of drugs prescribed for serious diseases where no effective therapy exists, initial testing is done in

9. 21 U.S.C. § 321(g)(1) (2018).

10. *Id.* § 355(b)(1).

11. See e.g., *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective> (last updated Nov. 24, 2017) [hereinafter *The FDA's Drug Review Process*]. An application to approve a new drug for marketing “includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.” *Id.*

12. See *Step 3: Clinical Research*, U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research> (last updated Jan. 4, 2018) [hereinafter *Step 3*].

13. *Id.*

14. *The FDA's Drug Review Process*, *supra* note 11.

patients with the disease.¹⁵ Phase 1 trials in diseased patients may provide some preliminary efficacy data.¹⁶ In addition to looking for adverse effects, a principal goal of the first phase of human testing is to generate significant information about the drug's in vivo metabolism in humans, including absorption, half-life, and distribution within the body.¹⁷ Such information is referred to as the drug's "pharmacokinetics."¹⁸

Phase 2 trials test multiple doses of the drug and involve further safety testing and efficacy testing on patients diagnosed with the disease or condition.¹⁹ The relationship between a drug's dose and its biological effects is referred to as pharmacodynamics.²⁰ If Phase 2 trials provide evidence that the drug continues to appear safe and potentially effective, then Phase 3 trials follow, which generally involve significantly more patients.²¹

15. *Step 3*, *supra* note 13 ("However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer."); *see also* Nam Q. Bui & Shivaani Kumar, *Evolution of Early Phase Clinical Trials In Oncology*, 96 J. MOLECULAR MED. 31, 33 (2018).

16. *See* Bui & Kumar, *supra* note 15.

17. Gerlie Gieser, Ph.D., U.S. Food & Drug Admin., Office of Clinical Pharmacology, Presenter at the 2012 Clinical Investigator Course: Clinical Pharmacology—Phase 1 Studies and Early Drug Development (2012), <https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm340007.pdf>.

18. Jennifer Le, *Overview of Pharmacokinetics*, MERCK MANUAL, <https://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics> (last updated May 2019).

19. *The FDA's Drug Review Process*, *supra* note 11; U.S. National Library of Medicine, *Glossary of Common Site Terms*, NIH, <https://clinicaltrials.gov/ct2/about-studies/glossary> (last updated June 2019).

20. Abimbola Farinde, *Overview of Pharmacodynamics*, MERCK MANUAL, <https://www.merckmanuals.com/professional/clinical-pharmacology/pharmacodynamics/overview-of-pharmacodynamics> (last updated June 2019).

21. *See Overview of Clinical Trials*, CENTERWATCH, <https://www.centerwatch.com/clinical-trials/overview.aspx> (last visited Sept. 16, 2019). The difference between statistical and clinical significance is worth noting. Statistical significance is merely an indication that the difference between experimental groups is relatively unlikely to be due to chance. The generally accepted standard for statistical significance is that the difference between experimental groups would occur by chance less than five times in one hundred. *See Getting Started with Statistics Concepts*, STATSOFT, <http://www.statsoft.com/textbook/esc.html> (last visited Sept. 16, 2019). Clinical significance is largely a function of the extent to which the difference between the experimental groups reflects a difference that doctors and patients would recognize as meaningful to the

Phase 3 trials vary widely in size depending on the seriousness of the disease for which the drug is being tested, the prevalence of the disease, and the estimated magnitude of the drug's effect.²² These are usually multicenter studies conducted to prove safety and efficacy and look for adverse reactions in a larger population.²³ The less frequently an adverse effect occurs, the bigger the trial will need to be to have any likelihood of detecting it. For example, an adverse reaction likely to occur in one percent of the population has only about a sixty-three percent chance of occurring even once in any particular one hundred-person clinical trial.²⁴ Thus, clinical trials of a few hundred patients are unlikely to detect serious adverse reactions that occur only once in one thousand patients.

Although in most cases Phase 3 trials should be sensitive enough to provide at least preliminary evidence of the most significant safety issues, for conditions that have a significant likelihood of mortality within a relatively short term, safety concerns become less significant and much smaller studies may be accepted. For a disease such as metastatic pancreatic cancer, with a twelve-month or more survival rate of twelve percent of patients,²⁵ a one in one hundred risk of a serious adverse effect

patient. See W-C Leung, *Balancing Statistical and Clinical Significance in Evaluating Treatment Effects*, 77 POSTGRADUATE MED. J. 201, 201 (2001). For example, in a large enough trial, a 30 mm. difference in tumor size between treated and untreated groups might be statistically significant, while that difference may have no real "clinical" significance on either patient quality of life or survival. See *id.*

22. See *The FDA's Drug Review Process*, *supra* note 11. When a drug is tested in a clinical trial, the greater the difference between the outcome of the patients who received the drug and the outcome of those receiving the control agent (placebo or other drug) the stronger the "signal" produced by the trial. When the signal is expected to be strong, a smaller trial would be sufficient to reach statistical significance. See Caroline Helwick, *Update on Overall Survival for Newly Diagnosed Patients With Metastatic Pancreatic Cancer*, ASCO POST (Mar. 10, 2017), <http://www.ascopost.com/issues/march-10-2017/update-on-overall-survival-for-newly-diagnosed-patients-with-metastatic-pancreatic-cancer/>.

23. Adam Cheng et al., *Conducting Multicenter Research in Healthcare Simulation: Lessons Learned from the INSPIRE Network*, 2 ADVANCES IN SIMULATION 1 (2017) ("Multicenter research confers many distinct advantages over single-center studies, including larger sample sizes for more generalizable findings and . . . are more likely to improve provider performance and/or have a positive impact on patient outcomes.").

24. ROBERT A. BOHRER, A GUIDE TO BIOTECHNOLOGY LAW AND BUSINESS 228 (2007).

25. Helwick, *supra* note 22.

may be of little concern. Given the grim prognosis of the disease, approval of the drug could be based on a Phase 3 trial of approximately two hundred patients.²⁶ Similarly, drugs for serious and very rare diseases are often tested in much smaller groups. For example, the study leading to the approval of Aldurazyme “for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms”²⁷ was based on forty-five patients, twenty-two in the drug group and twenty-three who received a placebo.²⁸

At the end of the three phases of clinical trials, the manufacturer or “sponsor” of the drug may submit a New Drug Application, or NDA, to the FDA.²⁹ If the application is sufficiently complete, the FDA will “file” the application and begin its review process.³⁰ In recent years, the median time from the filing of an NDA to approval has been eight months for “priority review” drugs—those which may provide a significant improvement in safety or efficacy of treatments for the particular indication—and ten to twelve months for non-priority review drugs.³¹ Critics of the FDA consider a delay of even a few months to review a drug unjustifiable,³² however, the review of a drug’s safety and efficacy is an extraordinarily complex undertaking. To provide a better understanding of the scope and complexity of that review effort, Table 1 shown below lists the twenty-two FDA staff, in addition to the team leaders—all of whom were Ph.D.s, or M.D.s—who participated

26. See U.S. FOOD & DRUG ADMIN., FULL PRESCRIBING INFORMATION: ONIVYDE 15 (2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/2077931bl.pdf. The study upon which approval was based included 236 randomized patients. See *id.*

27. U.S. FOOD & DRUG ADMIN., FULL PRESCRIBING INFORMATION: ALDURAZYME 1 (2010), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125058s01861bl.pdf.

28. *Id.* at 4.

29. See *The FDA’s Drug Review Process*, *supra* note 11.

30. *Id.*

31. U.S. FOOD & DRUG ADMIN., CDER APPROVAL TIMES FOR PRIORITY AND STANDARD NDAS AND BLAS: CALENDAR YEARS 1993–2016 (2016), <https://www.fda.gov/media/102796/download> (showing the statistics of new priority and non-priority review requests for drugs).

32. *Theory, Evidence and Examples of FDA Harm*, FDAREVIEW.ORG., <https://www.fdaireview.org/issues/theory-evidence-and-examples-of-fda-harm/> (last visited Sept. 26, 2019).

in the review of Blincyto (blinatumomab), an antibody developed by Amgen and approved for the treatment of a specific form of relapsed or refractory acute lymphoblastic leukemia (ALL).³³

Table 1.³⁴

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Donna Przepiorka, MD, PhD
Clinical Pharmacology	Pengfei Song, PhD, Ping Shao, PhD, Vikram Sinha, PhD, Qi Liu, PhD, and Nitin Mehrotra, PhD
Biostatistics	Chia-Wen Ko, PhD, and Lei Nie, PhD
Pharmacology/Toxicology	Brenda J. Gehrke, PhD, Haw-Jyh Chui, PhD, Tiffany K Ricks, PhD, Christopher M Sheth, PhD
Immunogenicity	Laura Salazar-Fontana, PhD, and Susan Kirshner, PhD
Division of Monoclonal Antibodies, DTP	Zing Zhou, PhD, Deborah Schmiel, PhD, and Rashmi Rawat, PhD
OC/OMPQ/DGMPA/BMAB	Candace Gomez-Broughton, PhD, Reyes Candau-Chacon, PhD, and Patricia Hughes, PhD
DRISK/Office of Medication Error Prevention and Risk Management/OSE/CDER	Carolyn L. Yancey, MD
Project Manager	Kris Kolibab, PhD

33. ALBERT DEISSEROTH, CTR. FOR DRUG EVALUATION & RESEARCH, CROSS DISCIPLINE TEAM LEADER REVIEW 1 (2014), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125557Orig1s000CrossR.pdf.

34. *Id.*

After reviewing all of the data, including the design of the Phase 3 trials and the results of those trials, the FDA may request an advisory committee meeting.³⁵ Advisory committees enable the FDA to obtain the opinion of independent experts on particular scientific, technical, or policy issues raised in connection with the application.³⁶ At the end of the review, the FDA will either approve the application or send the applicant a Complete Response Letter (CRL) detailing the reasons for the denial.³⁷ The CRL may require relatively minor additional action by the sponsor, such as revising the statistical analysis of some of the data, requesting additional clinical trials, or, in the worst case from a sponsor's perspective, stating that the data does not indicate that the benefits of the drug outweigh the risks of the drug.³⁸ The FDA's approval of a drug includes the approval of a drug's labeling, detailing the "Full Prescribing Information" relied upon by physicians, as well as summaries of the drug's mechanism of action, its pharmacology, and the clinical trial evidence supporting the drug's approval.³⁹ This full prescribing information is then available on the FDA's website.⁴⁰ While the studies that provided the basis for the FDA's approval are often available in the published literature, this full prescribing information is the "official" source of information about a drug for physicians.⁴¹

35. See *Advisory Committees: Critical to the FDA's Product Review Process*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/drug-information-consumers/advisory-committees-critical-fdas-product-review-process> (last updated May 4, 2016); see also *What is an FDA Advisory Committee?*, *supra* note 7.

