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Erika Lietzan

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## The Drug Innovation Paradox

Erika Lietzan \*

### ABSTRACT

*In medicine today, we face an innovation paradox. The companies that develop new medicines are highly dependent on a period of exclusive marketing after approval, to fund their research and development programs. But longer research and development programs are not associated with longer periods of exclusive marketing. Instead, the period of exclusive marketing may be shorter. Exclusivity that dwindles with each additional month of pre-commercialization research would ordinarily lead innovators to be more efficient, but the drug regulatory system leads to a different result. In this system, the length of any particular premarket program turns largely on considerations not within the firm's control. The design and length of the program are a function of variables that include the molecule and its chemical class, its mechanism of action, the disease and disease stage targeted, the outcomes that can be formally tested, the nature of other treatments on the market, and scientific obstacles and opportunities at the time. Certain types of medicine – for example, drugs for long-term use and prevention of disease, drugs to stop progressive or degenerative diseases, and drugs for early stage cancer – are more likely to require longer research and development programs. These findings have significant implications for innovation policy. There is a paradox in drug innovation: we have chosen to incentivize research and development with a post-market reward, but as the research and development timeline increases, the post-market reward for that innovation remains the same or decreases. If the length of the premarket process correlates with particular drug types, disease targets, or studied outcomes, we may be offering an inadequate incentive in entire areas of medicine where we desperately need new treatments.*

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\*Associate Professor, University of Missouri School of Law. This article would not have been possible without the support of a Thomas Edison Innovation Fellowship from the Center for the Protection of Intellectual Property (CPIP) at George Mason University's Antonin Scalia Law School. It benefitted also from discussion at a faculty workshop hosted by the Saint Louis University School of Law. I am grateful to many for comments, advice, and input, including Bill Chin, Eric Claeys, Richard Epstein, Chad Flanders, Joseph Gabriel, Rob Gatter, Jesse Goldner, Tim Greaney, John Griesbach, Sam Halabi, Peter Hutt, Jay Kesan, Zorina Khan, Yvette Liebesman, Kristina Lybecker, Carol Needham, Michael Risch, Ted Sichelman, Paul Tatum, Jane Wasman, Sidney Watson, and Patricia Zettler. I am especially grateful to Dr. Temple at FDA for a close read and challenging comments. Mistakes of course are my own. Finally, I am grateful for the research support of Cynthia Shearrer, Associate Law Librarian at the University of Missouri School of Law, and for the research assistance of Matthew Davis ('17), Erika Dopuch ('17), Jason Horne ('17), Max Mauldin ('18), and Emily Titus ('19) at the University of Missouri School of Law.

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## I. INTRODUCTION

In medicine today, we face an innovation paradox. Companies that develop new medicines depend on a period of exclusive marketing after approval, to fund their research and development programs. This period is made possible by patent protection and regulatory data exclusivity. But when a particular premarket research and development program is more challenging and time-consuming than other programs, the period for exclusive marketing is not longer and may, in fact, be shorter. This is a paradox; the relationship between the incentive (exclusive marketing) and the behavior we seek to encourage with

the incentive (research and innovation) is the opposite of what one would expect. The scheme contradicts itself.<sup>1</sup> This Article explores the drug innovation paradox, using scientific and historical regulatory sources and a new dataset constructed from publicly available sources. Its findings have profound implications for innovation policy. The length of the premarket period may correlate with particular drug types, disease targets, and studied outcomes, which means we may not be providing adequate incentive to develop new medicines in entire areas of need.

Federal patent law stimulates scientific and technological progress – innovation – by ensuring that innovators can enjoy a period of exclusivity in their inventions, meaning a period during which no others may manufacture and sell embodiments of their inventions.<sup>2</sup> Federal drug law prohibits the sale of new medicines, however, until those medicines have been approved by the U.S. Food and Drug Administration (“FDA”).<sup>3</sup> The tension between these two frameworks – one protecting exclusivity in an invention, the other precluding commercialization of that invention – gives rise to the paradox that is the topic of this Article.

Obtaining approval of a new drug generally entails testing the medicine in a laboratory and in animals (“preclinical” testing) and then completing several rounds of trials in humans (“clinical” trials), followed by preparation and submission of a marketing application. This process can take years and can cost in the high hundreds of millions of dollars (or more), and its outcome is uncertain.<sup>4</sup> After a new medicine reaches the market, it may face competition from other medicines for the same condition, but it generally enjoys a period of exclusive marketing before FDA will approve generic copies. Generic copies are usually priced at a fraction of the price of a new medicine (often known as the “brand” product) and are usually substituted by pharmacists for the brand

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1. See *Paradox*, THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (5th ed. 2016) (providing second definition of “paradox” as “a person, thing, or situation that exhibits inexplicable or contradictory aspects”).

2. See Kenneth W. Dam, *The Economic Underpinning of Patent Law*, 23 J. LEGAL STUD. 247, 247, 253 (1994) (explaining how the patent system “relies on property concepts” and “prevents others from reaping where they have not sown and thereby promotes research and development (R & D) investment in innovation”).

3. 21 U.S.C.A. § 355(a) (West 2018).

4. See Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 26 (2016) (estimating average out-of-pocket cost per approved compound of \$1.4 billion and total preapproval cost of \$2.56 billion); Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK. L. REV. 91, 107–08 (2016) (discussing range of estimates for the length of time and cost of developing a new drug).

product at the point of sale.<sup>5</sup> Their approval ends the brand product's exclusivity in the marketplace, and in fact, they usually take the lion's share of the market.<sup>6</sup>

There is a paradoxical relationship between the period for exclusive marketing and the premarket research and development performed for FDA approval. If a particular premarket research and development program is more challenging and time-consuming than other programs, the period for exclusive marketing is not longer and may, in fact, be shorter. The exclusive marketing period prior to generic market entry is largely a function of the company's patents. Certain aspects of patent law doctrine effectively require the application for a patent claiming the active ingredient of a new drug to be filed early in the research and development process. Patents last for a fixed term, which used to start when the patent issued but now starts on the date of the patent application. Either way, much of the patent term can elapse while the company is performing the research needed for approval.<sup>7</sup> And the more research performed, the more of the patent term elapses. The period for exclusive marketing of a medicine is also a function of the "data exclusivity" available to the innovator. During this time, generic companies may not rely on the research generated and submitted by the innovator for approval of their own drugs.<sup>8</sup> Data exclusivity suffers from a slightly different problem; even where the premarket study period is much longer, the length of the data exclusivity period does not change.

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5. Substitution is typically required or at least encouraged by state law. *New York ex rel. Schneiderman v. Actavis PLC*, 787 F.3d 638, 644–45 (2d Cir. 2015) (describing state substitution laws). It may also be required by insurers. *Id.* at 646.

6. Henry Grabowski et al., *Recent Trends in Brand-Name and Generic Drug Competition*, 17 J. MED. ECON. 1, 6 (2013) (finding that the average new molecular entity experiencing initial generic entry in 2011 and 2012 retained only sixteen percent of market share after one year).

7. The design of our patent system – making early patent filings not only possible but preferable – has its proponents as well as its critics. In the late 1970s, for instance, Professor Kitch argued that early patenting allows a patentee to coordinate later investment and development of embryonic technology. Edmund Kitch, *The Nature & Function of the Patent System*, 20 J. LAW & ECON. 265 (1977). More recently, Professor Duffy has argued that the race to win an early patent effects an efficient adjustment in the patent life, in part because a race to patent is also a race to patent expiry. John Duffy, *Rethinking the Prospect Theory of Patents*, 71 U. CHI. L. REV. 439 (2004). These rosy views of early patenting are tempered by the views of others. Professor Abramowicz, for example, notes that early patenting leads to less time on the market with the patent in force, which in turn can lead to underdeveloped technologies. Michael Abramowicz, *The Danger of Underdeveloped Patent Prospects*, 92 CORNELL L. REV. 1065 (2007). He sees this as a particular risk for embryonic inventions, where the post-patent cost of development and time to market are substantial, citing pharmaceuticals as an example. *Id.* at 1095–96. In the case of pharmaceuticals, as this Article explains, the commercialization delay that results from post-invention research is a legal condition of market entry.

8. See Lietzan, *supra* note 4, at 105–07, 110–20 (explaining reliance-based applications).

The problem of patent life that runs before new medicines may be launched is not new. It has been an issue since the middle part of the twentieth century, when the premarket paradigm at FDA began to evolve into today's preapproval regime. In 1984, therefore, Congress took steps to address the problem. The Hatch-Waxman Amendments to the drug approval law included a new section 156 of the Patent Act, allowing the U.S. Patent and Trademark Office ("PTO") to restore some of the lost time to one patent selected by the drug applicant.<sup>9</sup> This provision was directed to the general problem that some patent life elapses during premarket testing. It was not directed specifically to the paradox that longer research programs result in shorter effective patent life. And it did not remove the paradox. Under section 156, a patent owner recovers none of the time spent in preclinical testing and only half of the time spent in clinical trials. Also, it cannot recover more than five years, no matter how long premarket research took. As a result, the drug approval scheme still works at cross purposes with the patent scheme. Where the premarket study period is longer, the "effective life" of the patent – the term remaining after approval of the medicine – is shorter.

This paradox is not unique to medicines. In any field of technology, research activities prior to commercialization lead to a decline in effective patent life, and the longer the research period the shorter the effective patent life. This should generally drive inventors to efficient pre-commercialization behavior. The concern with medicines, however, stems from the basic theory of our drug approval system, on the one hand, and the scientific and regulatory realities of clinical trial design, on the other hand.

There are two components to drug approval theory. *First*, FDA's authority derives from and revolves around the words used to describe a new drug. When it approves a new drug, it approves the new drug *plus* its labeling. More precisely, it approves a specific combination of active ingredient (or, in some cases, more than one active ingredient), product features (such as formulation, route of administration, dosage form, and strength), and labeling that describes the product's intended uses, its conditions of safe and effective use, and the outcomes that can be expected. *Second*, the company developing the product and submitting the application – the drug's "sponsor" – must perform hypothesis-testing trials designed to prove that its product achieves this outcome under the conditions of use specified. The labeling will be precise. The disease state might not be hypertension but instead severe hypertension when rapid emergency reduction is clinically indicated. The outcome might be specific: improved memory in patients with mild Alzheimer's disease, for instance, or delayed progression in patients with breast cancer. The company's trials must have established *precisely* what is said in the labeling.

Put another way, a new drug approved by FDA is *both* the tangible item administered to patients *and* the words that describe what the item is and does. A premarket research and development program is thus tailored to generate

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9. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 201, 98 Stat. 1585 (1984).

specific information about a drug, disease, and outcome. The theory of our drug approval system is that a new drug approved by FDA – itself both the tangible item *and* the words describing its uses – is the product of a research design and the data generated.

The scientific and regulatory realities of clinical trial design complete the picture. The premarket research process is highly idiosyncratic, and many aspects relevant to the length of a research program turn on considerations beyond a sponsor's control. The design and length of studies reflect not only the statutory and regulatory framework applied by FDA but also the chemical structure of the molecule, its mechanism of action, the disease and disease stage under study, the outcomes that the firm can study, current scientific capabilities and impediments, and sometimes even the nature of other products on the market. Moreover, although premarket programs are highly individual, certain types of products almost always take longer to develop than others. For instance, as both a scientific matter and a statistical matter, how one proves an antihistamine reduces itching in the eye is very different from how one proves a cytotoxic (cell-killing) compound prolongs survival in patients with early-stage colon cancer. The latter will probably require longer trials.

This means that if the post-approval reward gets shorter when research takes longer, certain types of research – and therefore certain *types of drugs* – will be affected more than others. Because the prospect of post-approval reward stimulates the innovation and investment in the first place, development of these drugs may therefore be under-incentivized.

It may not be possible to measure the impact of the innovation paradox on public health. Companies rarely describe the compounds that they decline to pursue or abandon in the earliest stages, and we have no way to know whether those compounds would have satisfied the FDA approval standard for any particular clinical use. Still, signs of trouble may be emerging. One recent study found that firms are under-investing in the development of cancer drugs that require long-term trials.<sup>10</sup> Several research-based pharmaceutical companies abruptly terminated their neuroscience research programs in the late 2000s, citing the higher failure rate and the longer development time than for other medicines.<sup>11</sup> The President's Council of Advisors on Science and Tech-

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10. Eric Budish et al., *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044, 2047 (2015) (examining clinical trials for cancer conducted between 1973 and 2011 and finding a negative correlation between investment in research and development, measured by the number of trials in a national cancer registry compiled by the National Cancer Institute and a drug's "commercialization lag," or time to market, for which they used longer survival time as a proxy).

11. Alison Abbott, *Novartis to Shut Brain Research Facility*, 480 NATURE 161, 161–62 (2011) (noting withdrawals of Novartis, GlaxoSmithKline, and AstraZeneca); David Nutt & Guy Goodwin, *ECNP Summit on the Future of CNS Drug Research in Europe 2011*, 21 EUR. NEUROPSYCHOPHARMACOLOGY 495, 496 (2011) (listing factors cited by the companies in a closed summit of companies, government officials, patient

nology reported in 2012 that venture capital to fund drug development activities appears to be declining at least in part due to “unfavorable returns in the drug-innovation sector,” and it expressed concern that companies “are exiting important fields of critical public health need.”<sup>12</sup>

This Article contributes to the literature on incentives for pharmaceutical innovation by explaining and exploring the innovation paradox. *First*, it explains the theory of new drug approval and uses historical scientific and regulatory materials to illustrate that the premarket paradigm at any given time depends heavily on the state of clinical trial methodology, statistical methodology, and clinical pharmacology, as well as the prevailing regulatory climate. The length of any particular program is a function of the molecule and chemical class, disease and disease stage, and outcome that a firm tests, as well as scientific obstacles and opportunities that present themselves. *Second*, it presents empirical findings about the length of premarket programs from 1984 to 2016 using a dataset of regulatory milestones made public through FDA’s implementation of the patent term restoration provisions of the 1984 statute. This is the first piece of scholarship to combine these data with the listed patents on those drugs, the initial labeling approved by FDA for those drugs, and their therapeutic categorizations, and the first to use these data to offer comprehensive descriptive statistics about the relationship between drug types and premarket timelines.<sup>13</sup>

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organizations, and academics convened to explore the “well-reported pull-out of pharmaceutical companies from neuroscience research” in the prior year); Kenneth Singletary, *Pfizer Will Cut 300 Jobs as It Halts Development of Alzheimer’s and Parkinson’s Drugs*, BOS. GLOBE (Jan. 7, 2018), <https://www.bostonglobe.com/2018/01/07/pfizer-will-cut-jobs-halts-development-alzheimer-and-parkinson-drugs/AQPNfKywb1KWQBbWrLuTmN/story.html>.

12. PRESIDENT’S COUNCIL OF ADVISORS ON SCI. & TECH., EXEC. OFFICE OF THE PRESIDENT, REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION 9–10 (Sept. 2012), <https://www.broadinstitute.org/files/sections/about/PCAST/2012%20pcast-fda.pdf> [hereinafter PCAST REPORT].

13. The focus and methodology of this Article differ from what has been done in the handful of empirical pieces working from patent term restoration data in the past. See Jaime F. Cárdenas-Navia, *Thirty Years of Flawed Incentives: An Empirical and Economic Analysis of Hatch-Waxman Patent-Term Restoration*, 29 BERKELEY TECH. L.J. 1301 (2014) (presenting analysis that does not examine therapeutic categories or consider the regulatory paradigm and that does not differentiate human drugs from animal drugs, although they are subject to different approval requirements); Suzan Kucukarslan & Jacqueline Cole, *Patent Extension Under the Drug Price Competition and Patent Term Restoration Act of 1984*, 49 FOOD & DRUG L.J. 511 (1994) (presenting analysis that does not examine therapeutic categories, did not find all relevant regulatory milestones, and relied on secondary sources for information about exclusivity); Lisa Larrimore Ouellette, *How Many Patents Does It Take to Make a Drug? Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 311, 331 (2010) (relying on list of restored patents published on PTO website, which omits more than fifty restored drug patents, and relying on Kucukarslan’s characterization of exclusivity status).



The findings are significant. The time from earliest patent filing to the earliest human trials has been getting shorter. The average clinical testing period generally hovers between five and seven years, but applications submitted at the end of the time period in the dataset had longer clinical programs than applications submitted earlier. There is an upward trend. One in ten drugs in the dataset had a clinical testing period exceeding ten years, and more than one in four had a clinical testing period exceeding seven years. There are significant differences in the length of the average clinical testing period by therapeutic category; for instance, central nervous system drugs, antipsychotics, antidepressants, anticonvulsants, and anti-Parkinson's agents take significantly longer in clinical testing than antibiotic and antiviral drugs. Drugs intended for acute use take less time to develop than drugs intended for chronic use, and there may be a correlation between the pharmacologic class of a drug and the length of the clinical timeline.

As the conclusion explains, these findings have implications for innovation policy. To avoid systematically under-incentivizing entire areas of medical research, we may need to *break* the paradox – that is, ensure that longer premarket programs do *not* lead to shorter (or flat) marketing exclusivity.

## II. THE THEORY OF NEW DRUG APPROVAL

The theory of new drug approval lies at the heart of the drug innovation paradox. FDA approves a product – meaning not only a tangible article but the words that recommend the conditions of the drug's use and describe the expected outcome if the article is administered under those conditions – on the basis of what is *known* about the product. What is *known* about the product, in turn, depends on the premarket research and development performed by the product's sponsor. This theory of new drug approval was forged in the middle part of the last century.<sup>14</sup> Today the premarket paradigm implements that theory *and* reflects decades of continuous (and continuing) evolution in clinical trial design and statistical methodology. The relationship between *what we can say* about a particular product, on the one hand, and *how exactly we know it*, on the other hand, has grown more sophisticated and complex.

### A. The Early Decades

The modern drug approval paradigm emerged in the middle part of the twentieth century. In the early decades of the century, the predecessors of today's large pharmaceutical companies were beginning to develop methods of testing their drugs for effectiveness, but both their testing and the regulatory oversight were minimal by today's standards. Many believed that physicians were the best judges of the effectiveness of medicines.

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14. Kara W. Swanson, *Food and Drug Law as Intellectual Property Law: Historical Reflections*, 2011 WIS. L. REV. 331, 373 (2011).

U.S. drug companies in the 1800s and early 1900s fell mainly into two categories. *First*, some companies offered “patent medicines.”<sup>15</sup> These medicines should not be confused with “patented” drugs. They were heavily advertised to the general public and available without a doctor’s prescription (though sometimes prescribed), and the ingredients were typically kept secret. Some claims were grandiose.<sup>16</sup> *Second*, the predecessors of today’s pharmaceutical industry, including many companies still in existence today in one form or another, instead offered “ethical drugs” – generally to physicians, for prescribing to patients.<sup>17</sup> The ethical drug companies usually disclosed the ingredients of their products and explained the basis for the claims they made about their products.<sup>18</sup> Even in the 1800s many studied their products both before and after market entry, although this mainly consisted of drawing conclusions from case histories and surveys of physicians.<sup>19</sup>

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15. *Id.* at 352–53; Joseph M. Gabriel, *The Testing of Sanocrysin: Science, Profit, and Innovation in Clinical Trial Design, 1926–31*, 69 J. HIST. MED. & ALLIED SCI. 604, 609 (2013).

16. The traditional view holds that patent medicine was little more than quackery. See JAMES HARVEY YOUNG, *THE TOADSTOOL MILLIONAIRES: A SOCIAL HISTORY OF PATENT MEDICINES IN AMERICA BEFORE FEDERAL REGULATION* 209 (1961); ERIC W. BOYLE, *QUACK MEDICINE: A HISTORY OF COMBATING HEALTH FRAUD IN TWENTIETH-CENTURY AMERICA* 10–11 (2013). Recent archival work suggests a much more nuanced view and does *not* seem to support the idea that patent medicine makers were duplicitous. See generally JOSEPH M. GABRIEL, *MEDICAL MONOPOLY: INTELLECTUAL PROPERTY RIGHTS AND THE ORIGINS OF THE MODERN PHARMACEUTICAL INDUSTRY* 2–3 (2014) [hereinafter *MEDICAL MONOPOLY*] (with also an emphasis on chapters 1 and 2).

17. Nicolas Rasmussen, *The Drug Industry and Clinical Research in Interwar America: Three Types of Physician Collaborator*, 79 BULL. HIST. MED. 50, 53 (2005).

18. *Id.*

19. *MEDICAL MONOPOLY*, *supra* note 16, at 157–58; see also Suzanne White Junod, *FDA and Clinical Drug Trials: A Short History*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm> (last visited Feb. 28, 2018) (providing historical background). It is possible that pre-market effectiveness testing would have run into problems under state law, which at the time viewed experimentation on actual patients (at least with respect to surgery) as medical malpractice. See, e.g., *Jackson v. Burnham*, 39 P. 577, 580 (Colo. 1895) (“There must be some criterion by which to test the proper mode of treatment in a given case; and, when a particular mode of treatment is upheld by a consensus of opinion among the members of the profession, it should be followed by the ordinary practitioner; and, if a physician sees fit to experiment with some other mode, he should do so at his peril.”); see also WILLIAM BLACKSTONE, 3 COMMENTARIES ON THE LAWS OF ENGLAND 122 (1768) (“For it hath been solemnly resolved that *mala praxis* is a grave misdemeanor and offence at common law, whether it be for curiosity and experiment, or by neglect; because it breaks the trust which a party has placed in his physician, and tends to the patient’s destruction.”). Views on experimentation did not begin to change until the 1930s. See, e.g., *Fortner v. Koch*, 261 N.W. 762, 765 (Mich. 1935) (“We recognize the fact that, if the general practice of medicine and surgery is to pro-

Reformers at the turn of the last century, which included the orthodox medical community and more progressive members of the ethical drug industry, sought to shut down patent medicine or at least rein in exaggerated claims and ensure safety testing.<sup>20</sup> In 1906 they succeeded in securing passage of the Pure Food and Drugs Act, which – although a brief statute by today’s standards – prohibited statements in drug packaging or labels that were “false or misleading in any particular.”<sup>21</sup> After a Supreme Court decision in 1911 put an end to the Bureau of Chemistry’s efforts to prosecute companies for false claims of effectiveness,<sup>22</sup> Congress amended the statute to prohibit false and fraudulent claims regarding the curative or therapeutic effects of a drug.<sup>23</sup> Again, though, despite the Bureau of Chemistry’s now explicit authority to police effectiveness claims, the Court reined the agency in; a company could defend itself on the basis of a personal belief in its claims.<sup>24</sup>

The Court’s reluctance to permit the government oversight authority with respect to therapeutic claims may have reflected prevailing sentiment that effectiveness was a matter of personal opinion. In 1911, presented with a “Blood Purifier” (which “enters the circulation at once, utterly destroying and removing impurities from the blood and entire system” and “gives splendid results in the treatment of cancer”) and “Special No. 4” (which “will remove swelling, arrest development, restore circulation, and remove pain” and “[i]s indicated in all cases of malignancy where there is a tendency of the disease to spread”), the Court concluded that Congress would *not* have meant to regulate “in regions where opinions are far apart.”<sup>25</sup> It noted a case from nine years earlier, in which it had written that “the effectiveness of almost any particular method of treatment of disease is, to a more or less extent, a fruitful source of difference

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gress, there must be a certain amount of experimentation carried on; but such experiments must be done with the knowledge and consent of the patient or those responsible for him, and must not vary too radically from the accepted method of procedure.”).

20. BOYLE, *supra* note 16, at 17–19.

21. Pure Food Act, Pub. L. No. 59–384, 34 Stat. 768, 768–72 (1906). This Article does not consider biological products, which have been regulated under a different statutory scheme since 1902. *See* Pub. L. No. 57–244, 32 Stat. 728, 728–29 (1902).

22. *United States v. Johnson*, 221 U.S. 488, 498–99 (1911) (holding that the scheme prohibited only false statements about the identity of the product).

23. Pub. L. No. 62–301, 37 Stat. 416, 416–17 (1912).

24. *See, e.g.*, *Seven Cases v. United States*, 239 U.S. 510, 513, 517 (1916) (holding that “statement . . . regarding the curative or therapeutic effect” of a drug is “false and fraudulent” only if made “with actual intent to deceive”); *see also* RUTH DEFOREST LAMB, *AMERICAN CHAMBER OF HORRORS: THE TRUTH ABOUT FOOD AND DRUGS* 64–66 (1936) (discussing acquittal of patent medicine maker following sale of horsetail weed combined with peppermint oil and sugar to cure diabetes, largely because he had received letters from patients praising the concoction and he therefore had “faith in his product”).

25. *Johnson*, 221 U.S. at 498–500.

of opinion, even though the great majority may be of one way of thinking.”<sup>26</sup> The Court’s reluctance may also have reflected the view – which the American Medical Association (“AMA”) encouraged – that treating physicians were the best judges of the effectiveness of medicines they prescribed.<sup>27</sup> Indeed, the AMA stepped forward with a scheme for assessing effectiveness claims; it would provide a stamp of approval if, in its judgment, the claims about a drug’s therapeutic properties were not false.<sup>28</sup> The scheme was voluntary, but the AMA expected clinical data and developed a set of principles for support of claims, which the agency – renamed the “Food and Drug Administration” in 1930 – embraced.<sup>29</sup>

### B. Premarket Testing for Effectiveness

Tragedy struck in 1937: more than one hundred deaths, many of them children with *streptococcus* infections, from a sulfanilamide preparation that had not been adequately tested for safety.<sup>30</sup> This provided the final impetus for reform legislation, which had been brewing for several years. The 1938 statute required companies to notify FDA *prior* to introducing new drugs to the market and required them to provide evidence of safety, generated in “adequate tests by all methods reasonably applicable” to determine whether the drug was safe.<sup>31</sup>

Although the statute did not require premarket proof of effectiveness, FDA considered the therapeutic value of new drugs when it reviewed new drug applications (“NDAs”).<sup>32</sup> Few drugs are safe in an absolute sense. The conclusion that a drug is “safe” must be contextualized; it means “safe, in light of the potential benefits.”<sup>33</sup> If a drug was offered for treatment of a serious and

26. *Am. Sch. of Magnetic Healing v. McAnnulty*, 187 U.S. 94, 105–06 (1902) (finding therefore that statements about effectiveness are not an appropriate focus for mail fraud prosecution).

27. *See, e.g.*, BOYLE, *supra* note 16, at 30. This view persisted well into the twentieth century. Richard Harris, *Annals of Legislation: The Real Voice – II*, NEW YORKER, Mar. 21, 1964, at 75 (quoting American Medical Association spokesperson that “only the individual physician [can] determine the efficacy of a given drug in the treatment of a given patient”).

28. BOYLE, *supra* note 16, at 39; *see also* HARRY M. MARKS, *THE PROGRESS OF EXPERIMENT: SCIENCE AND THERAPEUTIC REFORM IN THE UNITED STATES, 1900–1990* at 147 (1997).

29. *See* BOYLE, *supra* note 16, at 39–40; *see infra* Part II.C.

30. DANIEL CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* 85–92 (2010).

31. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75–717, 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 355 (1938)).

32. Junod, *supra* note 19.

33. Robert Temple, *Development of Drug Law, Regulations, and Guidance in the United States*, in *GOVERNMENTAL REGULATION OF DRUGS* 1643, 1644 (Paul L. Munson et al. eds., 1994) [hereinafter Temple, *Development of Drug Law*] (explaining that “the

progressive, or life-threatening condition or if it had the potential for toxic side effects, for instance, the agency of the 1940s and 1950s considered its therapeutic potential when assessing it under the statutory safety standard.<sup>34</sup>

Over these same decades, academic statisticians and scientists, industry, and regulators worked to develop a framework for clinical testing that would reliably separate drugs with therapeutic benefit from drugs without therapeutic benefit.<sup>35</sup> As a result of this work the modern clinical efficacy trial emerged in the 1940s and 1950s. Controlled trials, in which subjects receiving experimental treatment are compared with subjects who do not receive experimental treatment, were not new. Nor was the concept of a placebo – a sham treatment provided to some subjects to address concern that the psychological effect of receiving medicine contributes to patient improvement.<sup>36</sup> British epidemiologist and medical statistician, Austin Bradford Hill, added the final two elements: rigorous statistical analysis of the trial results and design of the trial with the final statistical analysis in mind.<sup>37</sup>

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required showing of safety in the 1938 law . . . had always had some elements of weighing benefit against risk”). Dr. Temple currently serves as Deputy Director for Clinical Science in the Center for Drug Evaluation and Research (“CDER”). *See also* United States v. Rutherford, 442 U.S. 544, 555–56 (1979) (“For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.”).

34. *Drug Safety: Hearings Before a Subcomm. of the House Comm. on Gov’t Operations Part I*, 88th Cong. 2d Sess. 150 (1964) (testimony of George Larrick, Commissioner of Food and Drugs) (“Of course the question of benefit was an integral part of the safety question in dealing with a product to be used in a life-threatening disease such as pneumonia or in dealing with a drug presenting grave risks. We required information about effectiveness for such drugs in order to reach a decision about safety.”).

35. Recent historical work suggests that the ethical drug firms embraced the new methods as a way to differentiate their drugs from quack medicine. *See, e.g.*, Gabriel, *supra* note 15, at 605–06 (arguing that the ethical companies were motivated by both commercial and scientific considerations and “enthusiastically embraced rigorous scientific research”); Rasmussen, *supra* note 17, at 50 (discussing the “mutual accommodation between ethical drug firms and academic clinical researchers” between the wars, when commercial sponsorship of modern clinical trials, at academic institutions, emerged). Earlier work suggested most of the impetus for this work came from reformers. *See, e.g.*, MARKS, *supra* note 28, at 138, 150–51.

36. The concepts had even been combined by Parke-Davis (now part of Pfizer) in 1926. Gabriel, *supra* note 15, at 604–05. The company tested Sanocrysin (an injectable gold compound) for the treatment of tuberculosis, separating twenty-four patients into two groups by coin toss and administering a placebo sterile water injection to the control group. *Id.*

37. *See* John R. Hampton, *Evidence-Based Medicine, Opinion-Based Medicine, and Real-World Medicine*, 45 *PERSP. BIOLOGY & MED.* 549, 556 (2002); Roger Collier, *Legumes, Lemons and Streptomycin: A Short History of the Clinical Trial*, 180 *CANADIAN MED. ASS’N J.* 23, 24 (2009).

Hill designed the 1946 trial of streptomycin, an antibiotic, for treatment of patients with tuberculosis.<sup>38</sup> Post-war funding constraints meant the United Kingdom's Medical Research Council received only a small supply of streptomycin for research, requiring the trial team to determine how to prove efficacy with only a small number of patients receiving treatment.<sup>39</sup> Hill devised a protocol with inclusion and exclusion criteria, a concurrent control, randomization of enrolled subjects to treatment or control using statistical methods and sealed envelopes, an objective endpoint (x-rays) read by radiologists who were "blinded" to whether the subject had received treatment or control, and rigorous statistical analysis of the results.<sup>40</sup> The patients knew if they were receiving streptomycin.<sup>41</sup> Even without the additional blinding of patients ("double-blinding") that is preferred today, the use of a concurrent control, combined with Hill's statistical approach, conclusively demonstrated cure of tuberculosis.<sup>42</sup>

### C. "Adequate and Well-Controlled" Clinical Trials

FDA embraced the emerging clinical trial and statistical methodologies, confirming repeatedly its interest in rigorous study design and its expectation that new drug applicants would submit effectiveness data. In the early 1940s three agency officials and a representative of the AMA published an article in the *Journal of the American Medical Association*, describing the clinical trial design and data analysis standards the AMA had been applying for evaluation of efficacy data.<sup>43</sup> In the 1950s, new regulations for marketing applications required that every application include a "full statement" of the "therapeutic results observed" – that is, information on effectiveness.<sup>44</sup> These regulations further conveyed an expectation of study rigor by indicating that safety testing should be performed by "experts, qualified by scientific training and experience to evaluate the safety of drugs."<sup>45</sup> In the fall of 1962, FDA proposed

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38. Geoffrey Marshall et al., *Streptomycin Treatment of Pulmonary Tuberculosis: A Medical Research Council Investigation*, 2 BRIT. MED. J. 769, 769–70 (1948).

39. *Id.* at 769.

40. *Id.* at 770.

41. *Id.*; see also Hampton, *supra* note 37, at 556.

42. Marshall et al., *supra* note 38, at 780–81; see also Jeffrey Peppercorn et al., *History of Clinical Trial Development and the Pharmaceutical Industry*, in PHARMACEUTICAL SCIENCES ENCYCLOPEDIA: DRUG DISCOVERY, DEVELOPMENT, AND MANUFACTURING 1, 7 (Shayne C. Gad ed., 2010).

43. Walton Van Winkle, Jr., et al., *Laboratory and Clinical Appraisal of New Drugs*, 126 JAMA 958 (1944).

44. Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act, 21 Fed. Reg. 5576, 5578 (July 25, 1956) (promulgating 21 C.F.R. § 130.4, describing the contents of a new drug application).

45. Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act, 21 Fed. Reg. at 5578.

regulations to reshape the premarket clinical trial process.<sup>46</sup> This proposal laid out the now well-accepted sequence of preclinical safety testing, followed by a formal submission to the agency – known today as the investigational new drug application (“IND”) – *before* clinical trials.<sup>47</sup> It also emphasized the role of effectiveness data; an IND would not be accepted unless the sponsor planned to collect a case history for every subject, with information about results and an opinion whether useful results were attributable to the drug under investigation.<sup>48</sup>

The Kefauver-Harris amendments, passed in October 1962, imposed a new drug approval requirement, formally shifting the burden of proof to drug sponsors.<sup>49</sup> The statute also expressly required proof of effectiveness, in addition to proof of safety.<sup>50</sup> But these are not the aspects of the legislation most important to understanding the impact of the innovation paradox in the field of medicine. The effectiveness requirement was not novel, after all. Instead, the most significant aspects were the specification of an evidentiary standard for new drugs, tied directly to the words used in the labeling to describe the results that could be expected, and the specification of a clinical trial methodology.<sup>51</sup> Specifically, a new drug application required substantial evidence of effectiveness under the conditions of use prescribed, recommended, or suggested in the labeling.<sup>52</sup> Substantial evidence in turn meant data from adequate and well-controlled investigations, including clinical (human) investigations.<sup>53</sup> By 1970, FDA had explained that this embodied the principles of study design and data analysis that had been developing in the preceding decades: a method of subject selection that reduces variability, assignment of subjects to test groups

46. New Drugs for Investigational Use: Proposed Exemptions, 27 Fed. Reg. 7990, 7990–91 (Aug. 10, 1962).

47. *Id.* An IND would describe the preclinical investigations showing that it was reasonably safe to start human trials, and it would identify and describe the clinical investigators. *Id.* at 7990. It would also explain the nature and duration of every planned stage of investigation. *Id.* at 7991. Prior regulations exempting investigational new drugs from the NDA requirement had imposed only modest labeling and record-keeping requirements. 21 C.F.R. § 130.3 (1962).

48. New Drugs for Investigational Use: Proposed Exemptions, 27 Fed. Reg. at 7992.

49. Drug Amendments of 1962, Pub. L. No. 87–781, § 103, 76 Stat. 780, 783 (1962) (amending Federal Food, Drug, and Cosmetic Act (“FDCA”) § 505).

50. *Id.* § 102(a), 76 Stat. at 781 (amending FDCA § 201(p)).

51. Cf. Temple, *Development of Drug Law*, *supra* note 33, at 1650 (“[T]he impression that the critical event in 1962 was the effectiveness requirement is wrong and over-simple.”); Junod, *supra* note 19 (arguing that the strength of the new law was not the substantial evidence provision but its focus on study methods); Leonard G. Schifrin, *Lessons from the Drug Lag: A Retrospective Analysis of the 1962 Drug Regulations*, 5 HARV. J.L. & PUB. POL’Y 91, 101–02 (1982) (suggesting that the thrust of the 1962 amendments was tying proof to claims and thus narrowing the scope of the latter).

52. § 102(c), 76 Stat. at 781 (amending FDCA § 505(d)).

53. *Id.*

in a way that minimizes bias, use of a control, methods of observing and recording results that minimize bias on the part of the subject and the observer, quantitative results, and evaluation of results using appropriate statistical methods.<sup>54</sup>

Over the years, FDA and the more experienced pharmaceutical firms have worked together to refine their shared expectations about clinical trial design and data analysis.<sup>55</sup> For instance, nearly three decades after the agency issued its regulation explaining “adequate and well-controlled trials,” it observed that the “science and practice of drug development and clinical evaluation ha[d] evolved significantly,” prompting it to issue comprehensive guidance on demonstrating efficacy.<sup>56</sup> In that same time, statistical methods also grew more complex and sophisticated.<sup>57</sup> Citing a “proliferation of statistical research in the area of clinical trials,” FDA and its peer regulators in Japan and Europe developed joint guidance on the principles of statistical methodology applied to clinical trials.<sup>58</sup> FDA’s 1998 document lays out the agency’s expectations regarding the statistical issues associated with trial design, trial conduct, and data analysis.<sup>59</sup>

FDA also notes in this document that better understanding of the pathogenesis of disease and disease staging as well as progress in clinical evaluation and clinical pharmacology affect the amount and type of data needed to support approval in any particular case.<sup>60</sup> Indeed, the evolution since 1962 has uncov-

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54. Hearing Regulations and Regulations Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations, 35 Fed. Reg. 7250, 7250–51 (May 8, 1970) (to be codified at 21 C.F.R. pt. 130); *see also* 21 C.F.R. § 130.12(a)(5)(ii) (1970) (claiming that the new regulation restated principles that had been “developed over a period of years” and were now “recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations”).

55. *See generally* CARPENTER, *supra* note 30, at 495–96 (arguing that some of the standards “were advanced by the Bureau of Medicine, but also . . . were developments . . . at the intersection of science, regulation, and more progressive elements of the pharmaceutical industry”).

56. FOOD & DRUG ADMIN., U.S DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUGS AND BIOLOGICAL PRODUCTS 2, 16 (May 1998), <https://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4227B1-02-02-FDA-Appendix1.pdf> [hereinafter CLINICAL EFFICACY GUIDANCE].

57. *See* Anthony C. Segreti et al., *Biopharmaceutical Statistics in a Pharmaceutical Regulated Environment: Past, Present, and Future*, 11 J. BIOPHARMACEUTICAL STAT. 347, 348–65 (2001) (providing an accessible history of biopharmaceutical statistical practices and requirements from 1975 to 2000).

58. FOOD & DRUG ADMIN., U.S DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: E9 STATISTICAL PRINCIPLES FOR CLINICAL TRIALS 1 (Sept. 1998), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf> [hereinafter FDA, E9 GUIDANCE].

59. *Id.* at 14–34.

60. *See id.* at 2.



ered an important truth: data expectations and the clinical trial designs to produce those data vary considerably. The agency has now issued more than two dozen guidelines regarding clinical trial design and data requirements, therapeutic class by therapeutic class.<sup>61</sup> Part IV of this Article explores this variability.

#### D. New Drug Approval Theory

The modern drug approval paradigm traces its origins to the 1962 amendments. As written in statute and implemented by FDA in the decades that followed, the paradigm reflects two basic principles that together comprise new drug approval theory: *first*, FDA's authority over a new drug derives from and revolves around the words used to describe the drug, and *second*, the research performed by the drug's sponsor defines the drug.

As a general rule, it is words – not substances – that trigger FDA's drug authority. Under federal law, an article is a “drug” regulated by FDA if the article is intended for a particular type of use – to treat a disease, for instance.<sup>62</sup> This refers to the objective intended use of the item, which is generally determined by reference to *express claims* made by the product's manufacturer.<sup>63</sup> Thus, for instance, thalidomide is simply a chemical substance unless and until it is labeled for use in treatment of multiple myeloma. Further, a drug is a “new drug” that requires an NDA if it is not generally recognized as safe and effective for the uses described *in its labeling*.<sup>64</sup> Labeling broadly means any written or printed material associated with both the manufacturer and the product.<sup>65</sup>

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61. Temple, *supra* note 33, at 1646 (noting FDA's “increasingly strenuous attempts to make known what its requirements for approval would be” and the “nearly 30 drug class clinical guidelines . . . describing in detail the study designs and expected data for particular therapeutic classes”).

62. 21 U.S.C. § 321(g)(1) (2012).

63. S. REP. NO. 74-361, at 4 (1935) (“The use to which the product is to be put will determine the category into which it will fall. . . . The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put.”); *Action on Smoking & Health v. Harris*, 655 F.2d 236, 238–39 (D.C. Cir. 1980) (treating this Senate passage as authoritative); *United States v. An Article Consisting of 216 Cartoned Bottles*, 409 F.2d 734, 739 n.3 (2d Cir. 1969) (following same interpretation); *United States v. 23, More or Less, Articles*, 192 F.2d 308, 310 (2d Cir. 1951) (same). Intended use is the intent communicated in the market generally through claims and representations in a product's labeling and advertising. *See* Brief for Respondent R.J. Reynolds Tobacco Co. at 12 n.11, *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (No. 98-1152) (brief authored by former Chief Counsel of FDA, noting that “intent is ‘objective’ in that its locus is not the mind of any person, but the marketing communications, themselves”); *see also* 21 C.F.R. §§ 201.128, 801.4 (2017) (defining intended use).

64. 21 U.S.C.A. § 321(p)(1) (West 2018).

65. *Id.* § 321(m); *Kordel v. United States*, 335 U.S. 345, 348, 350 (1948) (holding that pamphlets shipped by drug maker under separate cover were “labeling” because of their “textual relationship” to the drugs, that is, they “explained their uses”).

Words, in labeling written by a company about its product, make an article a new drug that requires an NDA.