36. *Learn About FDA Advisory Committees*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/patients/learn-about-patient-affairs-staff/learn-about-fda-advisory-committees> (last updated June 21, 2018).

37. 21 C.F.R. § 314.110(a) (2018).

38. *Id.* § 314.125(b) (listing reasons why FDA may refuse to approve an NDA).

39. See *id.* § 314.105; see also *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3921, 3926 (Jan. 24, 2006).

40. See *Drugs@FDA: FDA Approved Drug Products*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> (last visited Nov. 2, 2019).

41. *Cf. Wash. Legal Found. v. Henney*, 202 F.3d 331, 335–36 (D.C. Cir. 2000) (upholding the First Amendment rights of drug companies to provide physicians with unofficial non-misleading information not reviewed by the FDA). *Henney* explains why the full prescribing information database exists today. *Id.*

III. CURRENT APPROACHES TO PRE-APPROVAL ACCESS AND ACCELERATED APPROVAL FOR DRUGS FOR CRITICALLY ILL PATIENTS

The FDA has always been in the difficult position of being statutorily required to approve new drugs on the basis of sufficient evidence of their safety and efficacy on the one hand and meeting the needs of critically ill patients on the other.⁴² It is not hard to understand why patients who have been given a terminal diagnosis might be willing to try anything to find a drug that could provide them with a real chance at survival. It has always been hard to understand why the FDA would ever stand in the way of those desperate patients trying anything to survive; as a result, there has always been enormous pressure on the FDA simply to get out of the way.⁴³ In response, the FDA has always had a variety of programs to allow access to unapproved drugs “for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives.”⁴⁴

The FDA’s pre-approval access programs are all grounded in the statutory authority provided by provisions of the Federal Food, Drug, and Cosmetic Act (FDCA).⁴⁵ Nevertheless, the FDA, Congress, and state governments have taken several

42. See *Delivering Promising New Medicines Without Sacrificing Safety and Efficacy*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/delivering-promising-new-medicines-without-sacrificing-safety-and-efficacy> (last updated Aug. 27, 2019) (“[The FDA] must balance timely patient access to important new medicines with assuring they meet key standards. These standards exist to make sure that approved drugs have a high chance of helping those who use them. Medicines ultimately must lead to overall improvements in how patients feel, function, or survive.”).

43. See, e.g., *Remarks by President Trump at S.204, “Right to Try” Bill Signing*, WHITE HOUSE (May 30, 2018, 12:31 PM), <https://www.whitehouse.gov/briefings-statements/remarks-president-trump-s-204-right-try-bill-signing/> (“But [the FDA approval process is] still a process that takes years. Now it takes up to 15 years; even 20 years, some of these treatments are going. But for many years, patients, advocates, and lawmakers have fought for this fundamental freedom. And as I said, incredibly, they couldn’t get it.”).

44. See EXPANDED ACCESS, *supra* note 6, at 2.

45. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 356 (2018).

additional actions beyond these programs,⁴⁶ spurred by the widespread but inaccurate perception that the FDA is slower to approve drugs than agencies in other countries⁴⁷ and that it is difficult and time consuming for a critically ill patient's physician to obtain the FDA's approval to access a drug outside of a clinical trial. These actions include Right to Try laws,⁴⁸ accelerated access to experimental drugs,⁴⁹ and breakthrough drug approval.⁵⁰ Each of these approaches to earlier access for critically ill patients is discussed in the following sections.

A. *Right to Try*

One of the responses to the pressure from patients has been the enactment of Right to Try laws.⁵¹ In May of 2018, President Trump signed into law the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.⁵² State and federal Right to Try laws are generally based on the model legislation promoted by the libertarian Goldwater Institute and authorize drug companies whose drugs have "successfully completed phase 1" to distribute their drugs to any patient whose physician certifies that the patient has a

46. Robert Pear & Sheila Kaplan, *Senate Passes F.D.A. Funding and 'Right to Try' Drug Bills*, N.Y. TIMES, Aug. 4, 2017, at A15, <https://www.nytimes.com/2017/08/03/us/politics/fda-senate-experimental-drugs-terminally-ill-patients.html>.

47. Melissa Healy, *Speed Up Drug Approvals at FDA? It's Already Faster than Europe's Drug Agency*, L.A. TIMES (Apr. 6, 2017, 11:05 AM), <http://www.latimes.com/science/sciencenow/la-sci-sn-fda-european-medicine-20170405-story.html>.

48. See discussion *infra* Section III.A.

49. See *infra* Section III.B.

50. See *infra* Section III.C.

51. See generally Julie A. Jacob, *Questions of Safety and Fairness Raised as Right-to-Try Movement Gains Steam*, 314 JAMA 758 (2015) (discussing responsiveness of Right to Try laws and their implications on manufacturers); Rebecca Dresser, *The "Right to Try" Investigational Drugs: Science and Stories in the Access Debate*, 93 TEX. L. REV. 1631 (2015) (discussing real-life and policy implications of enacted Right to Try laws and tension between liberal access to investigational drugs and restrictive access); Alison Bateman-House & Christopher T. Robertson, *The Federal Right to Try Act of 2017—A Wrong Turn for Access to Investigational Drugs and the Path Forward*, 178 JAMA 321 (2018) (arguing that Right to Try laws are perilous to patients and create immunity for physicians and manufacturers who act negligently).

52. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub.L. No. 115-176, 132 Stat. 1372 (2018).

disease that “will soon result in death,” even if treated with available approved treatments.⁵³ Despite their popularity and adoption by many states and the federal government, Right to Try laws are unlikely to have any meaningful effect for a variety of reasons;⁵⁴ primarily, because the right of the patient to try an experimental drug does not mean an obligation to provide (or sell at cost, in fact) on the part of pharmaceutical companies developing the sought-after drug.⁵⁵ Right to Try laws are not fundamentally different in this regard from the FDA’s existing program for individual patient access to experimental drugs.⁵⁶ Drug companies have already shown they are unwilling to provide drugs outside of clinical trials under the existing program for a number of reasons.⁵⁷ First, providing the drug can be administratively burdensome for the companies and logistically difficult if the drug is being made in small quantities for purposes of meeting the clinical trial needs.⁵⁸ Second, granting such requests can make it more difficult for companies to enroll patients in the clinical trials necessary to determine the drug’s safety and efficacy.⁵⁹ Finally, although the manufacturer

53. *Right to Try Model Legislation*, GOLDWATER INST., https://goldwaterinstitute.org/wp-content/uploads/cms_page_media/2016/1/5/GoldwaterInstituteRighttoTryModel.pdf (last visited Sept. 19, 2019).

54. See, e.g., Alison Bateman-House, Kelly McBride Folkers & Arthur Caplan, ‘Right To Try’ Won’t Give Patients Access to Experimental Drugs. Here’s what Will, HEALTH AFF.: HEALTH AFF. BLOG (May 3, 2017), <http://healthaffairs.org/blog/2017/05/03/right-to-try-wont-give-patients-access-to-experimental-drugs-heres-what-will/> (explaining how for-profit companies “would be inclined to avoid” the risk of causing “severe adverse events” in patients using the expanded access given by Right to Try, as well as “financial and personnel constraints” small companies may have, which would not allow them to offer expanded access to patients).

55. Steven Joffe & Holly Fernandez-Lynch, *Federal Right-to-Try Legislation—Threatening the FDA’s Public Health Mission*, 378 NEW ENG. J. MED. 695, 697 (2018).

56. See 21 C.F.R. § 312.8 (2019); U.S. FOOD & DRUG ADMIN., CHARGING FOR INVESTIGATIONAL DRUGS UNDER AN IND—QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY (2016), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351264.pdf>; see also Dresser, *supra* note 51, at 1646–47.

57. Jonathan Darrow et al., *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279, 281 (2015) [hereinafter *Practical, Legal & Ethical Issues*]; see also Dresser, *supra* note 51, at 1646–47.

58. See *Practical, Legal & Ethical Issues*, *supra* note 57, at 281.

59. *Id.*

is allowed to charge a price sufficient to cover its costs,⁶⁰ determining such a price and revealing it makes it more difficult to justify the subsequent inevitably much higher price post-approval, a problem that is magnified in an era of increasing demands that pharmaceutical companies justify the prices of their drugs.⁶¹ The new Right to Try Act of 2017,⁶² however well-intentioned, fails to remedy any of these practical obstacles.

B. Accelerated Access to Experimental Drugs

While Right to Try statutes are, at best, of minor significance to desperately ill patients (and, at worst, a false illusion of hope), other already available mechanisms to accelerate access to such patients do have a significant impact and have resulted in widespread early or accelerated access to a significant number of drugs.⁶³ These mechanisms for accelerated access can be divided into two categories: mechanisms for access to experimental drugs prior to approval and mechanisms for accelerating approval.

1. FDA provisions for access prior to approval

In the “prior to approval” category, the barriers to individual patient access have already been discussed. However, in addition to single patient access requests, the FDA regulations provide for expanded access to experimental drugs in several additional categories:

60. *Id.*

61. Andrew Pollack, *Drug Prices Soar, Prompting Calls for Justification*, N.Y. TIMES, July 23, 2015, at B1, <https://www.nytimes.com/2015/07/23/business/drug-companies-pushed-from-far-and-wide-to-explain-high-prices.html>.

62. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372 (2018).

63. See *infra* Sections III.B.1, III.B.2.

- Individual Patient Expanded Access, Including for Emergency Use (also referred to as single patient expanded access)
 - 1) Individual patient expanded access IND
 - a) Individual patient expanded access IND for emergency use
 - 2) Individual patient expanded access protocol
 - a) Individual patient expanded access protocol for emergency use
- Intermediate-Size Patient Population Expanded Access
 - 1) Intermediate-size patient population expanded access IND
 - 2) Intermediate-size patient population expanded access protocol
- Treatment IND or Treatment Protocol
 - 1) Treatment IND
 - 2) Treatment protocol⁶⁴

The FDA provides updates on the number of requests received in each category and the number of requests the FDA allowed to proceed.⁶⁵ The numbers are substantial. Between 2009 and 2017 the FDA's Center for Drugs (CDER) and Center for Biologics (CBER) received a total 4476 emergency single-patient access requests and allowed 4444 of them to proceed—

64. EXPANDED ACCESS, *supra* note 6, at 6–7.

65. Note that all numbers discussed in this paragraph are taken from the source cited; however, I calculated the total application and applications allowed. See *Expanded Access (Compassionate Use) Submission Data*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/newsevents/publichealthfocus/expandedaccesscompassionateuse/ucm443572.htm#Expanded_Access_IND1 (last updated May 20, 2019).

more than 99%.⁶⁶ In those same years, CDER and CBER received 5980 non-emergency single patient access requests and allowed 5931 to proceed, which, again, is more than 99%. There are similar rates of allowance for the other categories of expanded approval access, which include intermediate size INDs and intermediate size protocols.⁶⁷ The FDA's programs for pre-approval access to critically-needed drugs, while far from the unrestricted open-access desired by the Abigail Alliance and other libertarian groups,⁶⁸ have proven to provide a meaningful, rapid, and efficient means of access for a significant number of patients.⁶⁹

2. Accelerated approval

While expanded access through the FDA's single patient, intermediate-size, and treatment access provisions provide access to drugs prior to approval, far more patients have obtained access through the FDA's efforts to accelerate approval of drugs for serious diseases.⁷⁰ The FDA has a number of programs in place to help get drugs to patients sooner by approving drugs more quickly.⁷¹ Some, such as the Fast Track⁷²

66. *Id.*

67. *See id.*

68. *See, e.g.,* Abigail All. for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 713 (D.C. Cir. 2007) (denying terminally ill patients the open access to experimental drugs that the Alliance advocated for because the FDA had a "rational basis for ensuring . . . knowledge about the risks and benefits of . . . a drug").

69. *See* EXPANDED ACCESS, *supra* note 6, at 21.

70. *See Novel Drugs Summary 2015*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drugs-summary-2015> (last updated Jan. 12, 2016) (explaining FDA's "[m]ethods for expediting innovative novel drugs to [the] market," including Fast Track, Breakthrough, Priority Review, and Accelerated Approval).

71. *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review> (last updated Feb. 23, 2018) (explaining the FDA's "four distinct and successful approaches to making [drugs that treat serious diseases] available as rapidly as possible").

72. *See* 21 U.S.C. § 356(b)(1) (2018); *see also* *Fast Track*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track> (last updated Jan. 4, 2018).

and Priority Review⁷³ programs, are aimed at facilitating interaction between the FDA and the company developing the drug in order to shorten development and review times without significantly changing the evidentiary basis by which drugs are approved.⁷⁴ However, for those drugs that go through the accelerated approval⁷⁵ or breakthrough drug approval,⁷⁶ there is a lower standard of evidence for approval and, as a result, even less certainty provided to doctors and patients that the benefits of the drugs do in fact exceed their risks.⁷⁷

Accelerated approval has often been used for cancer drugs, where the generally accepted endpoint to determine the real clinical benefit for patients is the change in median overall survival: Did patients taking the drug live longer than patients who received a placebo and, if so, how much longer?⁷⁸ Because it would often take a considerable length of time to answer that question, surrogate endpoints that can be measured sooner are used to shorten Phase III trials and provide earlier availability to patients.⁷⁹ For example, to be used to obtain accelerated approval, the surrogate endpoints, such as a decrease in the size of patients' tumors, must be "reasonably likely" to predict actual clinical benefit.⁸⁰ For example, a commonly used endpoint for the accelerated approval of a cancer drug is the change in the median duration of "progression-free survival" (often referred to as PFS).⁸¹ This is a measure of whether a drug increases the length of time before the cancer begins to grow or

73. See 21 U.S.C. § 360ff (2018); see also *Priority Review*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm> (last updated Jan. 4, 2018).

74. See sources cited *supra* notes 74–75.

75. 21 U.S.C. § 356(c) (2018).

76. *Id.* § 356(a).

77. See Bishal Gyawali & Aaron S. Kesselheim, *Reinforcing the Social Compromise of Accelerated Approval*, 15 NATURE REVIEWS CLINICAL ONCOLOGY 596, 596 (2018).

78. See Vinay Prasad et al., *The Strength of Association Between Surrogate End Points and Survival Oncology*, 175 JAMA 1389, 1390, 1395 (2015) [hereinafter *Strength of Association*].

79. See NCI Dictionary of Cancer Terms: *Surrogate Endpoints*, NAT'L CANCER INST., <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/surrogate-endpoint> (last visited Sept. 22, 2019) [hereinafter *Surrogate Endpoints*].

80. 21 U.S.C. § 356(c)(1)(A) (2018).

81. See *Strength of Association*, *supra* note 78, at 1390.

spread to other areas of the body or the patient dies (which may occur despite no recording of “progression” for that patient).⁸² There is a positive correlation between time to progression and overall survival for a number of cancers, and thus the endpoint is “reasonably likely to predict” actual clinical benefit; however, the magnitude of the effect, which is how much survival increases, is not certain and is very often of a significantly lower magnitude.⁸³ For example, in one study of the increase in overall survival in renal cell carcinoma, PFS had more than doubled from five months to eleven months, but the magnitude of the increase in overall survival eventually was determined to be about 4.6 months, from 21.8 months to 26.4 months, a far smaller percentage increase.⁸⁴

In many cases, drugs approved on the basis of PFS produced no improvement in overall survival.⁸⁵ For example, Avastin (bevacizumab) was being used as a first-line treatment for metastatic breast cancer for three years before the FDA ordered that indication to be withdrawn.⁸⁶ The post-approval data provided clear evidence that the increase in PFS that had supported Avastin’s accelerated approval had failed to translate into any increase whatsoever in overall survival and caused significant adverse effects.⁸⁷ Despite that evidence, the

82. U.S. FOOD & DRUG ADMIN., CLINICAL TRIAL ENDPOINTS FOR APPROVAL OF CANCER DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY 10 (2018), <https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf> (defining PFS “as the time from randomization until objective tumor progression or death, whichever occurs first”) [hereinafter ENDPOINTS: GUIDANCE FOR INDUSTRY].

83. 21 U.S.C. § 356(c)(1)(A); see also Darius N. Lakdawalla et al., *Predicting Real-World Effectiveness of Cancer Therapies Using Overall Survival and Progression-Free Survival from Clinical Trials: Empirical Evidence for the ASCO Value Framework*, 20 VALUE HEALTH 866, 874 (2017).

84. Robert J. Motzer et al., *Overall Survival and Updated Results for Sunitinib Compared with Interferon Alfa in Patients with Metastatic Renal Cell Carcinoma*, 27 J. CLINICAL ONCOLOGY 3584, 3589 (2009).

85. See *Strength of Association*, *supra* note 78, at 1390 (using bevacizumab as an example).

86. Final Decision on Withdrawal of Breast Cancer Indication for AVASTIN (Bevacizumab) Following Public Hearing, 77 Fed. Reg. 11,554, 11,554–11,555 (Feb. 27, 2012) (“Withdrawal of AVASTIN’s breast cancer indication was effective November 18, 2011.”).

87. See DEP’T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., DOC. NO. FDA-2010-N-0621-0544, PROPOSAL TO WITHDRAW APPROVAL FOR THE BREAST CANCER INDICATION FOR AVASTIN (BEVACIZUMAB): DECISION OF THE COMMISSIONER 33–41 (2011).

drug's sponsors, Genentech and Roche, unsuccessfully appealed the decision to the Commissioner of the FDA,⁸⁸ and Medicare continued to reimburse its use in the face of patient pressures.⁸⁹ In at least one case, such a drug actually decreased overall survival.⁹⁰ Gemtuzumab ozogamicin was on the market for ten years before it was withdrawn after further studies showed that the drug was ineffective and actually increased mortality.⁹¹

C. Breakthrough Drugs

The most recent addition to the efforts to further accelerate access for patients with serious or life-threatening diseases is the category of breakthrough drugs. Breakthrough drugs may be approved on the basis of *preliminary* clinical evidence that the drug *may* provide a substantial improvement over existing therapies on at least one clinically significant endpoint.⁹² Approval of new drugs on the basis of preliminary clinical evidence that “may” correlate with meaningful benefit allows doctors to prescribe drugs even earlier in the drug development process than accelerated access based on surrogate markers that are “reasonably likely to” correlate with clinically relevant measures.⁹³ In the views of at least some commentators, this lowering of the standard for entry into the marketplace goes a step too far.⁹⁴

The FDA's approval of eteplirsen, a new antisense drug for Duchenne Muscular Dystrophy (DMD), is perhaps the most

88. *Id.* at 40–41.

89. See Stacie B. Dusetzina et al., *How Do Payers Respond to Regulatory Actions? The Case of Bevacizumab*, 11 J. ONCOLOGY PRAC. 313–14 (2015). It is beyond the scope of this article to address the issue of whether or not patients should be free to buy drugs that are known to have no benefit and have significant adverse effects.

90. Jonathan J. Darrow et al., *New FDA Breakthrough-Drug Category—Implications for Patients*, 370 NEW ENG. J. MED. 1252, 1254 (2014) [hereinafter *New FDA Breakthrough-Drug Category*].

91. *Id.*

92. 21 U.S.C. § 356(a)(1) (2018).

93. *Id.* § 356(c)(1)(A).

94. See, e.g., *New FDA Breakthrough-Drug Category*, *supra* note 90, at 1255.

dramatic example of a “breakthrough” drug approved on the basis of very little evidence.⁹⁵ DMD is a devastating illness affecting children that causes muscle weakness, atrophy, and ultimately death.⁹⁶ No effective treatments for this terrible disease have ever been approved.⁹⁷ It is easy to understand why patient groups would press to approve the drug even without any evidence of functional or clinical improvement.⁹⁸ The advisory committee previously had recommended against approving the drug by a vote of seven to three with three abstentions.⁹⁹ The FDA’s reviewers had not only concluded that there was insufficient evidence that the drug worked, but one of the reviewers actually appealed FDA Center Director Janet Woodcock’s decision to approve the drug.¹⁰⁰

The drug is now being sold on the market at a cost of \$300,000 per patient per year, even though it will be years until additional clinical trials can provide substantial evidence of

95. See *FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy*, U.S. FOOD & DRUG ADMIN. (Sept. 19, 2016, 3:43 PM), <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy> [hereinafter *Accelerated Approval for DMD*].