The application in turn must show that the drug is safe for use under the conditions described *in the labeling*, and it must provide substantial evidence that the drug will have the effect it purports or is represented to have under the conditions described *in the labeling*.<sup>66</sup> The application therefore describes the product (including how it is made) and proposes labeling.<sup>67</sup> The company's research program and results – which are presented in its application – must *prove* what is *proposed* for the labeling of the product. Regardless of the accuracy of the initially proposed labeling, when FDA approves the drug product, it will approve only labeling that reflects what the research *proved*.<sup>68</sup>

The labeling approved by FDA tells prescribers about the specific medical conditions for which the drug has been approved (its “indications”) and describes the outcomes that can be expected under specific conditions of use (such as dosing). Agency regulations specify precisely what must, may, and may not be included in the labeling.<sup>69</sup> These regulations require the labeling to synthesize the information in the application – especially the research design and results – into digestible advice for prescribers.<sup>70</sup> For instance, the labeling must describe every clinical trial that would facilitate understanding how to use the drug safely and effectively.<sup>71</sup> If a particular study supported effectiveness for the labeled indication, the labeling must describe the study design and its results.<sup>72</sup> If evidence is lacking with respect to a particular subpopulation, the labeling must describe this limitation succinctly.<sup>73</sup> Special instructions for distinct populations may be included, based on the data in the clinical trials.<sup>74</sup> Every section of the labeling is grounded in the application submitted and in the company's and agency's analysis of the data and information in the application.

FDA's approval of an application and thus a product and labeling represents its conclusion that the drug is safe and effective under the conditions of use *in that labeling* – for that indication, with those dosing instructions, subject

66. 21 U.S.C.A. § 355(d) (West 2018).

67. *See* 21 C.F.R. § 314.50 (2017).

68. 21 U.S.C.A. § 355(d)(1)–(5), (7) (West 2018).

69. 21 C.F.R. § 201.57 (2017).

70. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082, 81082 (proposed Dec. 22, 2000) (to be codified at 21 C.F.R. pt. 201) (referring to the professional labeling as “the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals” and noting that it “is a compilation of information based on a thorough analysis of the new drug application”).

71. § 201.57(c)(15).

72. *Id.*

73. *Id.* § 201.57(c)(2)(i)(B).

74. *Id.* § 201.57(c)(9)(vi).

to those warnings and precautions.<sup>75</sup> The 1962 amendments linked clinical trial design and the resulting data to the words that would be approved by FDA in connection with approval of the drug. Because the agency approves both the tangible item and its labeling together as a single unit, modern drug approval theory means that research design and results dictate the scope of the approval and thus define the product approved for patients.

### III. INCENTIVES FOR DRUG INNOVATION

The primary incentive to discover and develop a new medicine in the United States is the prospect of a period for exclusive marketing – commercialization without competition from cheaper copycat products. During this period, the company may be able to recover the investment it made in developing the medicine as well as others that are less successful or that failed before approval, and it may be able to enjoy a profit.<sup>76</sup> This period is made possible by several features of federal law, the most significant of which are protection of patents associated with the medicine and protection of research data gathered during testing under the drug approval statute.

#### A. Patent Exclusivity

Federal law permits the patenting of any “new and useful process, machine, manufacture, or composition of matter” as well as any “new and useful improvement[s] thereof,” provided the other conditions and requirements of the Patent Act are satisfied.<sup>77</sup> The sponsor of a new drug may own (or exclusively license) a variety of patents in connection with that drug.

For instance, the sponsor may own a patent claiming the drug’s active ingredient, which in simple terms is the component of the product that furnishes its pharmacological activity.<sup>78</sup> The active ingredient directly effects the

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75. 21 U.S.C.A. § 355(d) (West 2018).

76. Henry Grabowski et al., *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, 34 HEALTH AFF. 302, 302 (2015) (“Patents and other forms of intellectual property protection are generally thought to play essential roles in encouraging innovation in biopharmaceuticals.”); Mark A. Lemley, *The Regulatory Turn in IP*, 36 HARV. J.L. & PUB. POL’Y 109, 114–15 (2013) (“In the pharmaceutical industry the government requires perhaps ten years of safety and efficacy review, costing hundreds of millions of dollars in research, development, testing, and marketing, before allowing the launch of a pharmaceutical product. . . . The patent system guarantees insulation from competition for a substantial period of time so companies can recover the money the government made them invest in the first place.” (footnote omitted)).

77. 35 U.S.C. § 101 (2012).

78. FDA uses the phrase “active moiety” for the biologically active substance at the site of action at the body and the phrase “active ingredient” for the substance as introduced to the body. 21 C.F.R. § 314.3(b) (2017); *Abbott Labs. v. Young*, 920 F.2d 984, 987–88 (D.C. Cir. 1990).

treatment of the disease in question.<sup>79</sup> FDA calls this a “drug substance” patent.<sup>80</sup> Patent law provides an inventor with a strong incentive to file the application for this patent as early as possible. This is because, as a general rule, a patent will be denied if the invention was in “public use” for more than a year before the patent application was filed.<sup>81</sup> Although the matter is not entirely free from doubt, use of an invention in a clinical trial may in some cases constitute public use.<sup>82</sup> Publication of the invention more than a year before the patent application can similarly lead to denial of the patent.<sup>83</sup> Conventional wisdom holds that new drug sponsors should and do file for active ingredient patents before clinical testing.<sup>84</sup>

It is possible to file well before clinical testing begins because patent law does not require proof of safety and effectiveness in the FDA regulatory sense. The goal of the regulatory premarket program for a new drug is to show that the benefits (the therapeutic outcomes assessed in hypothesis-testing human trials) of the finished product (active ingredient, formulation, route of administration, dosage form, and strength) outweigh its risks when the product is used as described in its labeling.<sup>85</sup> Safety and effectiveness are clinical and regulatory concepts and evolving ones at that. Patent law imposes its own “utility”

79. In addition to treating a disease, a drug (and thus its active ingredient, which is also a drug) can diagnose, cure, mitigate, or prevent a disease or affect the structure or function of the body. 21 U.S.C.A. § 321(g)(1) (West 2018).

80. 21 C.F.R. § 314.53(b) (2017).

81. 35 U.S.C. § 102(a)–(b) (2012). Congress reworked this provision in 2011, but the basic concept remains true today. See Leahy-Smith America Invents Act, Pub. L. No. 112–29, 125 Stat. 284, 285–86 (2011).

82. See Christopher M. Holman, *Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation*, 76 MO. L. REV. 645, 659–60 (2011) (discussing the “not entirely unambiguous” issue of whether human clinical trials are patent-invalidating public use of the claimed invention). In 2013, the Federal Circuit reversed a lower court summary judgment of invalidity grounded in a finding that a clinical trial constituted clear and convincing evidence of public use. *Dey, L.P. v. Sunovion Pharm., Inc.*, 715 F.3d 1351, 1356 (Fed. Cir. 2013). The matter was remanded to determine whether the study was conducted with a reasonable expectation of confidentiality as to the nature of the formulations tested. *Id.* at 1360.

83. See, e.g., *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs, Ltd.*, 476 F.3d 1321, 1324–25 (Fed. Cir. 2007) (explaining how a prior publication forced Ortho-McNeil to narrow the scope of its patent); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 522–24 (2009) (offering numerous examples).

84. See, e.g., Roin, *supra* note 83, at 539 (stating that “[p]harmaceutical patents are typically filed when drugs are in early preclinical research”); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 348 (2007) (noting that applications for “composition of matter” patents are filed before clinical testing of a molecule begins).

85. 21 C.F.R. § 314.50(d)(5)(viii) (2017) (requiring NDAs to discuss “why the benefits exceed the risks under the conditions stated in the labeling”); FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., CRITICAL PATH OPPORTUNITIES

requirement, the contours of which are admittedly much debated, but it has been clear for almost forty years that with respect to substances that may ultimately comprise part of a new drug product approved by FDA, utility is a question of having a desirable biological activity and ordinarily can be demonstrated with preclinical evidence.<sup>86</sup>

In addition to the active ingredient patent, the sponsor of a medicine may hold a patent claiming the formulation or composition of the particular finished product.<sup>87</sup> For instance, the patent might claim the particular combination of active and inactive ingredients or the particular dosage form and dosage.<sup>88</sup> FDA calls these “drug product” patents.<sup>89</sup> The sponsor might hold a patent claiming an approved method of using or administering the product, which FDA calls a “use” patent.<sup>90</sup> Other possibilities include patents claiming the manufacturing process, claiming an intermediate chemical entity used during the manufacturing process, or claiming a metabolite of the active ingredient.<sup>91</sup>

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REPORT at R-8 (2006), <https://www.fda.gov/downloads/scienceresearch/specialtopics/criticalpathinitiative/criticalpathopportunitiesreports/ucm077254.pdf> [hereinafter FDA CRITICAL PATH REPORT] (suggesting approval once “uncertainty” about benefit-risk balance has been “reduced to an acceptable level”); *see also* United States v. Rutherford, 442 U.S. 544, 555 (1979) (FDA “generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.”).

86. *See* Nelson v. Bowler, 626 F.2d 853, 856 (C.C.P.A. 1980) (finding utility on the basis of data demonstrating pharmacodynamic activity in animals, specifically, stimulating smooth muscle tissue in gerbils and modulating blood pressure in rats); Cross v. Iizuka, 753 F.2d 1040, 1052 (Fed. Cir. 1985) (finding utility on basis of in vitro demonstration of the claimed biological activity, that is, preventing aggregation of platelets); *see also In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (noting that “proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility” and stating court’s “firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans” (quoting *In re Krimmel*, 292 F.2d 948, 953 (C.C.P.A. 1961)); U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2107.03 (9th ed. 2017) (requiring evidence “that reasonably supports” pharmacological or therapeutic utility and noting that data from in vitro or animal testing “is generally sufficient”).

87. 21 C.F.R. § 314.53(b) (2017).

88. *Id.*

89. *Id.*

90. *Id.*; *see* FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS at ADB31–ADB78 (2017), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf> [hereinafter APPROVED DRUG PRODUCTS] (describing various use patents).

91. § 314.53(b); *see generally* JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 38–46 (2005) (listing numerous types of pharmaceutical patent claims).

Through the 1970s, as the modern new drug premarket paradigm took shape, scholars and policymakers became aware of diminishing effective patent life. Because inventors typically file active ingredient patent applications before clinical testing starts, these patents tend to issue before or during the trials. At the time, a patent lasted for seventeen years from issuance.<sup>92</sup> Today, it generally lasts for twenty years from the filing of the patent application.<sup>93</sup> In either case, a significant portion of the term of an active ingredient patent may lapse before FDA approves the marketing application. This shortens the period of time that the drug sponsor may exploit the invention in the market while enjoying patent rights. Numerous studies in the 1970s and early 1980s documented a significant decline in the effective patent life of new drugs over the preceding decades.<sup>94</sup> Other studies pointed out that the length of the premarket process had increased substantially,<sup>95</sup> and still others documented a decline in the rate of new drug introductions.<sup>96</sup> Some studies linked the decline in new drug introductions to increased regulatory requirements.<sup>97</sup> Others suggested

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92. 35 U.S.C. § 154(c)(1) (1984).

93. 35 U.S.C.A. § 154(a)(2) (West 2018). Congress changed the term in the Uruguay Round Agreements Act, Pub. L. No. 103–465, 108 Stat. 4809 (1994), to implement the Marrakesh Agreement of 1994, part of the Uruguay Round of multilateral negotiations that transformed the General Agreement on Tariffs and Trade into the World Trade Organization. For patents issued on or after June 8, 1995, the term is twenty years from the patent application or, if the application contains a specific reference to an earlier filed application, twenty years from the date of *that* application. § 154 (a)(2). Patents in force on June 8, 1995, or that issued on applications pending on that date, lasted either twenty years from application or seventeen years from issuance, whichever ended later. *Id.* § 154(c)(1).

94. See Schifrin, *supra* note 51, at 116–19 (surveying literature on decline in effective patent life by 1982); Peter Barton Hutt, *The Importance of Patent Term Restoration to Pharmaceutical Innovation*, 1 HEALTH AFF. 6, 16–17 (1982) (noting that “[t]he effective patent life of the NCE drugs approved by FDA in 1980 and 1981 was less than half the seventeen years provided by Congress” and listing studies to date).

95. See, e.g., SUBCOMM. ON SCI., RESEARCH AND TECH., 96TH CONG., THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS 81 (Comm. Print 1980) (finding it took four to six years on average to conduct clinical testing for approval); Martin Eisman & William Wardell, *The Decline in Effective Patent Life of New Drugs*, 24 RES. MGMT. 18, 19 (1981) (showing increase in clinical testing period from 5.9 years in 1968 to 8.3 years in 1979); Lewis H. Sarett, *FDA Regulations and Their Influence on Future R&D*, 17 RES. MGMT. 18, 18 (1974) (reporting that average product development time had increased from two years in 1958–62 to 5.5–8 years in 1968–72).

96. See Schifrin, *supra* note 51, at 93 (noting that comparisons of rates of introduction before 1962 and after 1962 generally showed decline in the 1960s and 1970s). In fact, new molecular entities had entered the market at a rate of nearly twenty per year in the 1950s, and the pace dropped to fifteen or below in the 1960s and 1970s. Michael S. Kinch et al., *An Overview of FDA-Approved New Molecular Entities: 1827–2013*, 19 DRUG DISCOVERY TODAY 1033, 1034 fig.1 (2014).

97. One influential study compared the actual flow of new chemical entities from 1962 to 1969 with the flow predicted from a regression of the determinants of the flow

that drug researchers had finished the easy work and that the challenges of developing treatments for chronic diseases were harder and more time consuming.<sup>98</sup> Still others noted that the explanations were not mutually exclusive.<sup>99</sup>

Together these studies informed enactment of section 156 of the Patent Act in 1984.<sup>100</sup> Section 156 allows the PTO to restore a portion of the term of one patent associated with a product that underwent regulatory review prior to commercial marketing.<sup>101</sup> Restoration of the patent is subject to numerous conditions, the most significant of which is that the regulatory review must result in the first permitted commercial marketing or use of the active ingredient in question.<sup>102</sup> Also PTO will not restore any portion of the regulatory review period that occurred prior to patent issuance.<sup>103</sup>

Patent protection for new drugs remains paradoxical, however, because the statutory formula limits the number of days recoverable. Although it directs PTO to restore all of the patent term that lapses while FDA reviews a new drug application, it permits restoration of only half of the clinical testing period.<sup>104</sup> The clinical testing period begins when FDA authorizes clinical trials by permitting an IND to go into effect and ends when the applicant submits its

prior to 1962. SAM PELTZMAN, REGULATION OF PHARMACEUTICAL INNOVATION: THE 1962 AMENDMENTS 10 (1974). This study showed that the actual flow in the 1960s was half of what had been predicted. *Id.*

98. *See, e.g.*, JOHN W. EGAN ET AL., ECONOMICS OF THE PHARMACEUTICAL INDUSTRY 104 (1982); *see also* Viviane Quirke, *From Alkaloids to Gene Therapy: A Brief History of Drug Discovery in the 20th Century*, in MAKING MEDICINES 177, 197 (Stuart Anderson ed., 2005) (noting theories for the slowing pace by 1975, including both the post-1962 regulatory requirements and the possibility that early drug discoveries had been providential, while “purposeful search[es] . . . take[] much longer”).

99. One study attributed fifty percent of the U.S. lag to a worldwide depletion of research opportunities and fifty percent to U.S. regulatory policy, after comparing the rate and timing of new drug introductions in the United States with the rate and timing in other countries. Henry G. Grabowski, *Drug Regulation and Innovation: Empirical Evidence and Policy Options*, 66 J. PHARM. SCI. 911 (1976).

100. Alan D. Lourie, *Patent Term Restoration*, 66 J. PAT. OFF. SOC’Y 526, 535–36 (1984) (providing history of the patent term restoration provisions of 1984); *see generally* Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187 (1999) (providing history of the 1984 statute).

101. In addition to new (human) drugs, patent term restoration is available for new animal drugs, human and veterinary biological products, food additives, color additives, and medical devices. 35 U.S.C.A. § 156 (West 2018). Veterinary biological products are regulated by the Animal and Plant Health Inspection Service (“APHIS”) within USDA. *See* 9 C.F.R. § 124.1 (2017). FDA regulates the other products. *What Does FDA Regulate?*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194879.htm> (last updated Dec. 19, 2017).

102. 35 U.S.C.A. § 156(a)(5)(A) (West 2018).

103. *Id.* § 156(c).

104. *Id.* § 156(c)(2).

NDA.<sup>105</sup> Thus, if the drug spent 1000 days in clinical trials, PTO will restore only 500 days.<sup>106</sup> Put another way, there is a fifty percent penalty for clinical testing. Moreover, PTO awards no more than five years.<sup>107</sup> Once the approval period and half of the testing period are added, the final number will be rounded down (if necessary) so that the new patent expiry date is no more than five years after the original expiry date.<sup>108</sup> Thus past a certain point in a research program, every additional day of testing translates to a lost day of patent life.<sup>109</sup> The paradox remains: the exclusive marketing period made possible by the patent is shorter for drugs with longer research programs.

### B. Data Exclusivity

The period for exclusive marketing also derives from data exclusivity, which is separate from patent exclusivity. In addition to adding section 156 to the Patent Act, the 1984 legislation created a statutory pathway for approval of generic drugs. A generic drug application omits safety and effectiveness information and instead relies on the research submitted by another applicant, without that applicant's permission.<sup>110</sup> It is thus an "abbreviated" new drug application. Data exclusivity is inherent in any licensure scheme that requires the submission of data and that permits one company to rely on data in another company's submission. The rules must state when the later abbreviated application is permitted. Data exclusivity is unrelated to any patent protection the first company might have.<sup>111</sup>

As a general rule, when FDA approves a new (never before approved) active ingredient, generic applications citing that active ingredient cannot be submitted for five years.<sup>112</sup> This is known as "new chemical entity" ("NCE") exclusivity, due to FDA's particular way of interpreting the statutory phrase

105. *Id.* § 156(g)(1)(B)(i).

106. If the patent in question issued on the 400th day of the testing period, PTO will consider only the final 600 days and will restore only 300 days. *See, e.g., id.* § 156(c)(2).

107. *Id.* § 156(g)(6)(A).

108. The rule was different for a drug already in clinical trials when Congress enacted the Hatch-Waxman Amendments. *See id.* § 156(g)(6)(A)–(C).

109. There is also a fourteen-year limit on the effective patent life. *Id.* § 156(c)(3).

110. 21 U.S.C.A. § 355(j)(2) (West 2018) (describing contents of ANDA); Lietzan, *supra* note 4, at 106 (explaining reliance).

111. There is confusion in the literature over the terminology, with some writers using "market exclusivity" to describe the period of time before generic applications may be submitted or approved. *See* Lietzan, *supra* note 4, at 110–12 (discussing confusion). This Article uses "data exclusivity" to refer to the period of time during which the innovator has exclusive rights to the *data* it submitted. *Id.* at 103.

112. § 355(j)(5)(F)(ii). This is shortened to four years if the generic applicant challenges a patent claiming the innovator's drug or a method of using that drug. *Id.* For a more detailed discussion of the nuances of data exclusivity, see generally Lietzan, *supra* note 4, at 134–50.



that mentions “active ingredient.” The agency focuses on whether the “active moiety” – the molecule responsible for the physiological or pharmacological action of the drug – has been approved before.<sup>113</sup> This is a narrower inquiry than whether the drug’s active ingredient is new for purposes of patent term restoration.<sup>114</sup> Data exclusivity is not paradoxical in the way that patent exclusivity is paradoxical. It is, however, invariable. No matter how much time and money a firm spends developing a new drug, its right to exclusive use of the data it generates expires five years after the new drug’s approval.

#### IV. DRUG INNOVATION AND PARADOX

Once a patent application has been filed, any further time spent developing, testing, and refining a product before market launch results in a shorter effective patent life.<sup>115</sup> This structural point is true regardless of the field of invention. Inventors face a variety of pressures that could increase their time to market, ranging from prudential legal considerations (e.g., safety testing to guide modifications that reduce liability exposure) to business considerations (e.g., testing to guide modifications that optimize commercial appeal). Generally the fact that increased time to market leads to decreased effective patent life should prompt efficient pre-launch behavior and may not raise public policy concerns.

With new drugs, however, there may be cause for concern. The design and length of any particular premarket program depend on the chemical structure of the active ingredient, its mechanism of action, the disease and its biological pathways, the disease state targeted, the outcome tested, and even the presence and nature of other treatments on the market. The *way* these factors affect premarket timelines is largely beyond the sponsor’s control. A drug’s sponsor has a different kind of control. Within a range of options largely dictated by the current state of scientific knowledge and by FDA regulatory requirements and culture, a company has choices about the disease and disease stage to pursue and the outcomes or uses to investigate. It also has the choice

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113. See Lietzan, *supra* note 4, at 135–36; 21 C.F.R. § 314.108(a) (2017).

114. The standard for patent term restoration is whether the active ingredient, or a salt or ester thereof, has previously been approved. § 156. It is more forgiving, which means that some new drugs receive patent term restoration but not NCE exclusivity. See, e.g., Photocure ASA v. Kappos, 603 F.3d 1372, 1376 (Fed. Cir. 2010) (rejecting use of FDA “active moiety” approach and finding that methyl aminolevulinate hydrochloride was entitled to restoration, even though it was a methyl ester of the previously approved aminolevulinate hydrochloride and therefore would not receive NCE status at FDA).

115. When the patent term was measured from patent issuance, time spent developing, testing, and refining the product after *issuance* (and before market launch) resulted in a shorter effective patent life. Now that the patent term is measured from the patent application, it is time after the *application* (and before market launch) that results in shorter effective patent life.

whether to continue with a project or examine another compound entirely. Rather than choices relating to the efficiency of a particular premarket process, these are choices about the research goals – meaning a program’s overall objectives and a trial’s hypothesis – and therefore the *type of product* it will pursue. Rather than steering drug firms towards efficient premarket behavior, the paradoxical effective patent life and flat data exclusivity period may steer them away from particular fields altogether.