96. *Id.*

97. Cf. *Duchenne Muscular Dystrophy (DMD)*, MUSCULAR DYSTROPHY ASS’N, <https://www.mda.org/disease/duchenne-muscular-dystrophy/medical-management> (last visited Sept. 16, 2019) (noting that although DMD currently has no cure, “the use of available treatments can help maintain comfort and function and prolong life”).

98. *Accelerated Approval for DMD*, *supra* note 95 (“The accelerated approval of Exondys 51 is based on the surrogate endpoint of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients.”).

99. Andrew Pollack, *Advisers to FDA Vote Against Duchenne Muscular Dystrophy Drug*, N.Y. TIMES, Apr. 25, 2016, at B1, <https://www.nytimes.com/2016/04/26/business/muscular-dystrophy-drug-fda-sarepta-etepirsen.html>.

100. ROBERT M. CALIFF, DEP’T HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., NDA 206488, SCIENTIFIC DISPUTE REGARDING ACCELERATED APPROVAL OF SAREPTA THERAPEUTICS ETEPLIRSEN—COMMISSIONER DECISION (Sept. 16, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf (memorandum of FDA Commissioner Robert M. Califf, M.D. to CDER Director Janet Woodcock); see also Heidi Ledford, *U.S. Government Approves Controversial Drug for Muscular Dystrophy*, NATURE (Sept. 20, 2016), <https://www.nature.com/news/us-government-approves-controversial-drug-for-muscular-dystrophy-1.20645>.

whether or not the drug actually improves patients' lives.¹⁰¹ The \$300,000 per year cost of providing patients the drug would be a terrible waste of our healthcare dollars if further clinical trials fail to show the drug actually works. On the other hand, if the further clinical trials show significant therapeutic benefit to Duchenne patients, the failure of insurers to provide coverage in the interim would have caused unnecessary suffering and death to patients who had been unable to pay for the drug. As of this writing, it appears that insurers are reluctant to cover Eteplirsen and other drugs that have received accelerated approval.¹⁰²

An examination of the data supporting two other drugs recently approved by the breakthrough standard of "preliminary clinical evidence" that the drugs "may" provide significant benefit further illustrates the vague nature of evidence sufficient to allow marketing of the drug.¹⁰³ There have been two breakthrough drugs that received their original marketing approval for overlapping multiple myeloma indications—Empliciti and Darzalex.¹⁰⁴ As the FDA summary review of Darzalex stated, "[m]ultiple myeloma remains a mostly incurable disease with only a few patients who receive an allogeneic transplant [and were] cured of their disease."¹⁰⁵ Darzalex was approved on November 16, 2015, for "treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor

101. See Katie Thomas, *Insurers Battle Families Over Costly Drug for Fatal Disease*, N.Y. TIMES, June 22, 2017, at A1, <https://www.nytimes.com/2017/06/22/health/duchenne-muscular-dystrophy-drug-exondys-51.html>.

102. Rawson, *supra* note 2.

103. Jeremy Puthumana, Joshua D. Wallach & Joseph S. Ross, *Clinical Trial Evidence Supporting FDA Approval of Drugs Granted Breakthrough Therapy Designation*, 320 JAMA 301, 301–03 (2018); see also Carolyn Y. Johnson, *The Truth About 'Breakthrough' Drugs*, WASH. POST (July 17, 2018), <https://www.washingtonpost.com/news/to-your-health/wp/2018/07/17/the-truth-about-breakthrough-drugs/> ("[E]fforts to speed up drug approval have been successful but come with a trade-off: uncertainty.").

104. *Novel Drugs Summary 2015*, *supra* note 70.

105. ANN T. FARRELL, CTR. FOR DRUG EVALUATION & RES., SUMMARY REVIEW, APPLICATION NO. 761036ORIG1S000 3 (2015), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761036Orig1s000SumR.pdf [hereinafter SUMMARY REVIEW: DARZALEX].

(PI) and an immunomodulatory agent, or who did not respond to a PI and an immunomodulatory agent.”¹⁰⁶ Empliciti received a somewhat broader approval two weeks later, on November 30, 2015, for “treatment of patients with multiple myeloma who have received one to three prior therapies.”¹⁰⁷ So any patient who meets the criteria for treatment with Darzalex would also meet the criteria for treatment with Empliciti. The variance between those two descriptions of patients for whom the drug is indicated is largely a function of the choice the drugs’ sponsors made in deciding on the patients to include in the Phase 3 clinical trials.¹⁰⁸ What could a doctor treating a patient with multiple myeloma and three prior therapies convey other than the fact that the drug may work for some patients and not others, and may work for some unknown but limited period of time?

The data on which each drug was approved is different. Empliciti was approved on the basis of a significant difference in progression-free survival (PFS), which, as discussed above, is a commonly used endpoint that has some reasonable correlation with improvement in overall survival.¹⁰⁹ At the time of approval, the data supporting Empliciti’s market entry was based on a 646 patient trial, where patients were randomized to

106. Press Release, Janssen Biotech, Inc., Johnson & Johnson, DARZALEX® (daratumumab) Approved by U.S. FDA: First Human Anti-CD38 Monoclonal Antibody Available for the Treatment of Multiple Myeloma (Nov. 16, 2015), <https://www.jnj.com/media-center/press-releases/darzalex-daratumumab-approved-by-us-fda-first-human-anti-cd38-monoclonal-antibody-available-for-the-treatment-of-multiple-myeloma> (footnote omitted).

107. RICHARD PAZDUR, CTR. FOR DRUG EVALUATION & RES., APPROVAL PACKAGE, APPLICATION NO. 761035ORIG1s000 1 (2015), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2015/761035Orig1s000ltr.pdf.

108. Compare U.S. NAT’L LIBRARY OF MED., *Phase III Study of Lenalidomide and Dexamethasone with or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma (ELOQUENT – 2)*, NIH, <https://clinicaltrials.gov/ct2/show/NCT01239797> (last updated Nov. 1, 2018), with Janssen Research & Development, LLC, *Study Comparing Daratumumab, Lenalidomide, and Dexamethasone with Lenalidomide and Dexamethasone in Participants with Previously Untreated Multiple Myeloma*, NIH, <https://clinicaltrials.gov/ct2/show/NCT02252172> (last updated Mar. 8, 2019) (using different sets of eligibility criteria, including different inclusion and exclusion criteria, in determining whether to allow participant involvement in the specific studies).

109. See ANN T. FARRELL, CTR. FOR DRUG EVALUATION & RES., SUMMARY REVIEW, APPLICATION NO. 761035ORIG1s000 5–6, 11 (2015), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761035Orig1s000SumR.pdf.

receive either Empliciti plus a regimen of two other drugs or the two drug regimen alone.¹¹⁰ Patients in the trial who received Empliciti had a 4.5 month longer median duration of progression-free survival, and there was very preliminary evidence of an increase in overall survival.¹¹¹ The original approval of Darzalex was based on the endpoint of overall response rate (ORR), a less reliable marker of clinical effectiveness,¹¹² from a much smaller number of patients in two single-arm trials, meaning there was no control group.¹¹³ In the larger of those two studies involving one hundred and six patients, thirty-one achieved an ORR with a median duration of 7.4 months, while fifteen patients (36%) of the forty-two patients in the smaller trial achieved an ORR with a median duration of 6.9 months.¹¹⁴ Given the grim prognosis for patients with multiple myeloma, that change in ORR may be enough for patients and doctors to evaluate whether or not taking those drugs is worthwhile, but it is hardly enough for either patients or payers to evaluate the actual clinical benefit of those drugs.¹¹⁵ For desperate patients, allowing the early approval of drugs such as Empliciti and Darzalex provides those patients with a degree of hope. However, providing that hope for drugs with an unknown probability of real clinical benefit is a very

110. U.S. FOOD & DRUG ADMIN., FULL PRESCRIBING INFORMATION: EMPPLICITI 13, 15 (2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s0001bl.pdf [hereinafter FULL PRESCRIBING INFORMATION: EMPPLICITI].

111. *Id.* at 16–17.

112. See ENDPOINTS: GUIDANCE FOR INDUSTRY, *supra* note 82, at 3–7.

113. See SUMMARY REVIEW: DARZALEX, *supra* note 105. Note that the endpoint of overall response rate (ORR) used in the Darzalex study is, somewhat confusingly, a variation on the endpoint of objective response rate.

114. *Id.*

115. Both drugs now have data showing an improvement in overall survival at twelve months, while Empliciti has longer term data that shows the overall survival (OS) advantage persisting but narrowing considerably for several years. See FULL PRESCRIBING INFORMATION: EMPPLICITI, *supra* note 110, at fig.1; see also Meletios A. Dimopoulos et al., *Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma*, 375 NEW ENG. J. MED. 1319, 1326–27 (2016). Longer term data on OS for Darzalex has not yet been published. At this point, doctors and patients may have a reasonable amount of information on both drugs and the similar increased likelihood of OS at 1 year and insurers may have some basis for determining the value of the drugs and negotiating prices.

expensive gamble for patients and their insurers. The next part of this article discusses the role of information about drug safety and efficacy in the pharmaceutical marketplace.

IV. THE FDA'S ROLE IN PROVIDING INFORMATION TO THE PHARMACEUTICAL MARKET

Markets are made up of buyers and sellers, and a familiar concept of basic economics is that the price in the marketplace reflects the balance between supply and demand.¹¹⁶ Demand in the pharmaceutical market depends on the availability to buyers, such as insurance companies, doctors, and patients, of information about a drug's benefit and risks.¹¹⁷ Buyers will increase demand, and be willing to pay more, for drugs that provide a significant expectation of a truly meaningful clinical benefit—such as a significant increase in the median duration of survival or a substantial reduction in pain—than for drugs which offer much less clinical benefit—such as a very small increase in the median duration of survival or a very minor reduction in pain.¹¹⁸ Most of the information patients need to make an informed decision regarding use of the drug, and insurers need to decide how much they are willing to pay for a drug, comes from the data produced in the clinical trials required to obtain FDA approval of a new drug.

Even though the results of the years of preclinical and clinical testing of a drug required for FDA approval is summarized in the full prescribing information, many questions remain unanswered. While the FDA has determined that the benefits of

116. *Econ 150: Supply and Demand*, BYU IDAHO, https://courses.byui.edu/econ_150/econ_150_old_site/lesson_03.htm (last visited Nov. 12, 2019) (“A market consists of those individuals who are willing and able to purchase the particular good and sellers who are willing and able to supply the good. The market brings together those who demand and supply the good to determine the price.”).

117. See, e.g., David Granlund & Niklas Rudholm, *Consumer Information and Pharmaceutical Prices: Theory and Evidence*, 73 OXFORD BULL. ECON. & STAT. 230, 230–31 (2011).

118. See Jonathan J. Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 363, 376 (2014) (“Like all market participants, patients have a natural incentive to act in their own best interests, which in the present context means consuming medicines that possess the greatest efficacy and do the least harm.” (parentheses omitted)).

the drug (or likely or potential benefits for accelerated or breakthrough approvals) exceed the risks of the drug for the targeted patient population, a patient may want answers to various other questions before taking a drug: Is it better than the other drugs that are used to treat my condition? Is this drug safer than the other drugs? Who is most likely to respond to this drug, and am I likely to be one of them? Am I more or less likely to suffer the most serious adverse effects? If this drug is not as safe as other drugs, is it likely to be sufficiently more effective for my condition than the other drugs to justify any increased risk?

Most patients would assume that their doctors have the answers to these questions about the drugs they recommend, but even for the majority of drugs that go through the normal, non-accelerated review process, it is unlikely that there are answers to most of these questions. In the “normal” drug review process, Phase III trials measure a drug’s effectiveness in patients who meet the precisely-described criteria for patient inclusion and exclusion¹¹⁹ on an endpoint or outcome that is considered to be significant for patients. This provides some assurance that the benefits of the drug exceed its risks for the patients whose condition and health is the same as the subjects in the clinical trial, which is all doctors or patients can be reasonably confident about for most drugs.¹²⁰ There generally is

119. See Russel E. Glasgow, Edward Lichtenstein & Alfred C. Marcus, *Why Don't We See More Translation of Health Promotion Research to Practice? Rethinking the Efficacy-to-Effectiveness Transition*, 93 AM. J. PUB. HEALTH 1261, 1262 (2003) (discussing Phase III studies testing drug effectiveness).

120. *Id.* (“Phase III studies can be conducted in settings and with samples that will ‘optimize interpretation of efficacy.’”). However, recently some drugs have been designed to treat patients with specific genetic mutations. Kalydeco, for example, which is approved for patients with specific mutations in the Cystic Fibrosis Transmembrane Receptor, has been designed to treat patients with Cystic Fibrosis. See U.S. FOOD & DRUG ADMIN., FULL PRESCRIBING INFORMATION: KALYDECO 1 (2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203188s026,207925s0051bl.pdf. In these “targeted therapies,” although the ultimate degree of effectiveness may still not be known, the patients most likely to benefit are identifiable by genetic testing. See U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., DEVELOPING TARGETED THERAPIES IN LOW-FREQUENCY MOLECULAR SUBSETS OF A DISEASE: GUIDANCE FOR INDUSTRY 1 (2018), <https://www.fda.gov/media/117173/download> (proposing that “certain targeted

no assurance that a drug will work for a particular patient, or work better than other drugs for the same condition, or even that a particular patient will not suffer the worst of the drug's adverse effects; but, at least, the approximate likelihood of risk and benefit could be known.¹²¹ While a doctor may have had experiences with patients who have taken a drug, and the doctor may have beliefs about the answers to all the patients' questions, the fact is that doctors' experiences are, in the language of science, anecdotal and not a reliable basis for assessing a drug's benefits and risks when given to a large number of patients.¹²²

It might be relatively easy for a pig farmer to inspect a pig and feel confident about the purchase before buying. However, drugs are a different story. To know whether or not a drug is effective requires a great deal of time, effort, and money—years of testing and hundreds of millions or billions of dollars.¹²³ In the marketplace for drugs, the FDA's statutory mission is to ensure that adequate evidence has been generated to provide some confidence that a drug's benefits exceed its risks when used according to the FDA-approved label.¹²⁴ The FDA really has no authority to require more information than that.

The relationship between adequate information and the ability of the market to set prices is fundamental.¹²⁵ In the context of drugs, the problem for the market is clear. The

therapies may be effective in multiple groups of patients who have different underlying molecular alterations," suggesting that genetic testing would help identify patients who the treatment would be most effective for) [hereinafter TARGETED THERAPIES].

121. See TARGETED THERAPIES, *supra* note 120, at 4–6 (showing that although the evidence found cannot assure the effectiveness of the drug—because it needs to be generalized over a population of people—it is still helpful information to have).

122. See Steven Novella, *The Role of Anecdotes in Science-Based Medicine*, SCIENCE-BASED MED. (Jan. 30, 2008), <https://sciencebasedmedicine.org/the-role-of-anecdotes-in-science-based-medicine/>.

123. TUFTS CTR. FOR THE STUDY OF DRUG DEV., *Cost to Develop and Win Marketing Approval for a New Drug is \$2.6 Billion*, TUFTS U. (Nov. 18, 2014), <https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5ac66adc758d46b001a996d6/1522952924498/pr-coststudy.pdf> [hereinafter TUFTS U.].

124. *Development & Approval Process (Drugs)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/> (last updated Oct. 28, 2019).

125. See, e.g., Granlund & Rudholm, *supra* note 117, at 231.

standard drug approval process generates at least the most basic information about the effectiveness of a drug. However, in the case of accelerated approval, there is even less of the information that patients and doctors need.¹²⁶ Critics of the FDA's approval process often argue that the need to speed up the availability of drugs to critically ill patients outweighs the value of the traditional approach to drug testing and approval, and physicians and patients can sort out the answers to their questions about drugs after the drug is widely available.¹²⁷ This argument places the value of the FDA's expertise and the traditional approval process squarely at issue.

V. IS THE FDA'S PROCESS REALLY NECESSARY OR COULD A FREE MARKET WORK AS WELL?

As one recent commentary by Chandra and Sachs stated: "It is fashionable in some circles to say that 'a Yelp for drugs' would be superior to the FDA."¹²⁸ However, while reviews of a restaurant may be useful in deciding whether or not to eat there, reviews of drugs by patients have far less value. Even reviews by physicians are far from a reasonably reliable resource.¹²⁹ One rather extraordinary study, examining all articles published from 2001-2010 in *The New England Journal of Medicine*—perhaps the most widely read and influential journal in American Medicine¹³⁰—found 363 of the articles published in that ten-year period reported on clinical trials examining the evidence for an

126. See *New FDA Breakthrough-Drug Category*, *supra* note 90, at 1252.

127. See, e.g., Caroline Chen, *FDA Repays Industry by Rushing Risky Drugs to Market*, PROPUBLICA (June 26, 2018, 5:00 AM), <https://www.propublica.org/article/fda-repays-industry-by-rushing-risky-drugs-to-market> (criticizing industry influence on FDA drug approval).

128. Amitabh Chandra & Rachel E. Sachs, *An FDA Commissioner for the 21st Century*, 376 NEW ENG. J. MED. 1, 1 (2017).

129. See Vinay Prasad et al., *A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices*, 88 MAYO CLINIC PROC. 790, 792 (2013) [hereinafter *A Decade of Reversal*].

130. NAT'L INST. ENVTL. HEALTH SCIS., *High Impact Journals: Superfund Research Program*, NIH, <https://tools.niehs.nih.gov/srp/publications/highimpactjournals.cfm> (last visited Nov. 12, 2019).

existing medical practice.¹³¹ For example, one study examined the efficacy and safety of dopamine in the treatment of shock.¹³² Dopamine had been widely used to treat shock and was even one of the two treatments recommended by consensus guidelines.¹³³ However, when a controlled study of dopamine's safety and efficacy in treating shock was finally done, it found that treatment with dopamine was actually associated with a greater risk of arrhythmias and an increase in the risk of death.¹³⁴ The astonishing conclusion of the study was that of the 363 articles that examined a preexisting and widely-used medical practice, only 138 provided evidence that supported the practice, while 146 found that the practice either provided no benefit or actually led to worse outcomes.¹³⁵ Clearly a Yelp review system for medical treatments that relied on the opinions of physicians would be of questionable value, and it is difficult to imagine that using online patients' reviews would be any better.

Some libertarians would do away altogether with the FDA's role in approving the safety and efficacy of new drugs.¹³⁶ Proponents of this extreme view believe that the cost of meeting FDA requirements is a major factor in the high cost of medicines and, even worse, that patients die because the process of obtaining FDA approval delays access to critically needed drugs.¹³⁷ These anti-regulation, free-market advocates believe

131. See generally *A Decade of Reversal*, *supra* note 129 (highlighting the abundance of articles providing evidence supporting widely used medical practices versus the abundance of articles discounting the same widely used medical practices for not providing benefit or leading to worse outcomes).

132. *Id.* app. at 27, n.133, <https://www.mayoclinicproceedings.org/cms/10.1016/j.mayocp.2013.05.012/attachment/4359ae39-8377-4a2a-9d13-d3a6ec62cc68/mmc2.pdf> (supplemental appendix showing each of the reviewed articles for Prasad's analysis).

133. Yasser Sakr et al., *Does Dopamine Administration in Shock Influence Outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study*, 34 *CRITICAL CARE MED.* 589, 589 (2006).

134. See *id.* at 594–95.

135. *A Decade of Reversal*, *supra* note 129, at 790, 791–93.

136. See, e.g., *FDA and Drug Regulation*, *CATO INST.*, <https://www.cato.org/research/fda-drug-regulation> (last visited Nov. 12, 2019) (proposing the political philosophy that individuals should be able to “choose the medical treatments they think best”).