#### A. Trial Design, Efficacy Endpoints, and Scope of Approval

A modern drug development program culminates in adequate and well-controlled phase 3 trials designed to generate substantial evidence of effectiveness.<sup>116</sup> The “endpoint” used in those trials has a profound influence on the length of the trials and therefore the overall clinical program. As explained in Part II.D., the research results dictate the content of the labeling and therefore the scope of approval. This means the endpoints acceptable to FDA in any particular situation will define the product that can be approved, and a firm’s selection of one endpoint among choices (if there are any) is tantamount to selection of the product to be pursued. In the end, certain products will require phase 3 effectiveness endpoints that necessitate longer trials, triggering the innovation paradox.

#### 1. Traditional Endpoints

The endpoint of a trial is a variable intended to reflect a desired outcome that can be statistically analyzed to answer a research question.<sup>117</sup> The basic goal in endpoint selection is identification of a variable that will – if measured as described in the protocol and assessed as specified in the data analysis plan, and assuming positive results – support regulatory approval. As a practical matter, the results generally must demonstrate diagnosis, cure, mitigation,

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116. It is possible to obtain approval on the basis of one adequate and well-controlled trial. FDA approved the first HIV/AIDS drug, Retrovir (zidovudine), on the basis of data from a single randomized trial – which some characterize as a phase 2 trial – that was stopped on ethical grounds when the therapeutic value became clear. CARPENTER, *supra* note 30, at 436; *see generally id.* at 428–57 (discussing in detail FDA’s development of accelerated approval and fast-track processes in connection with the AIDS crisis); *see also* CLINICAL EFFICACY GUIDANCE, *supra* note 56, at 3 (noting history of approvals on the basis of a single trial); Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 115, 111 Stat. 2296, 2312 (1997) (codified at 21 U.S.C. § 355(d)) (clarifying that FDA may rely on data from one adequate and well-controlled trial plus “confirmatory” evidence).

117. U.S. FOOD & DRUG ADMIN. & NAT’L INSTS. OF HEALTH, BEST (BIOMARKERS, ENDPOINTS, AND OTHER TOOLS) RESOURCE 51 (Nov. 14, 2017).

treatment, or prevention of disease.<sup>118</sup> As a result, the trial protocol customarily specifies an endpoint that directly measures how the patient feels, functions, or survives or an endpoint that represents or characterizes the clinical outcome of interest, such as disease exacerbation or a clinical event like a stroke.<sup>119</sup> Upon review of the resulting data, FDA approves the drug for a particular use, and it approves the precise wording of the labeling that describes the conditions of this use.<sup>120</sup> The use, and this wording, in turn depend on the clinical trial design, including the endpoints, as well as the statistical analysis of the resulting data. To give a concrete example, FDA does not approve a new drug for Alzheimer's disease in some general sense. Instead, it approved Exelon (rivastigmine tartrate) for "treatment of mild to moderate dementia of the Alzheimer's type," after Novartis provided the results from double-blinded, randomized, placebo-controlled trials in patients with mild to moderate dementia.<sup>121</sup> The endpoint in those trials, in turn, was the drug's ability to improve cognitive performance, using parameters like concentration, memory, orientation (as to date, for instance), word recognition, and word finding.<sup>122</sup> Clinical trial design *always* shapes the scope of approval, meaning the wording that describes the approved use and expected outcomes.

The customary clinical endpoint for a drug that treats a life-threatening condition is overall survival.<sup>123</sup> Investigators generally follow each research

118. 21 U.S.C.A. § 321(g)(1) (West 2018) (defining a drug as, among other things, an "article[] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"); 21 C.F.R. § 201.57(c)(2) (2017) (requiring Indications and Usage section of labeling to state that the drug is indicated "for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition").

119. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS 17 (May 2014) [hereinafter EXPEDITED PROGRAMS GUIDANCE] (defining clinical endpoint as "a characteristic or variable that directly measures a therapeutic effect of a drug – an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives").

120. See *supra* Part II.D.

121. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., NDA 20-823, STATISTICAL REVIEW(S) (Nov. 30, 1997), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20823\\_Exelon\\_statr\\_P1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20823_Exelon_statr_P1.pdf) [hereinafter EXELON EFFICACY]; Exelon Package Insert (2000).

122. Cognitive performance was measured using the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and overall clinical effect was assessed using a Clinician's Interview Based Impression of Change with caregiver information (CIBIC-Plus). EXELON EFFICACY, *supra* note 121.

123. See TOM BRODY, CLINICAL TRIALS: STUDY DESIGN, ENDPOINTS AND BIOMARKERS, DRUG SAFETY, AND FDA AND ICH GUIDELINES 191 (2012). Alternative endpoints might be death itself or (depending on the drug and goal of the program) a relevant clinical event such as recurrent heart attack or stroke.

subject from randomization to the time that death occurs from any cause.<sup>124</sup> The statistical analysis basically compares the survival times in the treatment group with the survival times in the control group.<sup>125</sup> One significant challenge with overall survival analysis for drug sponsors is that it requires larger and longer trials than other endpoints would.<sup>126</sup> To begin with, if the disease has a long course until death (prostate cancer, for instance, instead of pancreatic cancer), an overall survival analysis may require a longer period of follow-up with subjects.<sup>127</sup> Also, overall survival may require a larger sample size – more trial subjects – to achieve statistical significance.<sup>128</sup> This is particularly true if the sponsor anticipates a small incremental increase in survival time, that is, a small effect size.<sup>129</sup> A larger sample size will, in turn, generally lengthen the trial. This is because most phase 3 trials enroll subjects on a rolling basis.<sup>130</sup> That is, subjects enroll one by one as they volunteer and are found to meet the inclusion and exclusion criteria.<sup>131</sup> Thus, a trial that requires more subjects to achieve statistical significance with a selected endpoint can take longer to enroll and complete, and this can be exacerbated if disease prevalence or the trial's inclusion criteria limit the pool of potential volunteers in the first instance.

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124. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: CLINICAL TRIAL ENDPOINTS FOR THE APPROVAL OF CANCER DRUGS AND BIOLOGICS 5 (May 2007), <https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf> [hereinafter CANCER ENDPOINTS GUIDANCE].

125. *Id.* at 6. As a practical matter, the protocol must specify a cut-off date for final data analysis, with the understanding that some subjects may not have experienced death yet. For these subjects, the data reflect minimum survival time rather than true survival time. See Taane Clark et al., *Survival Analysis Part I: Basic Concepts and First Analyses*, 89 BRIT. J. CANCER 89 (2003).

126. See CANCER ENDPOINTS GUIDANCE, *supra* note 124, at 4; BRODY, *supra* note 123, at 191.

127. BRODY, *supra* note 123, at 216; e.g., Carolyn Compton, *Cancer Survival Analysis* 28–29, in *AJCC CANCER STAGING ATLAS* (Carolyn Compton et al. eds., 2012) (“In diseases with a long natural history, the duration of study could be 5–20 years, and survival intervals of 6–12 months will provide a meaningful description of the survival dynamics. If the population being studied has a very poor prognosis (e.g., patients with carcinoma of the esophagus or pancreas) the total duration of study may be 2–3 years, and the survival intervals may be described in terms of 1–3 months.”).

128. Ross L. Prentice, *Surrogate Endpoints in Clinical Trials: Definition and Operational Criteria*, 8 STAT. MED. 431 (1989).

129. Martin Abeloff, *Biostatistics and Bioinformatics in Clinical Trials*, in *ABELOFF'S CLINICAL ONCOLOGY* 309, 311 (Martin D. Abeloff et al. eds., 4th ed. 2008) (“A small study will have low power to detect small differences.”).

130. BRODY, *supra* note 123, at 122.

131. See *id.*

## 2. Surrogate Endpoints

Use of a surrogate endpoint can shorten the duration of a trial, particularly a trial that requires an overall survival analysis or another potentially distant endpoint like death, heart attack, or stroke.<sup>132</sup> A surrogate endpoint is a measurement used to *predict* a clinical benefit but does not establish a clinical effect in itself.<sup>133</sup> Surrogate endpoints include laboratory measurements (such as viral loads or counts of certain blood cell types) and measurements obtained through MRI or other imaging technology.<sup>134</sup> A surrogate endpoint can shorten a trial's duration because it can usually be measured earlier in time for each subject in the trial.<sup>135</sup> A trial with a surrogate endpoint generally also requires fewer study subjects to achieve statistical significance, shortening the period from the first patient's first visit to the last patient's last visit.<sup>136</sup> A biostatistics team from the National Institutes of Health ("NIH") illustrated both advantages in 1989: an antihypertensive drug would require 25,000 subjects for five years if the stroke endpoint were used, but the surrogate of maintenance of a blood pressure drop permits a trial in 200 subjects for a year or two.<sup>137</sup> Surrogate endpoints thus have the potential to mitigate some of the problem faced by companies considering development of drugs that would otherwise require very long trials due to the clinical endpoints needed.

Surrogate endpoints can be further divided into validated surrogate endpoints and novel (not yet validated) surrogate endpoints.<sup>138</sup> Validated surrogate endpoints are *known* to predict clinical benefit.<sup>139</sup> Prior to validation, a surrogate endpoint is merely *thought* to be predictive.<sup>140</sup> There has been increased interest in use of novel surrogate endpoints since the early 1980s,<sup>141</sup>

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132. Prentice, *supra* note 128, at 431 ("A primary motivation for the use of a surrogate endpoint . . . concerns the possible reduction in sample size or trial duration that we can expect when a rare or distal endpoint is replaced by a more frequent or proximate endpoint." (footnotes omitted)).

133. FDA CRITICAL PATH REPORT, *supra* note 85, at R-9, R-11.

134. Abeloff, *supra* note 129.

135. *Id.* at 324; *see also* FDA CRITICAL PATH REPORT, *supra* note 85, at R-11 ("In disorders where the clinical endpoint is hard to assess (e.g., joint deterioration in rheumatoid arthritis) or takes a long time to occur (e.g., certain preventive therapies), use of a qualified surrogate endpoint can markedly accelerate the development process for treatment breakthroughs.").

136. Prentice, *supra* note 128, at 431.

137. Janet Wittes et al., *Surrogate Endpoints in Clinical Trials: Cardiovascular Diseases*, 8 STAT. MED. 415, 417 (1989).

138. Thomas R. Fleming & John H. Powers, *Biomarkers and Surrogate Endpoints in Clinical Trials*, 31 STAT. MED. 2973, 2975 (2012).

139. *Id.*

140. *See generally id.*; *see also* Thomas R. Fleming & David L. DeMets, *Surrogate End Points in Clinical Trials: Are We Being Misled?*, 125 ANNALS INTERNAL MED. 605 (1996).

141. FDA CRITICAL PATH REPORT, *supra* note 85, at R-9, R-11.

but there are also concerns. *First*, the disease of interest could affect the biomarker and the clinical endpoint separately, that is, on different biological pathways.<sup>142</sup> In this case, a change in the biomarker would not predict a change in clinical outcome.<sup>143</sup> The opposite could also be true: the treatment could have no effect on the biomarker but a meaningful effect on the clinical outcome of interest, in which case the clinical benefit would be missed.<sup>144</sup> *Second*, the disease process could achieve the clinical outcome, or increase the risk of the clinical outcome, through multiple biological pathways, and the biomarker might lie on only one pathway.<sup>145</sup> In this case, too, a change in the biomarker might not predict a change in clinical outcome.<sup>146</sup> Confirmation of a particular drug's clinical benefit thus does not in itself validate – for other drugs – the surrogate endpoint used in its initial approval.<sup>147</sup> *Third*, the drug could have a separate, not previously appreciated, mechanism of action that is independent of its effect on the disease process and, perhaps, undesirable; this is sometimes called an off-target effect.<sup>148</sup>

These concerns are not hypothetical. For instance, a difference in response rate without a difference in survival has been noted in both non-small-cell lung cancer and squamous cell carcinoma of the head and neck.<sup>149</sup> In contrast, patients with colorectal cancer sometimes receive a meaningful survival benefit without showing a comparably meaningful objective response.<sup>150</sup> And

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142. Thomas R. Fleming, *Surrogate Endpoints and FDA's Accelerated Approval Process*, 24 HEALTH AFF. 67, 69 (2005).

143. *Id.*

144. FDA, E9 GUIDANCE, *supra* note 58, at 9; Temple, *supra* note 33, at 1655 (noting possibility “that the presumed relation of a surrogate to a clinical end-point may not exist”).

145. Fleming, *supra* note 142, at 69–70.

146. *Id.*

147. *Id.* at 71–72 (discussing how to validate and explaining that post-approval confirmation of clinical benefit does not necessarily validate the surrogate, and validation for one pharmacologic class does not validate for all); *cf.* FDA, E9 GUIDANCE, *supra* note 58, at 9 (noting that relationship between surrogate and clinical endpoints “for one product do not necessarily apply to a product with a different mode of action for treating the same disease”).

148. Fleming, *supra* note 142, at 70; Temple, *supra* note 33, at 1655 (noting possibility “that the surrogate end-point only measures what is thought to be the good effect of a drug . . . but ignores potential adverse effects that may be rarer . . . but can undermine a beneficial effect”). Surrogate endpoints also present a statistical challenge; patients may fail to return for follow-up, leading to missing data. The overall survival endpoint does not present this challenge, because vital status can always be determined. Wittes et al., *supra* note 137, at 419.

149. Susan S. Ellenberg & J. Michael Hamilton, *Surrogate Endpoints in Clinical Trials: Cancer*, 8 STAT. MED. 405, 408 (1989) (citing these and other studies in which differences in tumor response did not correlate with differences in survival time).

150. *See, e.g.*, Axel Grothey et al., *Response-Independent Survival Benefit in Metastatic Colorectal Cancer: A Comparative Analysis of N9741 and AVF2107*, 26 J. CLINICAL ONCOLOGY 183, 183 (2008) (finding that objective response did not predict

it was incorrectly assumed that reducing the incidence of ventricular premature beats (surrogate endpoint) in patients after myocardial infarction would improve their survival (clinical endpoint).<sup>151</sup> A three-year study of the anti-arrhythmic drugs Enkaid (encainide) and Tambocor (flecainide) in nearly 2000 patients found the opposite; possibly due to an off-target effect, the drugs increased mortality.<sup>152</sup>

FDA has therefore been cautious with respect to novel surrogate endpoints. Although the agency initially approved some cancer drugs on the basis of objective response, usually tumor shrinkage, by the mid-1980s it was expressing concern about the clinical relevance of these findings.<sup>153</sup> The agency's hesitation pushed drug researchers towards the less risky approach of studying overall survival.<sup>154</sup> This led to a clash with the National Cancer Institute, the head of which complained that "having to do survival data" was "another way of denying access" to cancer drugs.<sup>155</sup> FDA yielded in March 1989, approving Paraplatin (carboplatin), a second generation platinum-based chemotherapy agent, on the basis of objective response.<sup>156</sup> The drug had been developed as a replacement for Platinol (cisplatin), which was one of the most

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the magnitude of survival benefit from the superior therapy and concluding that "tumor response in metastatic colorectal cancer is not a necessary factor for a therapy to provide benefit to an individual patient").

151. Temple, *supra* note 33, at 1655; Hampton, *supra* note 37, at 558.

152. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators, *Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression After Myocardial Infarction*, 321 NEJM 406 (1989).

153. Richard Pazdur, *Endpoints for Assessing Drug Activity in Clinical Trials*, 13 ONCOLOGIST 19, 19–21 (2008) (noting that in the 1970s FDA used objective overall response, i.e., tumor assessment, and then shifted to direct evidence of clinical benefit, i.e., overall survival, health-related quality of life, tumor-related symptoms, and physical function). Dr. Pazdur was the director of FDA's Division of Oncology Drug Products from 1999 to 2005 and the director of the Office of Hematology and Oncology Products from 2005 to 2017; he is now director of FDA's Oncology Center of Excellence.

154. See CARPENTER, *supra* note 30, at 574.

155. *Id.* at 574–75; see also *Phase II Cancer Drug Clinical Trials Showing Anti-tumor Effect Should Be Sufficient Basis for Approval*; National Cancer Institute's Bruce Chabner, PINK SHEET (Jan. 9, 1989) [hereinafter *Phase II Cancer Drug Clinical Trials*] (noting "ongoing argument" between FDA and NCI over approval criteria for anticancer agents, and quoting NCI Division of Cancer Treatment Director that a "demonstration of partial or complete responses in a significant fraction, perhaps 20%, of patients with stages or types of cancer refractory to standard therapy should be sufficient for approval").

156. Paraplatin Package Insert (1990) ("In two randomized controlled trials in patients with advanced ovarian cancer previously treated with chemotherapy, Paraplatin achieved six clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71+ weeks."); see also CARPENTER, *supra*, note 30, at 575.

significant breakthroughs in cancer therapy, but was also highly toxic.<sup>157</sup> Because Platinol was available, however, FDA would approve Paraplatin only as a second-line treatment for advanced ovarian cancer, meaning for patients experiencing a relapse after treatment with another medicine.<sup>158</sup> The agency would not approve the drug for first-line treatment until July 1991, when Bristol-Myers Squibb had data from an overall survival endpoint and a time-to-progression endpoint.<sup>159</sup> FDA then adopted regulations describing approval on the basis of novel surrogate endpoints. These “subpart H” regulations permit “accelerated” approval of a new drug for a serious or life-threatening condition on the basis of a surrogate endpoint “reasonably likely to predict clinical benefit” or a clinical endpoint other than survival (also known as an “interim” or “intermediate” endpoint).<sup>160</sup> The applicant must study, verify, and describe the clinical benefit after approval. Congress later codified accelerated approval.<sup>161</sup>

Despite the creation of an accelerated approval pathway, FDA remains conservative. Medical reviewers as well as officials responsible for medical policy continue to prefer two randomized, placebo-controlled, double-blinded clinical trials, showing a statistically significant difference in measurement of a clinical endpoint.<sup>162</sup> From 2010 to 2014, less than a quarter of the drugs and

157. See *Discovering Early Chemotherapy Drugs*, INST. CANCER RES., <https://www.icr.ac.uk/about-us/our-achievements/our-scientific-discoveries/we-discovered-chemotherapeutic-agents-which-are-still-in-use-more-than-50-years-later> (last visited Mar. 3, 2018).

158. Paraplatin Package Insert, *supra* note 156 (“Paraplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.”); see also *Bristol-Myers’ Paraplatin (Carboplatin) for Ovarian Cancer Recommended for Approval as Second-Line Therapy in Relapsed Patients by FDA Advisory Committee*, PINK SHEET (Jan. 2, 1989). Dr. Temple explained in 1991 that because Platinol was known to improve survival, the agency’s advisors “felt that it was appropriate that the data be mature enough to conclude that the use of carboplatin would not be associated with worse survival.” *Bristol-Myers Squibb’s Paraplatin (Carboplatin) Data Support First-Line Ovarian Cancer Indication Despite Survival Profile Concerns, FDA Finds*, PINK SHEET (July 8, 1991).

159. The revised labeling stated that Paraplatin had demonstrated an “equivalent overall survival rate compared to cisplatin when both were given in combination with cyclophosphamide.” *Bristol-Myers Squibb’s Paraplatin (Carboplatin) Data Support First-Line Ovarian Cancer Indication Despite Survival Profile Concerns, FDA Finds*, *supra* note 158.

160. 21 C.F.R. §§ 314.500–314.560 (2017).

161. 21 U.S.C.A. § 356(c)(2)(A) (West 2018); 21 U.S.C.A. § 355(d) (West 2018).

162. *E.g.*, Joseph W. Cormier, *Advancing FDA’s Regulatory Science Through Weight of Evidence Evaluations*, 28 J. CONTEMP. HEALTH L. & POL’Y 1, 9 (2011); Miriam E. Tucker, *FDA Panel Reviews Nitroglycerin for Anal Fissure: Opinion Was Divided on Whether Three Phase III Trials Demonstrated a “Clinically Meaningful” Effect*, INTERNAL MED. NEWS (June 1, 2006), <https://www.thefreelibrary.com/FDA+panel+reviews+nitroglycerin+for+anal+fissure%3a+opinion+was+divided...-a0147354087> (quoting Dr. Temple that substantial evidence generally requires



biologics approved on the basis of surrogate endpoints (eighteen of the eighty-four) relied on novel surrogate endpoints.<sup>163</sup> The rest used well-established surrogates, like hemoglobin A1C for type 2 diabetes and bone marrow density for osteoporosis.<sup>164</sup> In the twenty-four years since FDA published its accelerated approval regulations, the agency has approved only nineteen non-cancer, non-HIV drugs on the basis of a novel surrogate or interim endpoint.<sup>165</sup>

### 3. Scope of Approval

Use of a surrogate endpoint is meant to shorten time to market and should have benefits in effective patent life. Paraplatin illustrates this. The shortened clinical period for Paraplatin took just over three and a half years. At approval, the drug had roughly seven years of effective life remaining on U.S. Patent No. 4,140,707, which became 9.5 years after patent term restoration. If the company had waited another twenty-four months for approval with overall survival data, it would have had only five years of effective patent life left, which would have become 8.5 years after patent term restoration.<sup>166</sup> Thus, using a clinical endpoint instead of a surrogate endpoint would have cost the company a year of effective patent life, meaning a year of exclusive sales before generic market entry.<sup>167</sup> And it would have extended the premarket research and development period, with no corresponding increase in the data exclusivity period after approval. This product, though, could have been labeled for first-line treatment. Using the surrogate endpoint and accepting the more limited labeling was presumably the rational choice for Bristol-Myers. After all, it provided a revenue stream from the second-line treatment during the clinical outcomes trial, and it resulted in an additional year of effective patent life. It may also have been the

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“at least one study showing a very large effect, or two studies for which the P value is less than .05”).