137. *Theory, Evidence and Examples of FDA Harm*, *supra* note 32.

that the determination of a drug's effectiveness should be left to "free-market testing."¹³⁸ While the problem of high-priced drugs and the desperate plight of critically ill patients is very real, the idea of some sort of Yelp or even a privately published Consumer Reports for prescription drugs fails to answer how the marketplace would provide the funds to cover the many millions of dollars that well-designed trials cost.¹³⁹

Although the role of scientific evidence and data in providing decision-makers with the most reliable basis for their choices is becoming an increasingly politicized issue,¹⁴⁰ it is still generally accepted within the scientific and medical community that the "gold standard"¹⁴¹ of evidence about a drug is well-designed randomized clinical trials in which the drug in question is tested against a placebo or, in the case of a serious disease for which a standard treatment exists, a placebo plus the standard therapy.¹⁴² A well-designed clinical trial satisfies multiple criteria, but primarily it provides a relatively clear and replicable answer to the question the trial is designed to resolve: is the drug effective or, in the cases of comparative effectiveness trials, does the drug work better than the drug to which it is being compared?¹⁴³ No amount of individual physician experience can really provide the same confidence in a drug's,

138. *Healthcare*, LIBERITARIANPARTY, <https://www.lp.org/issues/healthcare/> (last visited Nov. 8, 2019).

139. See Linda Martin et al., *How Much Do Clinical Trials Cost?*, 16 NATURE REVIEWS DRUG DISCOVERY 381, 381 (2017) ("For the trials in the data set, the median cost of conducting a study from protocol approval to final clinical trial report was . . . \$3.4 million for phase I trials involving patients, \$8.6 million for phase II trials and \$21.4 million for phase III trials.").

140. Gordon Gauchat, *Politicization of Science in the Public Sphere: A Study of Public Trust in the United States, 1974 to 2010*, 77 AM. SOC. REV. 167, 178 (2012).

141. Laura E. Bothwell et al., *Assessing the Gold Standard—Lessons from the History of RCTs*, 374 NEW ENG. J. MED. 2175, 2175 (2016).

142. See David W. Parke II, *RCTs: The Gold Standard's Future*, EYENET MAG., Feb. 2019, at 12 ("Phase 3 RCTs constitute large scale studies of effectiveness, safety, dosage, and comparisons to placebo or treatment alternatives.").

143. See *The Basics*, NAT'L INSTITUTES HEALTH, <https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics> (last updated Oct. 20, 2017).

or procedure's, effectiveness. Well-designed clinical trials are the core requirement for FDA approval of a new drug.¹⁴⁴

There are two key statutory provisions that describe the FDA's role in approving the sale of new drugs and evaluating the design of the trials. The first provision requires that applicants seeking approval of a new drug provide "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."¹⁴⁵ The second provision sets a standard that those "investigations" must meet:

adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use . . . [and] adequate and *well-controlled investigations*, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, *on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have.*¹⁴⁶

The statute requires the FDA to determine whether or not the clinical trials of a drug provide substantial evidence from which experts would conclude that a drug is both safe and effective and whether or not the clinical trials were reasonably designed to provide good evidence or, in the language of the statute, "substantial evidence."¹⁴⁷

However, while it is the FDA's statutory role to ensure that the clinical trials used to support the marketing of a drug are well designed and provide adequate evidence that a drug's benefits exceed its risks, that does not compel the conclusion that the FDA's role in evaluating those studies and the evidence

144. *Id.*; see also *The FDA's Drug Review Process*, *supra* note 11.

145. 21 U.S.C. § 355(b)(1)(A) (2018).

146. *Id.* § 355(d) (emphasis added).

147. *Id.* ("Grounds for refusing application; approval of application; 'substantial evidence' defined.").

they provide is essential. Advocates of deregulation argue that peer-reviewed publications can better and more efficiently serve the need of physicians and patients for good information without a requirement for FDA oversight or approval.¹⁴⁸ This argument rests entirely on a misplaced faith in the peer-review system. Drug companies can all too easily design a study that is very likely to give the desired result or that is lacking in adequate controls or analytic rigor and yet will nevertheless be published in a peer-reviewed journal, even a prestigious peer-reviewed journal.¹⁴⁹

One way to understand the difference between the rigor of the FDA's "substantial evidence" approval standard and the peer-review standard for journal publication is to look at recent drugs that were denied FDA approval and the peer-reviewed publications that preceded the FDA's rejection. For example, in 2018 Eli Lilly suffered a major setback when the FDA issued a complete response letter denying approval to Lilly's oral rheumatoid arthritis drug baricitinib.¹⁵⁰ According to Lilly, "[s]pecifically, the FDA indicated that additional clinical data are needed to determine the most appropriate doses. The FDA also stated that additional data are necessary to further characterize safety concerns across treatment arms."¹⁵¹ The FDA's rejection came despite the fact that two positive reports of trials of the drug were published in *The New England Journal of Medicine* just prior to the FDA's action.¹⁵² Similarly, Cempra received a complete response letter from the FDA requiring "additional clinical safety information" for approval of its

148. See *Theory, Evidence and Examples of FDA Harm*, *supra* note 32.

149. See Lexchin et al., *supra* note 8, at 1169–70.

150. See U.S. FDA Issues Complete Response Letter for Baricitinib, LILLY INV. (Apr. 14, 2017), <https://investor.lilly.com/releasedetail.cfm?ReleaseID=1021392>.

151. *Id.*

152. Mark C. Genovese et al., *Baricitinib in Patients with Refractory Rheumatoid Arthritis*, 374 NEW ENG. J. MED. 1243, 1251 (2016); Peter C. Taylor et al., *Baricitinib Versus Placebo or Adalimumab in Rheumatoid Arthritis*, 376 NEW ENG. J. MED. 652, 660–61 (2017).

antibiotic solithromycin¹⁵³ despite the prestigious British journal *The Lancet* publishing a favorable report of the results of a major study of the drug in its journal for infectious diseases.¹⁵⁴ According to *The Lancet Infectious Diseases* article, “[t]he overall safety profile of solithromycin was similar to that of moxifloxacin,” an already approved drug for the same condition.¹⁵⁵ In yet another example, in 2012 Amgen received a complete response letter from the FDA refusing to approve Amgen’s drug XGEVA for castration-resistant prostate cancer.¹⁵⁶ According to Amgen:

The FDA determined that the effect on bone metastases-free survival (BMFS) was of insufficient magnitude to outweigh the risks (including osteonecrosis of the jaw) of XGEVA in the intended population, and requested data from an adequate and well-controlled trial(s) demonstrating a favorable risk-benefit profile for XGEVA that is generalizable to the U.S. population.¹⁵⁷

The FDA’s rejection of XGEVA came despite the conclusion of the authors from another major study which determined “denosumab is better than the established therapy, zoledronic acid, for the delay or prevention of skeletal-related events in

153. *Cempra Receives Complete Response Letter From FDA For Solithromycin NDAs*, GLOBENEWSWIRE (Dec. 29, 2016, 6:55 AM), <https://globenewswire.com/newsrelease/2016/12/29/902088/0/en/Cempra-Receives-Complete-Response-Letter-From-FDA-For-Solithromycin-NDAs.html>.

154. See generally Carlos M. Barrera et al., *Efficacy and Safety of Oral Solithromycin Versus Oral Moxifloxacin for Treatment of Community Acquired Bacterial Pneumonia: A Global, Double-Blind, Multicentre, Randomised, Active-Controlled, Non-Inferiority Trial (SOLITARE-ORAL)*, 16 LANCET INFECTIOUS DISEASES 421 (2016) (noting how solithromycin was “non-inferior,” in terms of efficacy and safety, to another approved medication (moxifloxacin) in treating community-acquired bacterial pneumonia).

155. *Id.* at 428.

156. *Amgen Receives Complete Response Letter From FDA for XGEVA® sBLA for Prevention of Bone Metastases*, AMGEN (Apr. 26, 2012), <http://www.amgen.com/media/news-releases/2012/04/amgen-receives-complete-response-letter-from-fda-for-xgeva-sbla-for-prevention-of-bone-metastases/>.

157. *Id.*

patients with advanced prostate cancer (panel)."¹⁵⁸ This study was also published in *The Lancet*.¹⁵⁹

Lurie et al. published a study of companies' public statements concerning the FDA's denial of approval for sixty-one drugs for which the FDA issued complete response letters from 2008 to 2013.¹⁶⁰ Although the study does not list the names of the individual drugs, it would be surprising if the great majority of the applications for approval had not been preceded by positive reports on the drugs in the peer-reviewed literature. Companies would hardly want to submit applications for new drug approval based on studies that had not been evaluated by the company as positive and had also been published in peer-reviewed journals with a positive conclusion. There are only two ways to look at the phenomenon of non-approvals in the wake of positive assessments by the company and published literature: either the FDA is acting arbitrarily and unreasonably denying marketing approval to safe and effective drugs, or alternatively, the FDA is adding an important objective and independent level of scrutiny that ensures that drugs are approved on the basis of adequate and reliable information concerning their effectiveness and safety.

The question of whether or not the FDA is unreasonable in turning down drugs or adding important value in their review function is clearly an important one. While there is no way to provide an absolute answer to that question, there is at least some evidence of the added value of the FDA's review of drug data that comes from the FDA's use of advisory committees in

158. Karim Fizazi et al., *Denosumab Versus Zoledronic Acid for Treatment of Bone Metastases in Men with Castration-Resistant Prostate Cancer: A Randomised, Double-Blind Study*, 377 LANCET 813, 819 (2011).

159. *Id.*

160. See generally Peter Lurie et al., *Comparison of Content of FDA Letters Not Approving Applications for New Drugs and Associated Public Announcements from Sponsors: Cross Sectional Study*, 350 BRIT. MED. J. 1 (2015) (describing the non-public complete response letters by the FDA when they did not approve marketing strategies by drug companies).

the new drug approval process.¹⁶¹ Advisory committees are used by the FDA to provide the agency with input into the drug approval decision-making process from scientific and medical experts outside the agency, as well as consumer and patient advocates.¹⁶² The majority of members of FDA advisory committees work on the front lines of research and clinical care for patients in their areas.¹⁶³ The input from such leading outside independent experts¹⁶⁴ certainly should be of real value in scrutinizing the evidence of a drug's safety and efficacy.

Studies of the FDA's use of advisory committees support the value of advisory committee review. There have been a number of studies that examine the correlation between the FDA's final decision and the recommendations of its advisory committees, as well as the factors that appear to be most likely to lead to

161. See Philip Ma et al., *FDA Advisory Committee Outcomes*, MCKINSEY & CO. (2013), https://www.mckinsey.com/~media/McKinsey/dotcom/client_service/%20Public%20Sector/Regulatory%20excellence/FDA_advisory_committee_outcomes.ashx (concluding that the study of the advisory committees' methods supports the utility of similar bodies if used in the pharmaceutical industry).

162. *Membership Types*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/MembershipTypes/default.htm> (last updated Mar. 27, 2018).

163. See, e.g., *Oncologic Drugs Advisory Committee Roster*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm107418.htm> (last updated Sept. 9, 2019) (summarizing the qualifications of each of the members of an example FDA advisory committee consistent with the ratio of scientific members to other representatives seen in other committees); see also *Membership Types*, *supra* note 162.

164. The membership of the Oncologic Drug Advisory Committee can serve as a useful illustration of the kind of expertise that advisory committees bring to the FDA review process. As of July 2019, the Oncologic Drug Advisory Committee membership included outside experts in oncology from leading universities and cancer centers in the United States, as well as an expert in biostatistics and a nonvoting industry representative. *Oncologic Drugs Advisory Committee Roster*, *supra* note 163. The listed affiliations were University of Chicago, Food and Drug Administration, University of Texas MD Anderson Cancer Center, Robert H. Lurie Comprehensive Cancer Center, Case Western Reserve University Cleveland Clinic Lerner College of Medicine, Duke University Medical Center, National Institutes of Health National Cancer Institute, Wake Forest University Health Sciences, Amgen Oncology (non-voting industry representative), St. Jude Children's Research Hospital, Memorial Sloan-Kettering Cancer Center, Massachusetts General Hospital, Duke University School of Medicine Duke Adult Blood and Marrow Transplant Clinic, Fred Hutchinson Cancer Research Center. *Id.*

negative decisions by advisory committees and the FDA.¹⁶⁵ One study of advisory committee decision-making focused just on the Oncologic Drug Advisory Committee (ODAC)—the committee that is closest to the heart of the controversy over the FDA’s role as gatekeeper to potentially life-saving drugs because it is concerned primarily with cancer drugs, including those intended for patients with very limited chances of long-term survival.¹⁶⁶ The members of the committee include cancer researchers and clinicians who are at the front lines of the battle for cancer patients’ survival.¹⁶⁷

It is difficult to argue that these leading cancer clinicians and researchers would not be eager to add an important new drug to the treatments they can offer desperate patients, yet the study found that of eighty-two drugs considered by the ODAC between 2000 and 2014, the committee voted against the approval of exactly half and for the approval of half.¹⁶⁸ The FDA approved all forty-one drugs that the ODAC recommended for approval and also approved seven of the forty-one drugs for which the ODAC had recommended denying or delaying approval.¹⁶⁹ On its face, this data supports two important conclusions about the FDA’s role in approving new drugs, including those for serious or fatal diseases. First, despite the

165. See, e.g., Mark Senak, *AdComm Recommendations – How Often FDA Does Not Follow Them?*, EYE ON FDA (Aug. 16, 2016), <http://eyeonfda.com/2016/08/adcomm-recommendations-how-often-fda-does-not-follow-them/> (analyzing the positive and negative outcomes of advisory committee meetings from 2011 through 2016); Philip Ma et al., *supra* note 161 (analyzing public data to discover potential implications of limitations in advisory committee meetings); Todd D. McIntyre, Mimi Pappas & James J. DiBiasi, *How FDA Advisory Committee Members Prepare and What Influences Them*, 47 THERAPEUTIC INNOVATION & REG. SCI. 32, 32–35 (2012) (surveying current and former advisory committee members and concluding sponsors “need to be clear, concise, and scientifically credible, and that some advisory committee members need to be more uniformly prepared”).

166. See Ariadna Tibau et al., *Oncologic Drugs Advisory Committee Recommendations and Approval of Cancer Drugs by the US Food and Drug Administration*, 2 JAMA ONCOLOGY 744, 745, 748–49 (2016) (“[A]nalyz[ing] the influence of the Oncologic Drugs Advisory Committee (ODAC) on the FDA’s oncologic drug approval process and factors associated with both ODAC recommendations and final FDA approval.”).

167. See *Oncologic Drugs Advisory Committee Roster*, *supra* note 163.

168. Tibau et al., *supra* note 166, at 744, 746.

169. See *id.* at 746.

fact that sponsors of such drugs clearly believe their data supports approval and often have peer-reviewed publications supporting their applications, independent experts from outside the FDA who have not been involved in those studies often conclude that there is inadequate evidence of the drugs' safety and efficacy.¹⁷⁰ Second, outside experts who actually treat patients with those diseases are frequently more skeptical of the evidence supporting a drug's safety and efficacy than the much-maligned bureaucrats at the FDA.¹⁷¹ Although it is commonly believed that peer-reviewed literature can provide doctors and patients with the information they need to allow the marketplace to function, the advisory committee evidence indicates that is not the case, as have numerous studies of publication bias in the pharmaceutical industry.¹⁷² Peer-reviewed publications simply do not have the objectivity or rigor that the FDA, together with its advisory committees, provides.¹⁷³ The FDA adds significant value in serving as an independent quality check of the evidence that supports a drug's safety and efficacy.

VI. CONDITIONAL APPROVAL COULD ACCELERATE ACCESS, REDUCE PRICES, AND MORE QUICKLY PROVIDE THE INFORMATION THAT DOCTORS, PATIENTS, AND PROVIDERS NEED

Part I of this Article noted that many critics of federal regulation believe that FDA regulation could be completely eliminated. Proponents of this extreme view believe that the cost of meeting FDA requirements is a major factor in the high cost of medicines, that those requirements are unnecessary, and that the determination of a drug's effectiveness could be left to

170. *See id.*

171. *See id.*

172. *See* Lexchin et al., *supra* note 8, at 1167–68. The authors review thirty different studies to investigate the bias in the design and reporting of pharmaceutical industry-funded research.

173. *Compare* Lexchin et al., *supra* note 8, at 1169–70 (discussing the influence of pharmaceutical manufacturers on the publication of negative studies), *with* Tibau et al., *supra* note 166, at 746–47, 749 (discussing the influence of FDA advisory committees on FDA approval of new pharmaceuticals).

a marketplace armed with the internet.¹⁷⁴ While the problem of high drug prices for new “specialty” drugs¹⁷⁵ is very real, this understanding of drug pricing and of the FDA’s role is wrong on both counts. The principal reason the prices of critically-needed drugs are high is not because of the high costs of development.¹⁷⁶ Pharmaceutical companies set prices in the same way that every for-profit business sets prices, based on what the sellers believe the market will bear in order to maximize profits.¹⁷⁷ In turn, what the market will bear should be based on the buyers’ perception of the value of a drug, that is the value of the health benefits attributable to a drug’s effectiveness. For example, a drug that offers a metastatic cancer patient a significant chance of long-term survival would command a higher price than a drug that offers those patients a median increase in survival of only a few weeks.¹⁷⁸

However, accelerated access allows a drug to reach the market quickly based on clinical trials that measure surrogate

174. *FDA and Drug Regulation*, *supra* note 136 (“In a free society, individuals should be free to care for their physical well-being as they see fit, which includes the freedom to choose the medical treatments they think best. Such liberty does not open the door for fraud or abuse any more than does a free market in other products. In fact, informed consent by patients will become more sophisticated as the market for information about medical treatments becomes more free and open.”). *But see* Chandra & Sachs, *supra* note 128, at 1 (criticizing the view that an internet marketplace such as “a Yelp for drugs” could substitute for the FDA).

175. There are several different definitions of a specialty drug, however nearly all definitions require that the drug be used for a serious or life-threatening condition and carries a high price. *See Specialty Medications*, NAT’L PHARMACEUTICAL SERVICES, <https://www.pti-nps.com/nps/index.php/specialty-medications/> (last visited Sept. 8, 2019).

176. *See* Vinay Prasad & Sham Mailankody, *Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval*, 177 JAMA INTERNAL MED. 1569, 1572–73 (2017) (finding the “cost to develop a single oncologic drug . . . is significantly [lower] than a widely publicized figure of \$2.7 billion”).

177. *See* Ellen Licking & Susan Garfield, *A Road Map to Strategic Drug Pricing*, IN VIVO (Mar. 16, 2016), <https://invivo.pharmamedtechbi.com/IV004481/A-Road-Map-To-Strategic-Drug-Pricing> (“It is time to acknowledge that our historical pricing model, which is built on unit-based pricing, is too one-dimensional for the marketplace’s current needs. It has resulted in incentives that encourage biopharma companies to make pricing decisions that are driven by what is possible rather than what other stakeholders consider reasonable.”).

178. Perhaps the clearest example of an insurer attempting to make pricing and purchasing decisions based on effectiveness is the British National Health Service’s National Institute for Clinical Excellence (NICE). *See* Michael D. Rawlins & Anthony J. Culyer, *National Institute for Clinical Excellence and its Value Judgments*, 329 BRIT. MED. J. 224, 224–25 (2004).

endpoints, such as the time between starting treatment and disease progression, rather than measures of clinical benefit, such as patient quality of life or longer survival.¹⁷⁹ Surrogate endpoints are used because they reduce the duration of clinical trials, while the actual clinical benefit of a drug can take years to measure.¹⁸⁰ But all too often the surrogate endpoints fail to correlate with meaningful clinical benefit such as overall survival.¹⁸¹ For the price of a drug to reflect the value of the drug substantial knowledge of a drug's real benefit to patients is required. When a drug is approved before there is evidence of its effect on the endpoints that patients care most about—survival and quality of life—drug prices can soar without any gain to patients. With Congress and the President both determined to lower drug prices,¹⁸² there is an opportunity to improve the process of accelerating patient access to critically needed drugs while also reducing the costs of those drugs. A new form of “conditional approval,” which would require prices to be significantly discounted until there is sufficient evidence to grant full approval, would continue to provide accelerated access to desperate patients while improving the balance between drug prices and patient benefit. It is also helpful in this era of political paralysis that most, but not all, of this can be done by the FDA without any need for new legislation.¹⁸³

179. *Surrogate Endpoints*, *supra* note 79.

180. *See id.*

181. *See Strength of Association*, *supra* note 78, at 1390. Although many physicians treat patients with atrial fibrillation with costly anti-arrhythmic drugs in a strategy to maintain sinus rhythm because it improves some surrogate endpoints, it has not been proven to improve survival. *Id.*

182. *See supra* note 1 and accompanying text.