163. See FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., NOVEL DRUGS APPROVED USING SURROGATE ENDPOINTS (2015), <https://www.fda.gov/downloads/NewsEvents/Testimony/UCM445375.pdf> [hereinafter NOVEL DRUGS].

164. *Id.* None of the ninety-one new molecular entities approved for treatment of rare diseases between 2009 and 2014 were approved on the basis of a novel surrogate endpoint. Emil D. Kakkis et al., *Assessing the Accelerated Approval Pathway for Rare Disease Therapeutics*, 34 NATURE BIOTECH. 380, 380 (2016).

165. Frank J. Sasinowski & Alexander J. Varond, *FDA’s Flexibility in Subpart H Approvals: Assessing Quantum of Effectiveness Evidence*, 71 FOOD & DRUG L.J. 135, 139 (2016).

166. 35 U.S.C.A. § 156(c)(2) (West 2018). Two more years in trials would have cost it two years of effective patent life, but only one of those years would have been recoverable. *Id.*

167. Once approved, generic drugs will capture most of the market. Henry Grabowski et al., *Recent Trends in Brand-Name and Generic Drug Competition*, 17 J. MED. ECON. 207, 212 (2013) (finding that the average new molecular entities experiencing initial generic entry in 2011 and 2012 retained only sixteen percent of the market after one year). The revenue from an additional year of exclusivity before this generic penetration will vary with the product.

socially desirable outcome because it made a less toxic alternative to Platinol available sooner to physicians and patients.

The surrogate endpoint is not, however, simply a shorter pathway to market. This is because FDA does not approve active ingredients alone. It approves a finished product, its intended use, and the words that describe that use. When the agency approves a product on the basis of a surrogate endpoint, the product generally receives a limited indication. Physicians and patients receive access to a prepared medicine containing the new active ingredient, and they may well have an inkling – or even a very good idea – of the hoped-for full indication. But the new product that has been approved is, from a regulatory perspective, a *different* product. Physicians will not have full instructions for the unapproved use, the company will be circumscribed in its ability to discuss what it knows about the unapproved use, and insurers may not cover the drug for unapproved use. Thus although the company may commercialize during this portion of the patent term, much of the regulatory impediment to fully exploiting the patent remains in place.<sup>168</sup> The narrow indication for Paraplatin put the drug in the middle of a debate about off-label prescribing, reimbursement for unapproved uses, and promotion of unapproved uses.<sup>169</sup>

The innovation paradox is that longer research programs lead to lesser rewards for innovation. In cases like Paraplatin, the paradox may be acceptable. In theory, the company had two choices with respect to its product: a surrogate endpoint and limited indication early, or a clinical endpoint and full indication later. We may want to steer companies facing this type of choice towards use of the surrogate endpoint, although if this is desirable because we assume oncologists will use the product for first-line treatment *anyway*, requiring the survival endpoint for the first-line labeling is something of a sham.

In some cases, however, the choice between a surrogate and clinical endpoint is not available, and here the innovation paradox may be unacceptable. Sometimes a firm may have *only* the choice to proceed through a long track, on the one hand, or abandon the compound for another, on the other hand. This is true even in oncology; the *availability* of a surrogate or interim endpoint depends largely on the type of cancer, the drug's mechanism of action, and the

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168. This is why suggestions that companies adopt premarket strategies with longer timelines in order to position the resulting product more competitively in the marketplace do not ring true. See Harold E. Glass et al., *Are Phase 3 Clinical Trials Really Becoming More Complex?*, 49 THERAPEUTIC INNOVATION & REG. SCI. 852, 857 (2015) (hypothesizing that increase in per-patient duration in clinical trials results in part from wanting to make comparative efficacy or cost-effectiveness claims). The history of new drug approvals is replete with examples of products approved on the basis of narrow indications, only to be expanded later to more competitively beneficial labeling as more robust data became available. This is true not only of drugs subject to accelerated approval, for instance, but also products like Jardiance, discussed *infra* note 201.

169. See U.S. GEN. ACCOUNTING OFFICE, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 32–33 (Sept. 1991), <https://www.gao.gov/assets/160/151121.pdf>.

availability of other treatments – considerations outside the sponsor’s control.<sup>170</sup> As to type of cancer: as noted objective response rate does not always predict overall survival in metastatic colon cancer.<sup>171</sup> Meta-analyses suggest progression-free survival correlates moderately well with overall survival in metastatic colon cancer,<sup>172</sup> though not in prostate cancer.<sup>173</sup> As to mechanism of action: whether a drug is cytotoxic (kills cancer cells) or cytostatic (slows or stops the growth of cancer cells, without killing them) can affect whether objective response accurately predicts overall survival.<sup>174</sup> To give another example, immunotherapy drugs for cancer work by stimulating the immune system and do not directly affect tumors, and they sometimes prompt a mild flare (apparent tumor growth) that is not actual disease progression.<sup>175</sup> In these cases, short-term objective response would be misleading. As to other treatments: just as the availability of Platinol meant that FDA expected overall survival data for Paraplatin, where there is no available therapy for the cancer and major tumor changes can be presumed due to the tested drug, FDA is open to objective response and possibly proceeding without a control.<sup>176</sup>

In short, in some cases there may be no alternative to the overall survival endpoint. For non-metastatic cancers, this may require a long follow-up period that triggers an intolerable innovation paradox, meaning that we will have to do without treatment. For example, as one physician from Sloan-Kettering commented at a recent meeting convened at FDA’s behest at Duke’s Margolis Center for Health Policy, “[W]e are not going to have new drugs approved for myeloma if we don’t get [minimal residual disease] as an endpoint.”<sup>177</sup>

So, too, with drugs to treat neurodegenerative disorders. If a disease is characterized by progressive degradation of the nervous system over an extended period of time, proving that a drug modifies the disease or meaningfully changes its ultimate outcome may require an unacceptably long clinical trial –

170. When FDA accepted a surrogate endpoint for Paraplatin, it told the National Cancer Institute that endpoint decisions would be made on a tumor-by-tumor basis. *Phase II Cancer Drug Clinical Trials*, *supra* note 155; *see also* CARPENTER, *supra* note 30, at 576–77; *see generally* BRODY, *supra* note 123, at 197–263 (exploring advantages and disadvantages of differing oncology endpoints based on the disease and other considerations); CANCER ENDPOINTS GUIDANCE, *supra* note 124, at 4–5 (table comparing options).

171. *See generally* Grothey et al., *supra* note 150.

172. Chiara Cremolini et al., *Surrogate Endpoints in Second-Line Trials of Targeted Agents in Metastatic Colorectal Cancer: A Literature-Based Systematic Review and Meta-Analysis*, 49 *CANCER RES. TREATMENT* 834, 841 (2017).

173. Beth Sherrill et al., *Review of Meta-Analyses Evaluating Surrogate Endpoints for Overall Survival in Oncology*, 5 *ONCO TARGETS & THERAPY* 287, 292 (2012).

174. BRODY, *supra* note 123, at 210–11.

175. Sue Sutter, *Cancer Immunotherapies Have FDA, Industry Looking for New Endpoints*, *PINK SHEET* (Oct. 19, 2016).

176. CANCER ENDPOINTS GUIDANCE, *supra* note 124, at 3. Historical controls are another possibility. 21 C.F.R. § 314.126(b)(2)(v) (2017).

177. Sue Sutter, *Cancer Trial Endpoints: Minimal Residual Disease Eyed as Surrogate*, *PINK SHEET* (Sept. 20, 2016).

particularly if the drug must be administered decades before death might be expected. In the therapeutic category of central nervous system drugs there are very few surrogate endpoints to shorten the pathway and lead to a different scope of approval. The innovation paradox may simply steer innovators to other drugs.

Alzheimer's disease provides a cautionary tale. To date, FDA has approved only treatments for relief of the clinical symptoms.<sup>178</sup> Additional treatments might someday delay the onset of dementia or even modify the disease's natural course by affecting its underlying pathophysiology.<sup>179</sup> But new drugs for Alzheimer's fail repeatedly in clinical trials.<sup>180</sup> One study found a 99.6% failure rate in trials performed between 2002 and 2012.<sup>181</sup> We still do not understand the causes of this disease, its genetic and molecular pathways, or why and how it progresses.<sup>182</sup> There are no measurable biological characteristics (biomarkers) that diagnose the disease, predict or measure its progression, or identify successful drug targets.<sup>183</sup> The amyloid hypothesis – that the neurodegeneration in Alzheimer's disease is caused primarily by the deposit of amyloid beta plaques in brain tissue – is nearly twenty-five years old,<sup>184</sup> but amyloid beta plaques have not proven to be a reliable biomarker. In trial after trial, drugs that reduce these plaques have had no measurable clinical impact.<sup>185</sup> The tau hypothesis holds that neurofibrillary tangles in the brain, mainly composed

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178. See FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., TARGETED DRUG DEVELOPMENT: WHY ARE MANY DISEASES LAGGING BEHIND? 6 (July 2015), <https://www.fdanews.com/ext/resources/files/07-15/7-15-FDA-Report.pdf?1519911049> [hereinafter TARGETED DRUG DEVELOPMENT].

179. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY, ALZHEIMER'S DISEASE: DEVELOPING DRUGS FOR THE TREATMENT OF EARLY STAGE DISEASE 5 (Feb. 2013), [https://isctm.org/public\\_access/FDAGuidance\\_AD\\_Developing\\_Drugs\\_Early\\_Stage\\_Treatment.pdf](https://isctm.org/public_access/FDAGuidance_AD_Developing_Drugs_Early_Stage_Treatment.pdf) [hereinafter ALZHEIMER'S GUIDANCE].

180. See Erin McCallister, *Diagnosing AD Trials: Why Diagnostics Are Key to the Development of AD Drugs*, BIOCENTURY (Mar. 3, 2017, 8:31 PM), <https://www.biocentury.com/biocentury/product-development/2017-03-03/why-diagnostics-are-key-development-ad-drugs>.

181. Jeffrey L. Cummings et al., *Alzheimer's Disease Drug-Development Pipeline: Few Candidates, Frequent Failures*, 6 ALZHEIMER'S RES. & THERAPY 37, 41 (2014).

182. TARGETED DRUG DEVELOPMENT, *supra* note 178, at 4.

183. *Id.* Rare genetic forms of the disease are the exception. *Id.*

184. See, e.g., John A. Hardy & Gerald A. Higgins, *Alzheimer's Disease: The Amyloid Cascade Hypothesis*, 256 SCIENCE 184 (1992).

185. Cummings et al., *supra* note 181, at 43; see Nicholas Kozauer & Russell Katz, *Regulatory Innovation and Drug Development for Early-Stage Alzheimer's Disease*, 368 NEJM 1169, 1169–70 (2013); TARGETED DRUG DEVELOPMENT, *supra* note 178, at 4; McCallister, *supra* note 180.

of the protein *tau*, are the primary causative factor, but the first anti-tau drug to reach phase 3 also failed to show any improvement in cognition.<sup>186</sup>

One possibility is that treatments need to intervene earlier in the natural history of the disease.<sup>187</sup> The problem is that Alzheimer's disease progresses slowly, and showing delayed onset of dementia would require a time-to-event endpoint, comparable to oncology's survival analysis.<sup>188</sup> So the question becomes whether surrogate endpoints are available. There are no validated surrogates, leaving only the possibility of novel surrogates and limited labeling. In the preclinical stages of Alzheimer's disease, although functional impairment has not begun, there are subtle cognitive deficits.<sup>189</sup> It is also possible to measure subtle cognitive improvements. Moreover, these improvements are viewed as reasonably likely to predict delayed onset of dementia.<sup>190</sup> As a result FDA will permit accelerated approval using improved cognitive benefit as a novel (not validated) surrogate marker for *delayed onset of dementia*, which will then be evaluated after approval.<sup>191</sup> But there is no pathway for accelerated approval of a drug to *modify the course of the disease itself*.<sup>192</sup> There is no reliable evidence that *any* biomarker is reasonably likely to predict a lasting effect on the disease course. So accelerated approval is not an option.<sup>193</sup>

If indeed trials for Alzheimer's treatments need to begin early in the natural history of the disease, during the preclinical stages, the conundrum is clear.<sup>194</sup> The paradoxical patent term and the flat exclusivity term may discourage companies from investing in these treatments rather than in drugs for short-term use that can be studied quickly or drug classes and diseases with validated surrogate endpoints.

186. See Andrew Pollack, *Alzheimer's Drug LMTX Falters in Final Stage of Trials*, N.Y. TIMES (July 27, 2016), [https://www.nytimes.com/2016/07/28/business/alzheimers-drug-lmtx-trial.html?\\_r=0](https://www.nytimes.com/2016/07/28/business/alzheimers-drug-lmtx-trial.html?_r=0).

187. Kozauer & Katz, *supra* note 185, at 1169–70 (noting a “leading theory” that “attempts at intervention [are occurring] too late in the progression of disease”). The authors are medical officers in FDA's Division of Neurology Products.

188. ALZHEIMER'S GUIDANCE, *supra* note 179, at 2 (“The underlying anatomical and pathophysiologic changes in AD begin many years before clinical symptoms emerge.”); *id.* at 4 (“The use of a time-to-event survival analysis approach (e.g., time to a diagnosis of dementia) is a particularly appealing primary efficacy measure in clinical trials in early AD. For practical reasons, trials designed with this endpoint have been generally conducted in the stages of the illness nearest to the onset of dementia . . .”).

189. *Id.*

190. *Id.*

191. *Id.*

192. *Id.* at 5.

193. *Id.*; TARGETED DRUG DEVELOPMENT, *supra* note 178, at 4.

194. Another possibility, of course, is that we misunderstand the disease mechanism altogether. See McCallister, *supra* note 180 (noting that researchers are also considering neuroinflammation, vascular pathology, loss of protein homeostasis, and mitochondrial dysfunction and noting the “lack of biomarkers for therapies with targets outside of amyloid and tau aggregation pathways”).

### B. Safety Testing Requirements

In recent years, concerns about long-term drug safety have led to an increase in premarket safety testing requirements for certain classes of drugs. Hostile congressional oversight and perennial funding problems (which leave the agency at the legislature's mercy) have always motivated agency officials to avoid approval of drugs that turn out, with broader and uncontrolled clinical use, particularly long-term use, to have an *unfavorable* balance of risk and benefit.<sup>195</sup> A series of high profile drug withdrawals in the 1990s and early 2000s may have made avoiding these errors more salient.<sup>196</sup> Although additional safety testing may reduce Type I errors, the concern from an innovation policy perspective is that it also delays the approval of drugs that turn out to have *acceptable* risk-benefit balances. The new requirements affect certain types of drugs – those intended for long-term use – more than others. For instance, after emerging long-term data suggested an elevated risk of heart attacks in patients treated with Avandia (rosiglitazone maleate) for type 2 diabetes, FDA decided that all sponsors of new diabetes treatments should conduct cardiovascular outcomes safety trials, even if no safety signal emerged in preclinical or clinical testing.<sup>197</sup> The requirement has now spread to new obesity drugs and may

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195. Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA. L. REV. 305, 320 (2011) (noting tendency to avoid “type 1” errors, meaning false positives, or approvals that should not have happened); Louis Lasagna, *Congress, the FDA, and New Drug Development: Before and After 1962*, 32 PERSP. BIOLOGY & MED. 322, 335 (1989) (noting that FDA is usually hauled before Congress for drug safety problems and not for failure to approve products).

196. See Michael Dickson & Jean Paul Gagnon, *Key Factors in the Cost of New Drug Discovery and Development*, 3 NATURE REVIEWS DRUG DISCOVERY 417, 419 (2004) (suggesting that a decline in submitted NDAs was attributable to increased testing requirements following recalls in the 1990s). The drugs in question were Redux (dexfenfluramine), Pondimin (fenfluramine), Posicor (mibefradil), and Duract (bromfenac) in 1997, followed by Rezulin (troglitazone) in 2000, and Vioxx (rofecoxib) in 2004 and Bextra (valdecoxib) in 2005. The safety issues varied. For instance, fenfluramine was associated with cardiac valvulopathy, while bromfenac was hepatotoxic. See generally Ruowei Li et al., *Dose-Effect of Fenfluramine Use on the Severity of Valvular Heart Disease Among Fen-phen Patients with Valvulopathy*, 23 INT’L J. OBESITY 926 (1999); Robert J. Fontana et al., *Acute Liver Failure Associated with Prolonged Use of Bromfenac Leading to Liver Transplantation*, 5 LIVER TRANSPLANTATION & SURGERY 480 (1999).

197. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., DIABETES MELLITUS – EVALUATING CARDIOVASCULAR RISK IN NEW ANTIDIABETIC THERAPIES TO TREAT TYPE 2 DIABETES 3–4 (Dec. 2008), <https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf>; Kate Rawson & Michael McCaughan, *CV Outcomes Trials in Diabetes: First Results Suggest “Goalpost” Model Here to Stay*, PINK SHEET (May 11, 2015) (noting connection to Avandia); Mervyn Turner, *Embracing Change: A Pharmaceutical Industry Guide to the 21st Century*, in TRANSLATIONAL MEDICINE AND DRUG DISCOVERY 328, 329 (Bruce H. Littman & Rajesh Krishna eds., 2011) (discussing requirement).

spread further.<sup>198</sup> To give another example, FDA recently asked the sponsor of a new antibiotic, solithromycin, to conduct a 9000-patient liver safety study prior to approval.<sup>199</sup> Whether the obligation to conduct long-term premarket safety studies will affect particular therapeutic categories or pharmacologic classes more than others remains to be seen.

These new requirements will protect premarket timelines. The primary goal in a cardiovascular outcomes safety trial, for instance, is to demonstrate no increased risk of cardiovascular events. By design the trials are often “event driven” – meaning that the design requires waiting until a pre-specified number of specific cardiovascular events (such as death, myocardial infarction, or stroke) have occurred. As a result, these trials can be larger and longer than other trials in the premarket clinical program – up to seven years in length, for instance, or involving as many as 16,000 patients.<sup>200</sup> It may be possible to obtain approval while such a trial is ongoing, once sufficient interim data have accrued for a cardiovascular safety meta-analysis.<sup>201</sup> But the additional testing

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198. Cathy Dombrowski, *CV Risk Assessment for All Obesity Drugs Seems Inevitable Pre-approval Requirement*, PINK SHEET (Mar. 29, 2012); Donna Young, *US FDA Panel Calls for Additional CV Studies for Weight-Loss Drugs*, PINK SHEET (Mar. 30, 2012); Michael McCaughan, *The Inevitable Outcome: Diabetes Safety Model Expands to Weight Loss . . . and Beyond?*, PINK SHEET (May 1, 2012).

199. Michael Cipriano, *Cempra’s Solithera Draws FDA Complete Response Letter on Liver Risks*, PINK SHEET (Dec. 29, 2016).

200. Boaz Hirshberg & Arie Katz, *Cardiovascular Outcome Studies with Novel Antidiabetes Agents: Scientific and Operational Considerations*, 36 DIABETES CARE S253, S254 (2013).

201. See, e.g., CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., NDA 204629, CROSS DISCIPLINE TEAM LEADER REVIEW (July 31, 2014), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2014/204629Orig1s000CrossR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000CrossR.pdf) (noting that clinical review of Jardiance (empagliflozin) presents cardiovascular safety analysis separately from main review, due to inclusion of interim data from ongoing trial and need to protect trial integrity by maintaining confidentiality); CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., NDA 204629, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S) (July 18, 2014), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2014/204629Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000ClinPharmR.pdf) (omitting pages 166–179 in the public version). Such a trial could also support a claim of superiority with respect to cardiovascular outcomes. These studies use a non-inferiority design, intended to show that the new drug is not materially worse than the control. A non-inferiority study that shows superiority to the active control can support a claim of superiority without statistical adjustment. Cf. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: NON-INFERIORITY CLINICAL TRIALS TO ESTABLISH EFFECTIVENESS 18 (Nov. 2016), <https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf>; see also Sue Sutter, *Can a Safety Study Support a Superiority Claim? Barely, US FDA Advisors Say*, PINK SHEET (July 4, 2016) (describing FDA’s recommendation to increase enrollment rather than conduct a second study of Jardiance to support superiority claim and describing the protocol changes needed); Michael McCaughan, *Diabetes Outcomes Trial Requirement Looks ‘Increasingly Wise’ – FDA’s Temple*, PINK SHEET (Sept. 1, 2016) (noting Dr. Temple’s view that the trial

has delayed approval, and each year of this testing costs half a year of effective patent life. In short, certain therapeutic categories associated with long-term use of medicines are now associated with a safety testing burden that could lengthen their time to market – with a direct cost in effective patent life – relative to other therapeutic categories.

### C. Continuing Evolution in the Paradigm

In recent years, as we have gained a better understanding of the molecular basis of pathological disease processes and the body's response to drugs, the basic approach to drug discovery has evolved.<sup>202</sup> Some hope this shift will reduce the number of failed drugs (the attrition rate) and shorten research and development timelines for successful drugs.

The traditional approach was phenotypic, working from observable results. It involved screening new compounds in animals to determine their pharmacological effects and then, on the basis of inference from the animal models, planning and conducting a clinical program for a human drug.<sup>203</sup> The new approach involves selection of a biological target – based on a greater understanding of disease pathways, enzymes that play important roles in those pathways, and cell surface receptors that bind to molecules and change cell behavior – and screening chemical libraries for compounds that affect the target in question.<sup>204</sup> The new approach results in a larger group of candidate compounds and requires a strategy for sorting out the most promising from the others.<sup>205</sup> Typically, this means clinical pharmacology work: a small human trial to prove the compound's mechanism of action, meaning its effect on the biological target of interest, not its effect on any particular disease or condition.<sup>206</sup> Proof of mechanism is followed by clinical studies to determine whether the proof of mechanism translates to clinical effectiveness, meaning its ability to accomplish a particular outcome with respect to a particular disease or condition.<sup>207</sup>

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reported “decreased CV mortality” and a reduction in “serious heart failure” which are “potential claims that are novel for the class”).

202. Editorial, *Looking Back on the Millennium in Medicine*, 342 NEJM 42, 48 (2000) (noting that “major advances in drug therapy could not occur until there was sufficient understanding of physiology and pathophysiology to permit rational identification of targets for drugs”).

203. Bruce H. Littman, *Translational Medicine: Definition, History, and Strategies*, in TRANSLATIONAL MEDICINE AND DRUG DISCOVERY, *supra* note 197, at 3, 3.

204. *Id.* at 4–6; *see also* ERLAND STEVENS, *MEDICINAL CHEMISTRY: THE MODERN DRUG DISCOVERY PROCESS* 15, 95–100 (2014).

205. Littman, *supra* note 203, at 4.

206. *Id.* at 7–13.

207. *Id.*



This is “translational” medicine, and it differs fundamentally from the experimental approach of screening compounds in animals.<sup>208</sup> Translational medicine is viewed as having an enormous upside. It will work from biological theory rather than trial and error; it is multidisciplinary, leveraging the expertise of statisticians, laboratory medicine, engineers, and programmers; and it should push promising compounds into clinical testing earlier. FDA has embraced translational medicine, for example by issuing guidance that accommodates the earlier shift to human testing.<sup>209</sup> The agency will accept a smaller and simpler submission – an “exploratory IND” – supporting what many call the “phase 0” trial.<sup>210</sup> This trial typically involves administration of a micro-dose, or a dose expected to have pharmacologic but not toxic effects, to a very small number of individuals.<sup>211</sup> Because the study size is small and the dose low, the preclinical safety package to support an exploratory IND can be smaller than the preclinical package required to support a conventional IND – perhaps five or six studies performed over three to six months, instead of the usual nine to twelve studies that take as long as eighteen months.<sup>212</sup> Moreover, the clinical program should itself be shorter. If compounds are correctly identified on the basis of biological theory, they could have a more significant effect on the disease in question, which could make it possible to show effectiveness with smaller and shorter phase 3 trials.<sup>213</sup> Thus, the thinking goes, translational medicine will reduce the number of failed drugs and shorten premarket timelines.

This potential has not yet been realized. The overall attrition rate for new drugs remains high – “horrendously high” according to NIH Director Francis

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208. FDA CRITICAL PATH REPORT, *supra* note 85, at ii; *see generally* Francis S. Collins, *Reengineering Translational Science: The Time is Right*, 3 SCI. TRANSLATIONAL MED. 1 (2011) (describing the process of translational medicine).

209. *See* FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND REVIEWERS: EXPLORATORY IND STUDIES (Jan. 2006), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078933.pdf> [hereinafter EXPLORATORY IND GUIDANCE]; *see also* OFFICE OF TRANSLATIONAL SCI., U.S. FOOD & DRUG ADMIN., FDA STAFF MANUAL GUIDES, VOLUME I—ORGANIZATIONS AND FUNCTIONS 1–2 (Dec. 10, 2012), <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM348370.pdf> (describing creation of Office of Translational Sciences and explaining its responsibilities); Collins, *supra* note 208, at 1 (announcing establishment of a new National Center for Advancing Translational Sciences, at the National Institutes of Health).

210. *See* Collins, *supra* note 208, at 3.

211. *Id.* at 1; *see also* DAVID JACOBSON-KRAM, OVERVIEW OF THE EXPLORATORY IND: DIFFERENCES FROM THE TRADITIONAL IND 7–8 (Oct. 4, 2007), <http://www.nationalacademies.org/hmd/~media/92B1B2A5B6A14D8496B3FF315DF50763.ashx>.

212. *See* EXPLORATORY IND GUIDANCE, *supra* note 209, at 4; JACOBSON-KRAM, *supra* note 211, at 14.

213. Abeloff, *supra* note 129.

Collins – and may be increasing.<sup>214</sup> Recent estimates place the phase 2 failure rate at sixty-five to seventy percent and even higher for drugs with new mechanisms of action.<sup>215</sup> Some research suggests the attrition stems mostly from lack of effectiveness, which may follow naturally from bringing a larger number of candidate compounds into human trials in the first instance, with less certainty about their ultimate clinical potential.<sup>216</sup> In translation medicine, an

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214. Collins, *supra* note 208, at 1; *see also* Bruce H. Littman, *Preface to TRANSLATIONAL MEDICINE AND DRUG DISCOVERY*, xix, xix (calling the attrition rate “unsustainable”); FDA CRITICAL PATH REPORT, *supra* note 85, at R-4 (stating that a “new compound entering human trials in 2000 was no more likely to reach the market than one entering human testing in 1985”); U.S. GOV’T ACCOUNTABILITY OFFICE, *NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS* 25 (Nov. 2006), <https://www.gao.gov/new.items/d0749.pdf> (noting that clinical trial failure rates increased during the period 1996 through 1999 to ninety-one percent during the period 2000 through 2003); Ismail Kola & John Landis, *Opinion, Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 *NATURE REVS. DRUG DISCOVERY* 711, 712 (2004) (noting the declining success rates of phase 3 trials from the 1990s to 2000s); Turner, *supra* note 197, at 330 (stating that translational medicine does not seem to increase success rates in phase 2 or phase 3).

215. Littman, *supra* note 203, at 21; *see also* David C. Swinney & Jason Anthony, *How Were New Medicines Discovered?*, 10 *NATURE REVS. DRUG DISCOVERY* 507, 507 (2011) (examining seventy-five first-in-class drugs with new molecular mechanisms of action approved between 1999 and 2008, finding that substantially more resulted from phenotypic screening than from target-based approach, and postulating that a target-centric approach “may contribute to the current high attrition rates and low productivity” in drug research and development); JACOBSON-KRAM, *supra* note 211, at 14–15.

216. Littman, *supra* note 203, at 21 (noting two studies that attributed failures to lack of effectiveness); Turner, *supra* note 197, at 330 (less certainty about their “properties and clinical potential”). The high failure rate could also stem from (1) the fact that the easy solutions to chronic diseases of aging have already been found, leaving the more difficult solutions to these diseases for now, and (2) the fact that researchers are now focusing on diseases that are simply harder to solve; progressive diseases of the central nervous system are one notorious example. *See id.* at 329 (arguing that after Hatch-Waxman, industry “entered a period of declining productivity, driven in large part by its own success in innovating therapies with clear-cut etiologies and treatment paradigms that essentially made differentiated new drugs more difficult to discover and develop”); *see also* Joseph Cook et al., *The Future Costs, Risks, and Rewards of Drug Development: The Economics of Pharmacogenomics*, 27 *PHARMACOECON.* 355, 360 (2009) (noting possibility that “past research has already addressed those medical needs most easily solved, causing the number of compounds that might need to be studied to resolve an unmet medical need to increase”). One recent empirical study, which examined a large international database containing information on research and development of more than 28,000 compounds since 1990, found that companies are increasingly focusing on more difficult targets characterized by high failure rates and that this “re-orienting” of investment accounted for most of the recent decline in productivity in research. Fabio Pammolli et al., *The Productivity Crisis in Pharmaceutical R&D*, 10 *NATURE REVS. DRUG DISCOVERY* 428, 436 (2011).

entire drug development program can crumble if the biological target is misunderstood. For instance, the biological target might turn out to be merely associated with the disease or with disease progression, rather than lying in the disease's causal pathway.<sup>217</sup> Or the disease may turn out to have redundant pathways; modulating the biological target may simply shut off one pathway, causing the body to compensate by enhancing disease progression through another pathway.<sup>218</sup> Unexpected safety problems may also account for a substantial amount of attrition.<sup>219</sup> In the end, we are still profoundly limited in our ability to predict, before phase 2 and 3 trials, whether modulating any particular biological target will achieve a desirable clinical outcome and whether it will have acceptable side effects.<sup>220</sup> The translational approach is limited by our lack of scientific capacity to predict the full spectrum of clinical effects that will result from modulating a particular biological target.

Industry has been slow to embrace the exploratory IND. Although the reasons for this are unclear, going into early human testing with less information about any ultimate clinical potential has important implications for the length of the post-market reward period. Proof of mechanism testing in humans – the initial phase 0 trial that screens a large number of compounds at micro-doses in very small numbers of human subjects – does not start a development project down the traditional runway to regulatory approval the way a phase 1 trial did in 1984. At this stage in translational drug development, researchers may have little idea of the nature of any eventual medicine that might be proposed at the end of the process. There may be a substantial gap before phase 2 trials occur and an even more substantial gap before trials to assess a clinical endpoint. Moreover, although the proof of mechanism testing might screen a large number of compounds, a company generally selects only one or a few for phase 2 and only one for the full clinical program. If the company

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217. TARGETED DRUG DEVELOPMENT, *supra* note 178, at 2 (“[B]iochemical targets and biomarkers that appear to be linked to the disease progression often fail because, while associated with the disease, they are not directly in the *causal* pathway . . . .”); Jack W. Scannell et al., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 NATURE REV. DRUG DISCOVERY 191, 195 (2012) (noting that “if the causal link between single targets and disease states is weaker than commonly thought, or if drugs rarely act on a single target, one can understand why the molecules that have been delivered by this research strategy into clinical development may not necessarily be more likely to succeed than those in earlier periods” (footnotes omitted)).

218. *See, e.g.*, STEVENS, *supra* note 204, at 20.

219. Business decisions may account for the remainder of the attrition. John Arrowsmith, *A Decade of Change*, 11 NATURE REV. DRUG DISCOVERY 17, 17 (2012) (“The weakest link in the chain was, and still is, in Phase II, where around 50% of failures are typically due to efficacy, 30% are due to strategic reasons and 20% are due to safety concerns.” (footnote omitted)).

220. PCAST REPORT, *supra* note 12, at 17–18 (noting that our current success rate is “around 9 percent” and that our “greatest need is for improved methods for target validation”); FDA CRITICAL PATH REPORT, *supra* note 85, at R-10 (arguing that academia, industry, and agency need to develop better predictive tools to screen candidates in the first instance).

must return to the drawing board because translation fails, it might select a runner-up compound, but this could be some time after the exploratory screening in humans. And yet, conventional wisdom still generally counsels that a patent application should be filed *before* clinical testing starts. If the preclinical period is shorter, this may mean the patent application is filed earlier in time (relative to market launch) and the effective patent life shorter, unless the clinical period (from phase 0 testing to NDA submission) is itself the same or shorter.

The high failure rate is therefore concerning. When a biological target and compound are generally understood but several rounds of clinical trials are required to optimize the compound's therapeutic potential, the clock is ticking on the active ingredient patent. One agency scientist noted in 2007 that the perception that exploratory INDs *protract* the clinical timeline may be one reason industry has not fully embraced them.<sup>221</sup> Perhaps not surprisingly there is renewed interest in the phenotypic approach to drug development.<sup>222</sup>

Continuing evolution in clinical trial and statistical methodologies also have the potential to shorten phase 3 trials in the years ahead.<sup>223</sup> One possibility is enrichment strategies, which use patient characteristics to select a study

221. JACOBSON-KRAM, *supra* note 211, at 22.

222. See generally Wei Zheng et al., *Phenotypic Screens as a Renewed Approach for Drug Discovery*, 18 DRUG DISCOVERY TODAY 1067 (2013) (arguing that use of cell-based phenotypic assays to screen compound libraries could lead to a new era of drug discovery); Bridget K. Wagner, *The Resurgence of Phenotypic Screening in Drug Discovery and Development*, 11 EXPERT OPINION DRUG ON DISCOVERY 121, 124 (2016) (arguing that “[i]n the interest of saving costs from late-stage clinical failures, it would seem attractive for the pharmaceutical industry to take phenotypic approaches more frequently during screening campaigns”); see also Michael Leviten, *The Phenomics Phenomenon: Why Phenotypic Screens are Making a Comeback*, BIOCENTURY (Mar. 23, 2017, 6:51 PM), <https://www.biocentury.com/bc-innovations/tools-techniques/2017-03-23/why-phenotypic-screens-are-making-comeback> (suggesting renewed interest in phenotypic approach “after several analyses published on the origins of new medicines surprisingly showed that most came from phenotypic studies rather than the target driven approaches dominating the industry”). Thanks to improved cell-based models of disease, better imaging techniques, and improved computation capabilities, the new phenotypic approach may be more efficient than the phenotypic screens of the 1980s. *Id.*

223. In addition to the enrichment strategies and adaptive design discussed in text, a shift from frequentist to Bayesian statistical methods may permit smaller trials and thereby shorten phase 3 timelines. PCAST REPORT, *supra* note 12, at 21 (noting that Bayesian design may allow smaller trials). Increased use of Bayesian methods has been anticipated for some time. See generally Edmund A. Gehan, *Biostatistics in the New Millennium: A Consulting Statistician's Perspective*, 9 STAT. METHODS MED. RES. 3 (2000) (predicting a shift from frequentist statistical analysis to Bayesian methods, or empirical Bayesian methods); Robert Temple, *How FDA Currently Makes Decisions on Clinical Studies*, 2 CLINICAL TRIALS 276, 276, 278–80 (describing several drug approvals where the agency had departed from frequentist analysis and used “some of the thinking processes that are involved in Bayesian approaches”); see also FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., PDUFA REAUTHORIZATION

population in which detection of drug effect is more likely (or the effect more significant or noticeable).<sup>224</sup> As a statistical matter, this allows a smaller and shorter trial.<sup>225</sup> To give a concrete example: Genentech used genetic information to prescreen breast cancer patients for trials of the biological medicine Herceptin (trastuzumab), which cut the trial from ten years to 1.6 years. Screening permitted enrollment of 470 patients who were expected to have a fifty percent response rate. To get the same number of positive responses *without* the genetic screen, Genentech would have needed to enroll 2200 patients with a ten percent response rate.<sup>226</sup> Another possibility is adaptive trial design. This innovation responds to the fact that post hoc subgroup analyses of large datasets often suggest that a trial limited to that subgroup would have been successful. FDA uniformly rejects post hoc subgroup analyses, however, and starting over protracts the timeline. An adaptive trial design pre-specifies subgroups of interest and plans protocol changes on the basis of accumulating data.<sup>227</sup> Whether the sponsor uses enrichment or adaptive trial design, however, the resulting approved new drug is labeled narrowly for the particular stratified patient subset. The sponsor, healthcare professionals, insurers, and patients thus face the same trade-offs as in the Paraplatin example.

## V. PREMARKET RESEARCH FROM 1984 TO 2016

The innovation paradox is that the post-market reward is flat or decreases if a company spends more time in premarket research and development. It is true of patents regardless of field of technology, and it should generally skew

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PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022, at 31, <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf> (last visited Mar. 3, 2018) (committing to facilitating the use of “complex adaptive, Bayesian, and other novel clinical trial designs”).

224. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: ENRICHMENT STRATEGIES FOR CLINICAL TRIALS TO SUPPORT APPROVAL OF HUMAN DRUGS AND BIOLOGICAL PRODUCTS 2 (Dec. 2012), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf> [hereinafter ENRICHMENT STRATEGIES].

225. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., PAVING THE WAY FOR PERSONALIZED MEDICINE 54 (Oct. 2013), [https://dx.adva-med.org/sites/dx.adva-med.org/files/resource/fda\\_report\\_on\\_paving\\_the\\_way\\_for\\_personalized\\_medicine.pdf](https://dx.adva-med.org/sites/dx.adva-med.org/files/resource/fda_report_on_paving_the_way_for_personalized_medicine.pdf) [hereinafter PAVING THE WAY] (stratifying a disease “can dramatically shorten overall drug development and review times”); see generally ENRICHMENT STRATEGIES, *supra* note 224.

226. Cook et al., *supra* note 216, at 357.

227. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: ADAPTIVE DESIGN CLINICAL TRIALS FOR DRUGS AND BIOLOGICS 7–14 (Feb. 2010), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>; see Anup Malani et al., *Accounting for Heterogeneous Treatment Effects in the FDA Approval Process*, 67 FOOD & DRUG L.J. 23, 25 (2012); see also Deepak L. Bhatt & Cyrus Mehta, *Adaptive Designs for Clinical Trials*, 375 NEJM 65 (2016) (offering four case studies).

firms to projects with shorter time to market or to decisions within a project that shorten the time to market. The concern is that in the field of medicine the impact is *different* – that due to the theory of our new drug approval system, the paradox will skew choices away from particular development programs and therefore types of medicine. The impact of the paradox may, however, be unknowable. FDA approves roughly as many new molecular entities per year as it ever did, but we have no way of knowing the drugs that would have been developed and approved had the incentive structure been different.

Parts II and IV of this Article suggest some hypotheses, however, that are relevant to understanding the paradox: (1) the preclinical research period has been getting shorter; (2) the clinical period has increased in length, at least for some types of product; (3) there is variability in the length of the clinical testing period by therapeutic category and perhaps also within therapeutic categories; (4) surrogate endpoints can shorten the clinical testing period; and (5) certain types of product will generally require a longer research and development period. Products that generally require a longer research and development period should be those intended for long-term use to prevent, delay, or mitigate a later-in-life clinical event (except where a validated surrogate endpoint is available) and those intended to modify the natural history of a progressive or degenerative disease. Because FDA publishes information about the length of the clinical testing period in connection with applications for patent term restoration, it is possible to describe these points empirically.

### A. Dataset and Methodology

The dataset used in this section relates to 570 distinct regulatory review periods – clinical testing followed by FDA review of a new drug application – each of which resulted in approval of a product with a new active ingredient, meaning an active ingredient not previously approved for use in humans.<sup>228</sup> The dataset of 570 regulatory review periods was generated as follows.

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228. Sometimes a single premarket program leads to more than one application. The analysis in this subsection focuses on distinct regulatory review periods rather than distinct applications. For instance, Parke-Davis and Warner Lambert collaborated with Sankyo in the development of troglitazone for treatment of type II diabetes. The companies submitted companion NDAs for Rezulin and Prelay, which were approved on the same day with identical labeling (apart from the brand name and manufacturer name). There was only one regulatory review period, and PTO restored only one patent, which protected both products. *See generally* U.S. PATENT & TRADEMARK OFFICE, APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 FOR U.S. PATENT 4,572,912 (Feb. 27, 1997). The regulatory review period was counted once in the analysis. In another instance, PTO restored two patents in connection with the same regulatory review period. Application 21,446 for Lyrica (pregabalin) covered treatment of neuropathic pain associated with diabetic neuropathy, and application 21,723 covered treatment of post-herpetic neuralgia. According to FDA, the Lyrica application was “administratively split” by indication because the review divisions and timelines were different. *See* CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., APPROVAL PACKAGE FOR NDA 21-446,

*First*, PTO provided a spreadsheet of all patent term restoration applications received between September 28, 1984, and September 30, 2016. PTO also maintains a table of patent term restoration grants on its website.<sup>229</sup> Neither is complete, and the lists were therefore combined and the duplicates deleted.<sup>230</sup> *Second*, the approved new drugs were pulled for analysis. Section 156 authorizes patent term restoration for other regulated products, such as food additives and medical devices. These were excluded.<sup>231</sup> *Third*, only approved new drugs for which FDA had published a regulatory review period on or before October 1, 2016, comprised the final dataset. The agency does this if it concludes that the NDA in question resulted in the first commercial marketing of the active ingredient, that is, if it concludes that the active ingredient was new.<sup>232</sup>

At the end of this process, the dataset contained 570 distinct regulatory review periods. This comprises every NDA for a new active ingredient as to which FDA had calculated a regulatory review period by October 1, 2016. This Part refers to these as *570 new drugs*, *NDAs*, or *products*; each corresponds to a distinct regulatory review period associated with a distinct and new active ingredient and usually only one NDA.<sup>233</sup> In five cases, however, the applicant

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ADMINISTRATIVE/CORRESPONDENCE REVIEWS (July 28, 2004) (Office Director's Sign-Off Memorandum); Pfizer Inc. v. Teva Pharm. U.S.A., Inc., 882 F. Supp. 2d 643, 656 (D. Del. 2012) (explaining that because FDA approved two Lyrica applications on the same day, PTO agreed that two patents were entitled to restoration). The regulatory review period was counted only once in the analysis.