183. *See* Joseph Gulfo, *The FDA Needs a Conditional Approval System*, FORBES (May 5, 2016, 3:06 PM), <https://www.forbes.com/sites/realspir/2016/05/05/the-fda-needs-a-conditional-approval-system/#1c157e1749c7> (suggesting the FDA adopt a conditional approval process similar to that used by the EMA). The EMA process is briefly described *infra* in text accompanying note 196.

A. *The New Conditional Approval*

History provides a very useful precedent for the FDA to implement the conditional approval proposed here in the form of a regulatory pathway for accelerated access and controlled pricing that was developed in response to an earlier era of crisis in pharmaceutical policy—the AIDS epidemic. The AIDS epidemic appears to be the first time that there was a significant public outcry for accelerated access.¹⁸⁴ Before the 1980's AIDS crisis, the focus of major patient advocacy groups, such as the American Cancer Society and the American Heart Association, was on raising money for research. These groups were largely unconcerned with the FDA.¹⁸⁵ However, when the AIDS epidemic struck, ACT UP (AIDS Coalition to Unleash Power) changed the world of patient advocacy dramatically.¹⁸⁶ ACT UP put unprecedented pressure on the FDA to make drugs available to patients without waiting for the safety and efficacy of those drugs to be demonstrated in traditional clinical trials.¹⁸⁷

The FDA responded to the AIDS crisis and the pressure of patient advocates with several new mechanisms to provide early access to unapproved drugs. The FDA's 1992 parallel track initiative, used only once for the drug Stavudine, is the most relevant for the conditional approval proposed here.¹⁸⁸

184. See FASTERCURES & HCM STRATEGISTS, *BACK TO BASICS: HIV/AIDS ADVOCACY AS A MODEL FOR CATALYZING CHANGE* 1, 16 (2011), http://www.meaction.net/wp-content/uploads/2015/05/Back2Basics_HIV_AIDSAdvocacy.pdf ("Clearly, one of the legacies of this movement was the fundamental shift in how patients and disease organizations interact with the federal government and Congress.").

185. Robert Bohrer, *A Better Balance Between Accelerated Access and High Priced New Drugs*, HEALTH AFFAIRS BLOG (Mar. 20, 2017), <https://www.healthaffairs.org/doi/10.1377/hblog20170320.059267/full/> [hereinafter *A Better Balance*].

186. See generally Jim Eigo et al., *FDA Action Handbook*, ACT UP (Sept. 12, 1988), <http://www.actupny.org/documents/FDAhandbook1.html> (developing an action handbook providing information about the FDA and the AIDS crisis, and criticizing the FDA for how it handled the AIDS crisis).

187. See Alice Park, *The Story Behind the First AIDS Drug*, TIME (Mar. 19, 2017), <http://time.com/4705809/first-aids-drug-azt/>.

188. Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and Other HIV-Related Disease, 57 Fed. Reg. 13250-01 (Apr. 15, 1992) [hereinafter *Expanded Availability*].

Under the 1992 parallel track mechanism, physicians treating AIDS patients could provide their patients with Stavudine, which had not yet been approved.¹⁸⁹ The drug sponsor was allowed to charge for the drug, but only a price sufficient to recover the costs of the trial.¹⁹⁰ To justify the proposed charge, the sponsor was required to provide sufficient financial information to the FDA.¹⁹¹ The parallel track also required the physicians who treated patients with the drug to monitor the patients' responses to treatment and to provide that data to the drug sponsor.¹⁹²

Adapting and building on the 1992 HIV-only parallel track initiative could enable a more balanced approach to both the need for accelerated access and for lower prices. The new conditional approval would be based on surrogate endpoints. This would allow wide distribution to desperate patients before final approval was permitted by the parallel track initiative. Conditional approval would also limit the price of the conditionally approved drugs until sufficient data is collected to warrant full approval.

The principal regulations for conditional approval already exist within the expanded access regulations of the FDA.¹⁹³ Under the conditional approval proposed here, a pharmaceutical company with promising data from the early stages of clinical trials for a drug to treat a life-threatening

189. Press Release, U.S. Food & Drug Admin., First AIDS Drug Tested Under Parallel Track Policy; Other d4T Related Press Releases (Oct. 5, 1992) (on file with AIDS Info), <https://aidsinfo.nih.gov/news/93/first-aids-drug-tested-under-parallel-track-policy—other-d4t-related-press-releases>.

190. Expanded Availability, *supra* note 188.

191. *Id.* PHS recognized that there could be “significant costs” to manufacturers when “sponsoring or participating in parallel track studies,” but unfortunately PHS has no control over manufacturers’ costs. *Id.* Sponsors may request approval from the FDA for additional funding if it is necessary to continue the study. 21 C.F.R. § 312.8 (2018).

192. Expanded Availability, *supra* note 188.

193. 21 C.F.R. §§ 312.305, 312.320 (2018). The expanded access provisions of § 312.320 specifically provide a for “widespread treatment use” of a drug where “all clinical trials have been completed” and, in the case of drugs for an “immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective . . . and would not expose patients to an unreasonable . . . risk of illness or injury.”

disease for which no satisfactory alternative therapy exists would file for an expanded access “conditional approval” to allow any physician treating a patient with the targeted indication to prescribe the drug. A “conditional approval,” when substituted for accelerated approval, would clearly meet the requirements of 21 C.F.R. § 312.310, which allows “widespread treatment use.”¹⁹⁴ Prescribing physicians would be required to provide the pharmaceutical company with basic data on their patients’ responses to the drug over time. The longer-term single arm trials that would be based on conditional approval are likely to provide adequate evidence of safety and efficacy when the patients are being treated for an otherwise untreatable serious disease.¹⁹⁵

The price for a drug being provided under conditional approval would be based on a set price formula until the sponsor provides sufficient data for the FDA to fully approve the drug. This would eliminate the need for pharmaceutical companies to disclose their costs and negotiate prices and would only require the FDA itself to publish and adopt a change to its current regulations restricting charging for investigational new drugs.¹⁹⁶ This differs from other accelerated access programs such as the European Medicines Evaluation Agency “conditional approval,” which does not limit prices and is reviewed annually.¹⁹⁷

B. Pricing Conditionally Approved Drugs

There are two ways that an FDA regulation establishing conditional approval could determine the price of a drug during the conditional approval period. The first possible

194. *Id.*

195. See Deborah Armstrong, MD, Johns Hopkins Kimmel Cancer Ctr., Engelberg Center for Health Care Reform 2014 Conference on Clinical Cancer Research: The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs (Nov. 21, 2014), <https://www.focr.org/sites/default/files/Non-Randomized%20Trials%20slides.pdf> (explaining application of single arm trials for oncology drugs, including their benefits and limitations).

196. See 21 C.F.R. § 312.8 (2018).

197. Commission Regulation 507/2006 of 29 March 2006, 2006 O.J. (L 92) 6.

mechanism for determining the prices of conditionally approved drugs would be based on the pharmaceutical company's intended initial market price for the new drug. This "initial market price" would be what the pharmaceutical company's internal business plan projects as the "list" price for the drug when it receives FDA approval. This method assumes that pharmaceutical companies would set the intended market price in the same way that pharmaceutical companies set prices for any of their drugs following FDA approval. The price during conditional approval could not exceed twenty-five percent of the specified initial market price. Alternatively, the FDA rule establishing a conditional approval pathway could set the conditional approval price formula as a predetermined percentage (e.g., twenty-five percent of the average price of breakthrough drugs approved for similar conditions during the prior two years). Under either mechanism, there would be no need for case-by-case negotiations between the pharmaceutical companies and the FDA.

The twenty-five percent pricing formula should cover the costs of manufacture (which are a small fraction of the price of drugs), distribution, a limited marketing outreach, and the process of data collection. Marketing expenses should be very low due to the demand by patients for a potentially life-saving drug for which there is no alternative.

This conditional approval update of parallel track would provide a better balance between access to potential breakthrough drugs and substantial evidence of real clinical benefit. By limiting profits on the conditionally approved drugs, pharmaceutical companies would be motivated to distribute the drug widely enough to provide the needed evidence quickly. Limiting profits would also avoid burdening consumers and insurers with skyrocketing prices for what are actually unproven, still-experimental drugs such as Eteplirsen.

CONCLUSION

Members of both parties in Congress are proposing a number of different solutions to the high cost of new drugs.¹⁹⁸ This provides an opportunity to take a new approach to accelerating access and limiting drug prices. Of course, even with a cap on the prices of conditionally approved drugs, insurers and government payers should be required to cover the drugs during the conditional approval period just as they now cover drugs approved under the accelerated access and breakthrough drug procedure. Payers would, of course, benefit from the cap on prices during the period of conditional approval and thus would have little reason to oppose the conditional approval regulations. The FDA already has the authority to establish the conditional approval pathway and conditional approval price, but it has no authority over insurance coverage or reimbursement. Thus, legislation requiring insurer and payer coverage is the only new legislative action required to implement conditional approval. If the data collected during conditional approval confirms the benefit of the treatment, full approval would be granted. As is the case with all newly-approved drugs, the drug sponsor could charge whatever price is justified by the marketplace. However, the conditional approval process would provide the marketplace with much better evidence as to the drug's real worth.¹⁹⁹ The conditional approval proposed here gives patients desperate for treatment access to drugs, reduces the prices that insurers pay under the current system, and generates the data that patients, providers, and insurers need to evaluate a drug's actual efficacy. It is time for a new approach to accelerating access. With pharmaceutical prices straining the health care system and pharmaceutical

198. Katie Thomas & Reed Abelson, *Lower Drug Prices: New Proposals Carry Lots of Promises*, N.Y. TIMES (Feb. 9, 2018), <https://www.nytimes.com/2018/02/09/health/trump-drug-prices-medicare.html>; *A Better Balance*, *supra* note 185.

199. See Brenda Sandburg, *Making Real World Evidence Less "Messy" To Help with Drug Pricing*, PINK SHEET (Sept. 17, 2018), <https://pink.pharmaintelligence.informa.com/PS123878/Making-Real-World-Evidence-Less-Messy-To-Help-With-Drug-Pricing>.

companies under attack,²⁰⁰ conditional approval would be a good for patients and good for us all.

200. See Carolyn Y. Johnson, *Pharma, Under Attack for Drug Prices, Started an Industry War*, WASH. POST (Jan. 2, 2018), https://www.washingtonpost.com/business/economy/pharma-under-attack-for-drug-prices-started-an-industry-war/2017/12/29/800a3de8-e5bc-11e7-a65d-1ac0fd7f097e_story.html.