229. *Patent Terms Extended Under 35 U.S.C. § 156*, U.S. PAT. & TRADEMARK OFF., <https://www.uspto.gov/patent/laws-and-regulations/patent-term-extension/patent-terms-extended-under-35-usc-156> (last visited Mar. 2, 2018).

230. For instance, the spreadsheet omitted – but the table included – Atrovent (ipratropium). The table omitted – but the spreadsheet included – more than fifty new drugs with restored patents, including Savella (milnacipran hydrochloride), Potiga (ezogabine), and Myfortic (mycophenolic acid). It is impossible to rule out the possibility that some patent term restoration applications were omitted from both documents, but no other regulatory review periods were published in the Federal Register.

231. This was done by categorizing the products on the basis of regulatory provisions – new drug approval, biological product licensure, medical device approval or clearance, new animal drug approval, or food additive petition – applied by FDA.

232. FDA calculated one regulatory review period and later concluded that the product did not contain a new active ingredient. The drug is Adsol, used for collection and storage of blood and blood components. It was excluded from the dataset because the dataset was defined as all approved *new active ingredient drugs* for which FDA had published a regulatory review period by October 1, 2016, when data collection closed.

233. Although FDA has calculated 570 regulatory review periods, these did not all result in patent term restoration. One request – Bextra (valdecoxib) – was ultimately denied because the request had not been timely filed, and another – Zemuron (rocuronium bromide) – received no actual restoration because the applicant already had fourteen years of effective life on the patent proposed for restoration. Also, there were thirty-four calculated regulatory review periods for which the patent term restoration request was still pending on October 1, 2016.

performed its clinical testing in another country.<sup>234</sup> These applicants therefore never filed INDs; they proceeded straight to NDAs. The problem is that section 156 defines the testing period, for purposes of patent term restoration, as beginning on the date the IND took effect. As a result, for these five NDAs, FDA calculated the testing period as zero days. This does not mean, however, that the drugs spent zero days in clinical trials; it simply means the patent term restoration notices do not provide data for analysis. These five drugs are *omitted* from the analysis that follows.

### B. Preclinical Testing Period

The shift to translational medicine should, in theory, put promising compounds into human trials earlier, truncating the preclinical testing period. The dataset does not provide reliable information about the date that the applicant, or any other company, started testing the molecule in the laboratory. For the length of the preclinical research period, therefore, the analysis uses an imperfect proxy: the time from the earliest filing of a patent application to the time that the clinical testing period began. The patents reviewed in each case were the patents listed by the NDA holder in the *Orange Book*, as well as the restored patent, if it was not listed.<sup>235</sup> The *Orange Book* lists any patent claiming the drug or an approved method of using the drug and should generally include the initial active ingredient patent, if there was one.<sup>236</sup> Because the goal was to identify the earliest possible point in time when preclinical work might have been underway, the earliest available date was used.<sup>237</sup> The effective date of the IND, published by FDA in the Federal Register, served as the end of the preclinical period.

Fourteen drugs were excluded from the preclinical analysis. These drugs were never associated with any listed patents, even though the drugs were eligible for patent listing. For these drugs, the only patent in the dataset is the patent proposed for restoration. The statute required these firms to list any patent claiming the drug itself,<sup>238</sup> so the lack of any listed patents means the

234. These are Xyzal (levocetirizine dihydrochloride), DaTscan (ioflupane I-123), Coartem (artemether; lumefantrine), Promit (dextran 1), and Lac-Hydrin (ammonium lactate).

235. The *Orange Book* is in its 37th edition. See APPROVED DRUG PRODUCTS, *supra* note 90. The information in the current print edition also appears in an electronic database on the FDA website, but neither lists expired patents. *Id.* To determine the patents listed for each NDA in the dataset, all prior annual print editions of the *Orange Book* were reviewed.

236. See *id.* (section titled “Patent and Exclusivity Lists”).

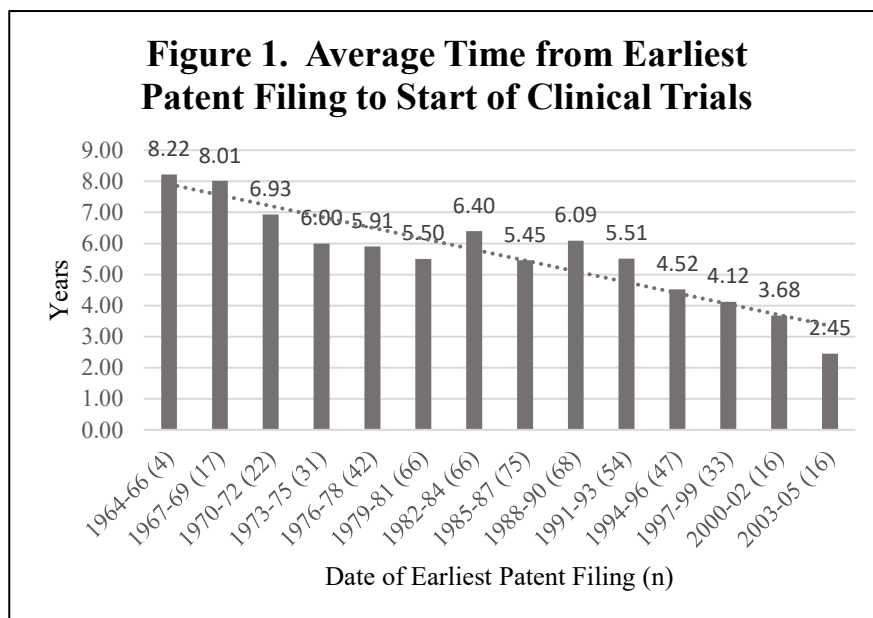
237. This was the earliest of the actual filing date of the application to hand, the filing dates of any related U.S. applications, the priority date of any foreign patent application cited by the patentee, and any Patent Cooperation Treaty (“PCT”) filing date. The goal was to identify a reasonable proxy for the earliest point in time that the applicant might have been doing preclinical work.

238. 21 U.S.C.A. § 355(b)(1) (West 2018).



restored patent was *not* an active ingredient patent. These drugs were therefore *omitted* from analysis of the preclinical period.

After excluding the fourteen drugs without patent listings and the five drugs tested overseas, the remaining 551 new active ingredient drugs had an average preclinical period of 5.61 years (median 4.8, standard deviation 4.13). To examine a possible time trend in the length of the preclinical testing period, the 551 drugs were sorted by the patent filing date, which had served as a proxy for the start of preclinical research. The earliest patent filing date was September 5, 1964, and the latest was May 13, 2005. The patent filing dates were arranged in three-year increments.



Although Figure 1 shows a downward trend line, caution is warranted. There is a potential for selection bias at both ends.

*First*, the Hatch-Waxman Amendments did not take effect until September 1984, and the earliest approved drug in the dataset received FDA approval in August 1984. Thus, if a drug that started *preclinical* testing in the 1960s appears in the dataset at all, the overall premarket program (preclinical plus clinical testing) took a long time. Other drugs from those years that completed testing more quickly will not appear in the dataset. The information for these years may be skewed to indicate a longer than warranted average preclinical period. *Second*, the opposite may be true for the final time intervals. If a drug that started preclinical testing in the late 1990s or early 2000s appears in the dataset, its overall premarket program may have been unusually short. Other drugs that started preclinical testing at the same time may yet be unapproved. Thus the information for the final time intervals may be skewed to suggest a

shorter than warranted average preclinical period. If one excludes the intervals before 1973 and after 1993, there is still a downward trend but it is less stark.

The inclusion of antibiotics could have skewed the trend line, but if anything it should have reduced the downward slope. Prior to 1997, new antibiotic drugs were not subject to the patent listing or exclusivity provisions of the Federal Food, Drug, and Cosmetic Act (“FDCA”),<sup>239</sup> and the pre-1997 antibiotics were not themselves subject to patent listing requirements until 2008.<sup>240</sup> The dataset includes thirty-two antibiotic drugs that were not subject to patent listing prior to 2008. For these drugs, the analysis considered the patent proposed for restoration and any patents listed after 2008. In any case where this approach overlooked an already expired active ingredient patent, the actual start of preclinical work could have been much earlier than assumed by using the proxy. In this case, the preclinical period would be longer than reflected in Figure 1. Because the lack of patent listings affects only antibiotics approved by FDA before 1997, however, any distortion would raise the averages at the beginning of the time sequence and should not change the fact that the preclinical period trends downward over time, although it might change the slope.

Assuming the downward trend line is correct, there is more than one possible explanation. *First*, it may mean that the preclinical testing period has been getting shorter. This is consistent with the shift to the translational approach to drug discovery, which puts compounds into patients faster. Interpreting the trend line to mean shorter preclinical testing periods is also consistent with the fact that industry investment in the preclinical phase has been declining for several decades.<sup>241</sup> *Second*, it may reflect a change in the timing

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239. Antibiotic drugs reached the market under section 507 of the FDCA rather than section 505 of the FDCA prior to November 1, 1997. 21 U.S.C. § 357 (1993) (repealed 1997). The Hatch-Waxman scheme did not apply to them. In addition to twenty-nine antibiotic drugs, FDA approved two cancer treatments under section 507 and one drug intended for prophylaxis of organ rejection: DaunoXome (daunorubicin citrate) approved in 1996 as a first-line cytotoxic therapy for treatment of Kaposi’s sarcoma; Idamycin (idarubicin hydrochloride), approved in 1990 for treatment of acute myeloid leukemia; and Cellcept (mycophenolate mofetil), approved in 1995 for prophylaxis of organ rejection. See DONALD O. BEERS & KURT R. KARST, *GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS* § 4.02(I) (8th ed. 2016) (discussing FDA’s use of section 507 for cancer drugs). Congress repealed section 507 in 1997 and enacted a new and unrelated section 507 in 2016. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 125 (1997) (repealing section 507); 21st Century Cures Act, Pub. L. No. 114–255 § 3011, 103 Stat. 1033, 1086 (2016) (adding a new section 507).

240. Q1 Program Supplemental Funding Act of 2008, Pub L. No. 110–379, § 4(b), 122 Stat. 4075 (2008) (to be codified at 21 U.S.C. § 355); Draft Guidance for Industry on the Submission of Patent Information for Certain Old Antibiotics, 73 Fed. Reg. 73,659 (Dec. 3, 2008).

241. Fredric J. Cohen, Opinion, *Macro Trends in Pharmaceutical Innovation*, 4 NATURE REVS. DRUG DISCOVERY 78, 81 (2005) (noting that since 1976, the industry has allocated “relatively more” resources to clinical and regulatory work and relatively less to preclinical work).

of patent filings. That is, sponsors may be applying for their initial patents later in the preclinical research process, for instance due to changes in patent law.<sup>242</sup> This dataset does not provide a basis for determining whether shorter preclinical periods, later patent filings, or both are responsible.

There is also a lag inherent in the dataset. Any trend in the length of preclinical testing periods or in the timing of patent filings since the early to middle 2000s is not reflected here.

### C. Clinical Testing Period

#### 1. Average Clinical Testing Period

The 570 products in this database – minus the five studied overseas – have an average clinical testing period of 2177 days, or 5.96 years (median 1910 days, standard deviation 1200 days). The shortest testing period in the dataset, 198 days, belongs to Geref (sermorelin acetate), an endocrine/metabolic agent approved in 1990 for the treatment of idiopathic growth hormone deficiency in children with growth failure. The longest testing period – 9569 days, or 26.22 years – belongs to Ampyra (dalfampridine), a potassium channel blocker approved in 2010 to improve walking in patients with multiple sclerosis.

The story of Ampyra's discovery and development illustrates some of the challenges of modern drug development.<sup>243</sup> Although multiple sclerosis is still not fully understood, it involves the immune system attacking myelin, which surrounds and insulates the nerve fibers, as well as the fibers themselves. The story begins with 4-aminopyridine (or 4-AP), a potassium channel blocker and potent nervous system toxicant used as a bird poison in the United States in the early 1970s.<sup>244</sup> Studies in insects, mollusks, and other animals in the 1970s and 1980s explored the impact of 4-aminopyridine on nerve fibers and suggested it could help electrical impulses travel across demyelinated nerves.<sup>245</sup> Establishing in animal studies that a chemical can help electrical impulses

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242. For instance, beginning in 1995 patent terms were calculated from the date of patent application rather than from the date of patent issuance. *See supra* note 93. This might have prompted later patent filings in industries subject to premarket regulatory review. Changes in patent doctrine due to significant judicial decisions could also affect patenting practices.

243. *See generally* Lisa Emrich, *FDA Approves Ampyra (Dalfampridine), Previously Known as Ampriva (Fampridine-SR), Amaya (Fampridine-SR), and 4-Aminopyridine or 4-AP*, BRASS & IVORY (Jan. 22, 2010), <http://www.brassandivory.org/2010/01/fda-approves-ampyra-dalfampridine.html>.

244. U.S. Env't Prot. Agency, *Reregistration Eligibility Decision for 4-Aminopyridine 7* (Sept. 27, 2007), [https://archive.epa.gov/pesticides/reregistration/web/pdf/aminopyridine\\_red.pdf](https://archive.epa.gov/pesticides/reregistration/web/pdf/aminopyridine_red.pdf) (noting initial pesticide registration in 1972).

245. *See generally, e.g.*, R. M. Sherratt et al., *Effects of 4-Aminopyridine on Normal and Demyelinated Mammalian Nerve Fibres*, 283 NATURE 570 (1980); J. I. Gillespie & O. F. Hutter, *The Actions of 4-Aminopyridine on the Delayed Potassium Current in Skeletal Muscle Fibres*, 252 J. PHYSIOLOGY 70P (1975).

travel through nerves is, however, a far cry from knowing the best way that chemical can be deployed to benefit human patients. The proof of a useful biological activity in animals is just the beginning.

Academic and commercial researchers explored possible ways this compound could be best developed for patients, considering not only multiple sclerosis but spinal cord injuries and Guillain-Barre syndrome.<sup>246</sup> Early clinical trials involved only a few patients and were essentially phase 0 studies designed for proof of principle. A trial in 1983 examined the effect of 4-aminopyridine on visual function in ten patients with multiple sclerosis.<sup>247</sup> Another trial in 1986 examined vision, oculomotor function, and motor function in twelve patients.<sup>248</sup> The first U.S. trial in humans was on February 10, 1983, and is the reason FDA calculated 9569 days for the testing period; because it occurred in the United States, this trial required an effective IND.<sup>249</sup> When the IND took effect, the pharmaceutical company that would eventually develop a sustained release formulation that delivered stable blood levels of the drug and that would establish this product's safety and effectiveness for the improvement of walking ability in patients with multiple sclerosis did not even exist.

In 1990, Elan Corporation acquired the rights to 4-aminopyridine from the Rush Multiple Sclerosis Center in Chicago and began developing a product, which it intended to call Neurelan.<sup>250</sup> Elan conducted larger trials examining the effect of the drug – then assigned the generic name “fampridine” and later changed to “dalfampridine” – on a wide variety of neurophysiological measurements.<sup>251</sup> Clinical testing indicated that fampridine has a narrow therapeutic index, specifically a risk of seizure when at peak concentration in the blood.

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246. See Sherratt et al., *supra* note 245.

247. Richard E. Jones et al., *Effects of 4-Aminopyridine in Patients with Multiple Sclerosis*, 60 J. NEUROLOGY SCI. 353 (1983).

248. Dusan Stefoski et al., *4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis*, 21 ANNALS NEUROLOGY 71 (1987).

249. Determination of Regulatory Review Period for Purposes of Patent Extension; AMPYRA, 76 Fed. Reg. 12,974, 12,974 (Mar. 9, 2011). The substance had been administered intravenously to a few people outside the United States in the 1970s. *E.g.*, H. Lundh et al., *Effects of 4-Aminopyridine in Myasthenia Gravis*, 42 J. NEUROLOGY, NEUROSURGERY & PSYCHIATRY 171, 171 (1979) (assessing effect in six patients).

250. See *Elan Adds U.S. Marketing Presence Through Athena Neurosciences Merger; Athena Alzheimer's Research Will Be More Independent, Biotech Firm Says*, PINK SHEET (Mar. 25, 1996).

251. *E.g.*, Christopher T. Bever, Jr., et al., *Preliminary Trial of 3,4-Diaminopyridine in Patients with Multiple Sclerosis*, 27 ANNALS NEUROLOGY 421 (1990); see also Christopher T. Bever, Jr., et al., *The Effects of 4-Aminopyridine in Multiple Sclerosis Patients: Results of a Randomized Placebo-Controlled, Double-Blind, Concentration-Controlled, Crossover Trial*, 44 J. NEUROLOGY 1054 (1994); Christopher T. Bever, Jr., *The Current Status of Studies of Aminopyridines in Patients with Multiple Sclerosis*, 36 ANNALS NEUROLOGY S118 (1994).

This led Elan to develop a safer sustained-release formulation, known as fampridine-SR.<sup>252</sup> In 1994 and 1996, Elan obtained patents for the sustained release technology associated with fampridine-SR, including U.S. Patent No. 5,540,938, which Acorda would license from Elan and for which the company would eventually seek restoration.

Acorda was founded in 1995 to develop treatments for spinal injuries and other central nervous system disorders. The two companies formed a joint venture in 1997, with Elan contributing rights to the sustained release formulation and Acorda conducting clinical trials.<sup>253</sup> The run-up to FDA approval of Ampyra began in earnest in November 2000, with a double-blind, placebo-controlled, dose-ranging study of fampridine-SR intended to settle on tolerable doses for a sustained release product.<sup>254</sup> This was seventeen years after the earliest administration of fampridine to humans in the United States. The company suffered a setback when the phase 3 program for treatment of spinal cord injury failed; both studies missed their primary endpoints, one in late 2003 and the other in early 2004.<sup>255</sup>

The multiple sclerosis development program had been proceeding in parallel but was slightly behind; Acorda met with the agency to discuss the results of the phase 2 testing in the summer of 2004.<sup>256</sup> Clinical trial design for the phase 3 multiple sclerosis trials was a significant hurdle, in part because the endpoint was unprecedented.<sup>257</sup> Those trials began in December 2005 and August 2007, and during phase 3 the company and agency met more than once to discuss study results and trial design.<sup>258</sup> FDA and Acorda met again in October 2008 to discuss the NDA and Acorda submitted the application the following April – twelve years after acquiring the rights to fampridine-SR.

The Ampyra story illustrates several points about new drug research and development. *First*, early research may occur with very little vision of a finished product. The initial work occurred after the basic mechanism of multiple sclerosis (demyelination) was understood. Researchers then considered the

252. See CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., NDA 22250, CROSS DISCIPLINE TEAM LEADER REVIEW 2 (Jan. 20, 2010), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022250s000\\_CrossR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000_CrossR.pdf) [hereinafter FDA MEMO].

253. *Elan Meltdown May End R&D Joint Ventures as Funding Vehicle for Biotech*, PINK SHEET (Feb. 11, 2002). The companies later entered a licensing agreement. *Id.*

254. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., NDA 22250, MEDICAL REVIEW(S) 18 (Dec. 10, 2009), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022250s000\\_MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000_MedR.pdf) [hereinafter AMPYRA CLINICAL REVIEW].

255. FDA MEMO, *supra* note 252, at 3.

256. *Id.*

257. See *id.* at 10; see also Mary Jo Laffler, *The Long Road to Approval: Acorda Experience with Ampyra Shows Success of Novel Analysis Plan*, PINK SHEET (Dec. 1, 2010).

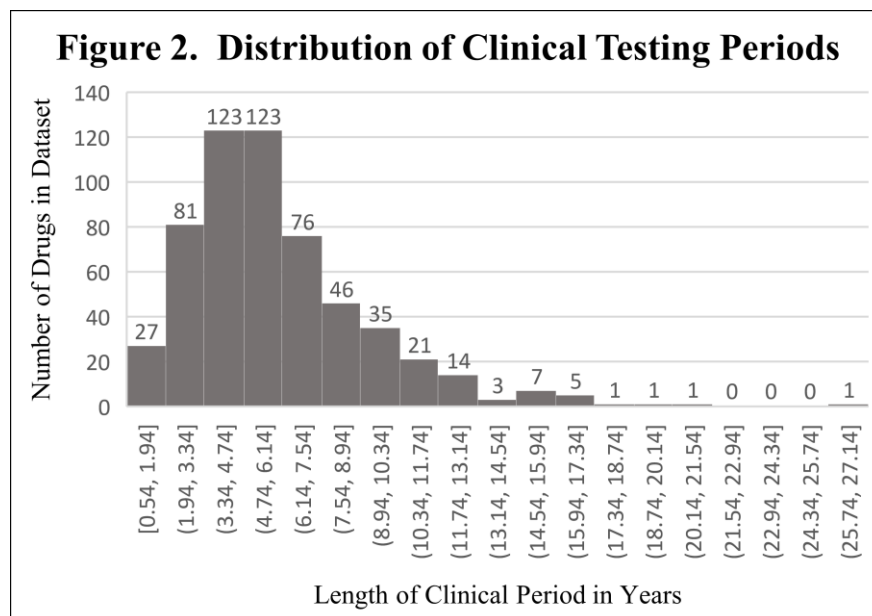
258. See AMPYRA CLINICAL REVIEW, *supra* note 254, at 20; FDA MEMO, *supra* note 252, at 4.

possibility that a compound with neurotoxic effects in animals would disrupt the effect of demyelination on nerve conductivity. This required very early testing in humans, long before any thought could be given to a potential product and before any thought could be given to an eventual clinical indication (i.e., visual acuity versus gait versus coordination, or – as it turned out – walking speed). Indeed the disease in which this promising compound could be most effectively deployed had not been determined.

*Second*, a product that fails to meet a particular endpoint in one disease or condition could succeed with a different endpoint in that disease or condition or, as in this case, a different disease or condition. Failure in a particular phase 3 program may have very little to do with the therapeutic potential of the invention or its value to society. Yet resource constraints may mean that a firm will not start the second phase 3 program until the first phase 3 program fails, which in turn has clear negative consequences for effective patent life.

*Third*, a commercial firm that acquires the rights to a molecule after basic research has been done may not gain a meaningful head start on account of the research. Phase 1 involved brief clinical pharmacology trials. The bulk of the work remained: phase 2, with its high attrition rates, and phase 3 (in this case, two rounds of phase 3), with its full-blown efficacy endpoints. In situations where the active ingredient patent application is filed before clinical testing, this company stands very little chance of having meaningful patent protection for the new product that it brings to market. The patent claiming the sustained release formulation and its use had only three and a half years of patent life left by the time Ampyra was approved. With restoration, it had eight and a half years of effective life.

Although the length of the clinical testing period of Ampyra seems striking, Fulyzaq (crofelemer), intended for treatment of diarrhea in patients with HIV taking anti-retroviral therapy, had a 20.2-year testing period. Strattera (atomoxetine hydrochloride), intended for treatment of attention-deficit hyperactivity disorder (“ADHD”), spent twenty years in trials. Two antibiotic drugs – Orbactiv (oritavancin) and Cubicin (daptomycin) – spent 17.2 years and 16.9 years, respectively, in clinical testing. It is tempting to suggest that these experiences were not classic or conventional new drug research and development programs – that some were programs abandoned and restarted, and others characterized by serendipity and accident. But the point is that this seems to happen with some frequency. Figure 2 illustrates the distribution of clinical testing period lengths; fifty-nine drugs in the dataset had clinical testing periods exceeding ten years, and 161 drugs (more than one in four) had clinical programs exceeding seven years. Thirteen of the 161 have patent term restoration requests still pending at the USPTO, but the remaining 148 had an average effective patent life *after* patent term restoration of 10.4 years.



To be sure, these findings suggest that companies continue to develop products that will have spent a very long time in development by the time they are approved. This invites the question whether the structural problem really harms innovation. But even if *some* companies continue to invest in drugs with longer premarket programs, we do not know how many others choose not to, or how many new drugs that require long-term research we *would* have if the incentive structure were different. We do know that several large companies have withdrawn from the neuroscience field citing the longer development time.<sup>259</sup> We also know that firms underinvest in the development of cancer drugs that require long-term trials.<sup>260</sup> Further, we do not know *why* companies pursue long-term premarket programs. It is possible that in some cases the length of the clinical program was not apparent at the outset, leading to a sunk cost effect.<sup>261</sup> It is possible that in some cases firms have reasons other than

259. See Abbott, *supra* note 11 at 161–62.

260. See Budish et al., *supra* note 10, at 2047.

261. The sunk cost effect – also known as “escalation of commitment” or, more colloquially, “throwing good money after bad” – characterizes behavior in which a firm continues to invest in a decision or process despite increasingly negative outcomes, rather than changing its course. *E.g.*, Barry M. Staw, *Knee-Deep in the Big Muddy: A Study of Escalating Commitment to a Chosen Course of Action*, 16 *ORG. BEHAVIOR & HUMAN PERFORMANCE* 27 (1976); see also *Sunk Cost Fallacy: Throwing Good Money After Bad*, *STRATEGIC THINKING & STRATEGIC ACTION* (Mar. 21, 2015), <http://leepublish.typepad.com/strategicthinking/2015/03/sunk-cost-fallacy.html>. Lilly’s continued investment in solenzumab might be an example of this. After the drug – which had been in clinical testing since 2004 – failed in two phase 3 trials that examined its impact

patent or data exclusivity to expect a long period of marketing exclusivity (or near-exclusivity) or (even in situations where the marketing exclusivity period is short) adequate post-approval reward. For example, a drug might be unusually difficult to manufacture, which could provide some assurance of near-exclusivity in itself. A drug to be taken daily for a chronic condition might generate more revenue during its marketing exclusivity period than a drug that will be administered as a single course of treatment lasting ten days.

## 2. Average Clinical Testing Period over Time

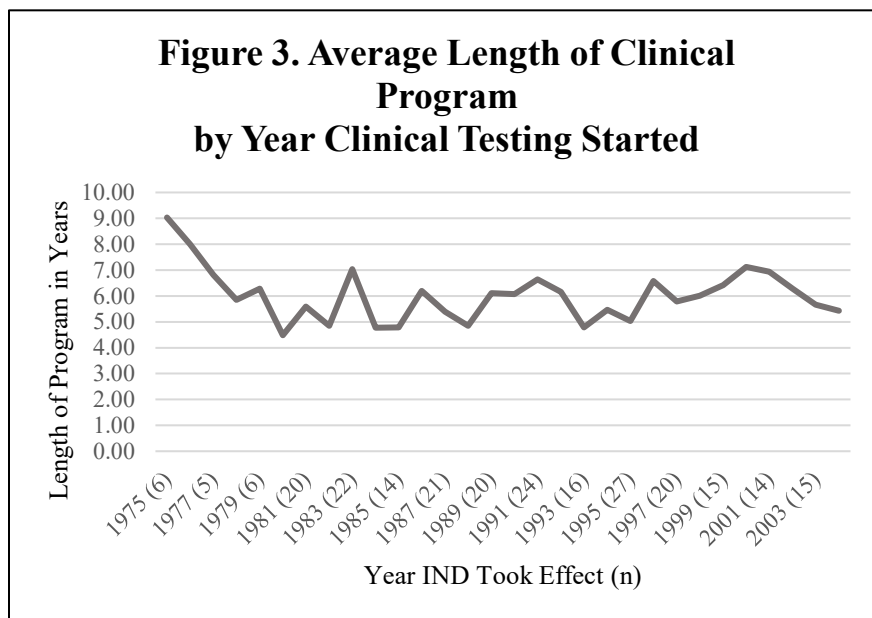
### a. By First-in-Human Date

The drugs in the dataset were sorted by the year their INDs went into effect, permitting testing in humans, to examine a trend in the clinical period over time. Data for the first five years and the last five years were dropped because of their potential for selection bias, as follows. *First*, the earliest IND in the dataset took effect in 1970. The Hatch-Waxman Amendments did not take effect until September 1984, which means the earliest approved drug in the dataset received FDA approval in August 1984. Thus every drug in the dataset with a clinical trial start in the early 1970s necessarily took a long time in trials. Put another way, any drugs that started trials in those years and took *less* time would have been approved before 1984 and would not appear in the dataset. Because the dataset inherently omits some drugs that started trials in the early 1970s, the information for those years is incomplete and systematically skewed to suggest a higher average testing period. *Second*, precisely the opposite is true for the clinical trials starting in the late 2000s. The latest IND in the dataset took effect in 2009. The latest approved drugs in the dataset received approval in early 2014. Thus every drug in the dataset that started trials in the late 2000s necessarily had a short clinical testing period – or it would not be in the dataset. Put another way, the drugs that started trials in those years and took more time, or are still taking more time, would not appear in the dataset yet. Because the dataset inherently omits some drugs that started testing in the late 2000s, the information for those years is incomplete and systematically skewed to suggest a shorter average testing period.

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on cognitive and functional impairment in mild and moderate Alzheimer's, the company realized that participants with *mild* Alzheimer's fared better than controls in the *cognitive* portion of the testing. Still blind to the data from its ongoing third trial, it shifted the data analysis plan to improvement of cognitive functioning in mild Alzheimer's. See Emily Underwood, *Why the Big Change to Lilly's Alzheimer's Trial Is Not Evidence Its Drug Has Failed Again*, SCIENCE (Mar. 21, 2016, 1:30 PM), <http://www.sciencemag.org/news/2016/03/why-big-change-lilly-s-alzheimer-s-trial-not-evidence-its-drug-has-failed-again>; Damian Garde, *A Big Alzheimer's Drug Trial Now Wrapping Up Could Offer Real Hope – or Crush It*, STAT (Oct. 13, 2016), <https://www.statnews.com/2016/10/13/alzheimers-drug-eli-lilly/>. This third phase 3 trial was also a failure. Jessica Merrill, *Lilly's Solanezumab Fails, but the Surprise Would Have Been Success*, PINK SHEET (Nov. 23, 2016).





Continuing selection bias could explain the high averages at the beginning of the period in Figure 3 and the apparent downward trend line at the end of the period.<sup>262</sup> Excluding five years at either end, rather than some other number of years, was arbitrary. If continuing selection bias is treated as likely, Figure 3 generally suggests that a company starting clinical trials in 2004 was not, on average, facing a meaningfully longer clinical program than a company starting clinical trials in 1984. Whether this remains true today is not known; the inherent lag in any dataset based on approved drugs with published Federal Register notices relating to patent term restoration requests means that the data do not reflect any changes that might be expected by a sponsor starting phase 1 work in 2010 or later.

#### b. By End-of-Phase 3 Date

Part IV explained that the design of a phase 3 trial to establish a drug's effectiveness for its proposed use – including the trial's endpoints, size, and duration – reflects many factors, including the drug's mechanism of action, its

262. The data from 1975 (average clinical period of 9.03 years) and 1976 (average clinical period of 8.0 years) may be biased because any drug that started trials in those years and had a moderately short clinical trial experience would have been approved before 1984 and would be missing from the dataset. The data from 2003 (average of 5.66 years) and 2004 (average of 5.43 years) could be biased for precisely the opposite reason; given the range of clinical program lengths in the broader dataset, some drugs that started trials in those years might not have reached FDA approval and patent term restoration in time for inclusion in the dataset.

physiological effect in the body, the disease under investigation, the hypothesized outcome, and possibly other products on the market. Because several phases of clinical testing precede phase 3, sorting the drugs by the start of testing in humans (commencement of phase 1 testing) risks obscuring trends in the length of the clinical program caused primarily by evolution in phase 3 design over time.

Trends in the length of the clinical program caused primarily by evolution in phase 3 design could be captured better by sorting the drugs by the year that phase 3 trials began. The dataset does not provide a basis for doing so, however, and the date that phase 3 trials started is not publicly available for every drug in the database. The drugs in the dataset were sorted instead by the year that the sponsor submitted its NDA. This provides a rough proxy for the timing of the phase 3 program because NDA submission generally occurs within a year of the completion of the final phase 3 trial.<sup>263</sup>

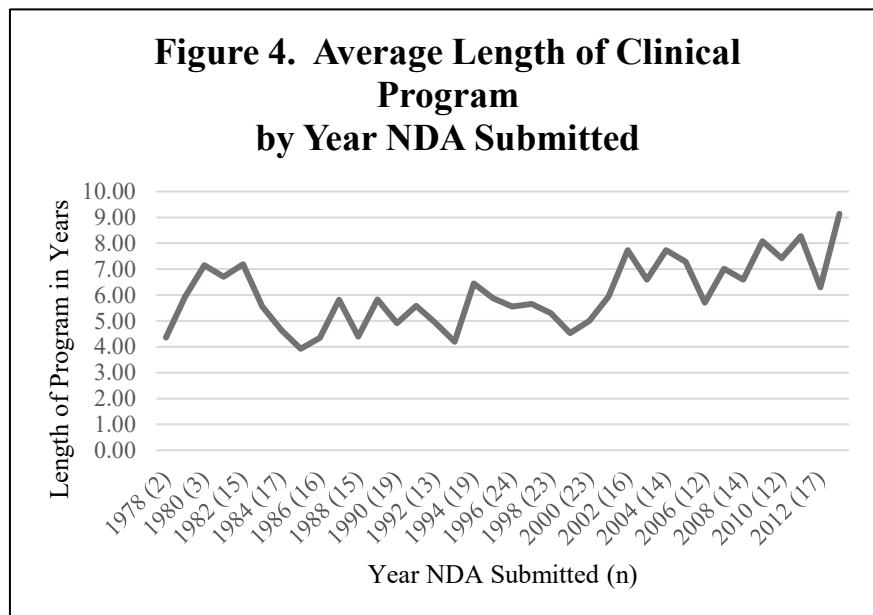


Figure 4 illustrates an upward trend in the length of clinical testing periods based on a proxy for the date when phase 3 trials ended. The length of clinical programs increases over time when drugs are sorted by NDA submission date even though it does *not* increase over time when the drugs are sorted by IND effective date. Considering Figure 3 and Figure 4 together, therefore, suggests that the length of the clinical program correlates at least in part with

263. *E.g.*, Agency Information Collection Activities; Proposed Collection; Comment Request; Application for Food and Drug Administration Approval to Market a New Drug, 79 Fed. Reg. 16,003, 16,006 (Mar. 24, 2014) (estimating that it takes a new drug sponsor 1921 hours to prepare and submit a new drug application).

the date of NDA submission. Because NDA submission generally follows within a year of phase 3 completion, this further suggests that the length of the clinical program correlates at least in part with the date that phase 3 trials ended. Without information on the phase 3 start date, it is impossible to determine whether the trend line reflects an increase in the length of phase 3 trials alone. But some studies have found that phase 3 trials are increasing in length.<sup>264</sup>

#### D. Surrogate Endpoints

Analysis of the impact of surrogate endpoints on the length of clinical programs is challenging because FDA has approved drugs on the basis of surrogate endpoints for nearly all of its history, and there is no reliable comprehensive list of these approvals. Well before the subpart H regulations took effect in 1993, for example, FDA approved osteoporosis drugs on the basis of total body calcium and bone mineral content, when the clinical outcome of interest was reduction in bone fractures.<sup>265</sup> Antihypertensives have always been approved on the basis of a surrogate endpoint. The clinical outcome of interest is reduction in cardiovascular events including cardiovascular mortality, but these drugs have always been tested for reduction of blood pressure and

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264. The consulting firm KMR Group examined 4100 oncology trials conducted over a ten-year span by thirty-two companies and, relying on proprietary data from those companies, found that phase 3 trials increased from an average of 3.5 years (for trials started between 2003 and 2005) to an average of five years (for trials started between 2013 and 2015). KMR GROUP, 2015 CLINICAL CYCLE TIME TRENDS: SELECT FINDINGS FROM KMR GROUP'S ANNUAL CLINICAL DATA PROGRAM (2015) (on file with author); *Why Are Oncology Clinical Trials Taking Longer?*, CLINICAL TRIALS ARENA (Oct. 22, 2015), <http://www.clinicaltrialsarena.com/news/operations/why-are-oncology-clinical-trials-taking-longer-4698649>. On the basis of entries in the NIH clinical trials databank, Glass found a thirty percent increase in the per-patient duration of phase 3 trials from 2008 to 2013 and a forty-one percent increase in per-patient duration of oncology trials over the same time period. Glass et al., *supra* note 168, at 856. Using a proprietary database, Getz analyzed 10,038 protocols for phase 2 and 3 trials of drugs to treat chronic illness and found that between 1999 and 2005 the period from first patient first visit to last patient last visit increased by fifty-three percent. KENNETH GETZ, PROTOCOL DESIGN TRENDS AND THEIR EFFECT ON CLINICAL TRIAL PERFORMANCE 315–16 (May 2008), [http://csdd.tufts.edu/\\_documents/www/2816Getz.pdf](http://csdd.tufts.edu/_documents/www/2816Getz.pdf).

265. *E.g.*, CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., REPRODUCTIVE HEALTH DRUGS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE 42–44, 141 (Mar. 5, 2013), <https://wayback.archive-it.org/7993/20170404145949/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM351018.pdf> (discussing approval of postmenopausal osteoporosis indication for Calcimar (synthetic calcitonin salmon) in 1984, on the basis of total body calcium assessed by neutron activation analysis and bone mineral content measured by single photon absorptiometry of the forearm).

were originally labeled only for reduction of blood pressure.<sup>266</sup> The only way to definitively categorize the basis of approval of the 570 drugs in the dataset would be to examine FDA's review documents.<sup>267</sup> There are, however, publicly available lists of the accelerated approvals under subpart H on the basis of novel (not validated) surrogate endpoints.<sup>268</sup> Certain comparisons of interest can therefore be made.

*First*, drugs approved on the basis of novel surrogate endpoints under subpart H can be compared with drugs approved under the conventional approval regulations after subpart H took effect. The latter include drugs approved on the basis of clinical endpoints and drugs approved on the basis of validated surrogate endpoints. Table 1 reports the results. There were 413 drugs in the dataset approved after January 11, 1993, the effective date of the subpart H regulations. Of these, three were tested overseas, leaving 410 with clinical testing information in the dataset. Of these, thirty-four received accelerated approval under subpart H, and 376 had traditional approval. Table 1 indicates that the thirty-four drugs approved on the basis of novel surrogate endpoints had an average clinical program of 5.61 years (median 5.08, standard deviation 2.41), while the traditionally based approvals had an average clinical program of 6.28 years (median 5.42, standard deviation 3.43). Drugs in the dataset approved on the basis of novel surrogate endpoints after January 11, 1993, spent an average of 247 fewer days, around eight fewer months, in clinical testing than drugs approved on the basis of traditional clinical endpoints or validated surrogate endpoints.

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266. Mehul Desai et al., *Antihypertensive Drug Development: A Regulatory Perspective*, in HYPERTENSION: A COMPANION TO BRAUNWALD'S HEART DISEASE 416, 422 (Henry R. Black & William Elliott eds., 2013). Today, many have clinical outcome claims in their labeling.

267. The review documents for older drugs in the dataset are not posted on Drugs@FDA and would need to be obtained through the Freedom of Information Act ("FOIA").

268. *E.g.*, Food & Drug Admin., U.S. Dep't of Health & Human Servs., *Accelerated & Restricted Approvals Under Subpart H (Drugs) and Subpart E (Biologics)*, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121597.htm> (last updated June 30, 2017).

<b>Table 1. Average Clinical Program Length in Years: New Active Ingredient Drugs Approved After January 11, 1993</b>		
	Accelerated Approval (n=34)	Traditional Approval (n=376)
Endpoints	Novel surrogate end- points	Validated surrogate end- points and clinical end- points
Mean	5.61	6.28
Median	5.08	5.42
St. Dev.	2.41	3.43
Range	2.74 to 12.07	1.04 to 26.22

*Second*, drugs in the dataset approved from 2010 through 2014 on the basis of either type of surrogate endpoint can be compared with drugs approved during the same window on the basis of clinical endpoints.<sup>269</sup> Table 2 reports the results. Of the eighty drugs in the dataset approved in this time period, one was tested overseas, leaving seventy-nine for analysis. The fifty-three drugs approved on the basis of clinical endpoints averaged 7.79 years in clinical trials (median 6.66, standard deviation 4.51). The twenty-six drugs approved on the basis of surrogate endpoints averaged 6.82 years in clinical trials (median 5.84, standard deviation 2.59). The twenty-one approved on the basis of validated surrogate endpoints averaged 6.79 years (median 5.74, standard deviation 2.77), while the five approved on the basis of novel surrogate endpoints averaged 6.93 years (median 6.21, standard deviation 1.62). Drugs in the dataset approved between 2010 and 2014 on the basis of validated surrogate endpoints spent an average of one full year less in clinical trials than drugs approved on the basis of clinical endpoints in the same time period.

<b>Table 2. Average Clinical Program Length in Years: New Active Ingredient Drugs Approved in 2010 Through 2014</b>				
	Clinical End- points (n=53)	All Surrogate Endpoints (n=26)	Surrogate Endpoints	
			Validated (n=21)	Novel (n=5)
Mean	7.79	6.82	6.79	6.93
Median	6.66	5.84	5.74	6.21
St. Dev.	4.51	2.59	2.77	1.62
Range	2.39 to 26.22	3.35 to 15.63	3.35 to 15.63	5.22 to 9.35

Together these tables indicate that programs using surrogate endpoints are generally shorter than programs using clinical endpoints and that the difference is most pronounced for validated surrogate endpoints. The fact that

<sup>269</sup> FDA has published a list of surrogate endpoint approvals during this time period. NOVEL DRUGS, *supra* note 163, at 2–7.

surrogate endpoints – validated or novel – are associated with shorter programs and less variability is generally consistent with the notion that surrogate endpoints can make an ordinary premarket paradigm possible for drugs that would otherwise require an unusually long clinical testing period or an unusually large sample size.<sup>270</sup> (It is not clear, however, why clinical programs using novel surrogate endpoints would take longer on average than clinical programs using validated surrogate endpoints.) It is, of course, impossible to know what sort of premarket program these particular drugs would have faced, had the surrogate markers not been available. But these tables suggest that when available, surrogate endpoints may be able to mitigate the innovation paradox, ensuring that companies will not be deterred by a long premarket program and correspondingly shortened period for post-approval exclusive marketing. As Part IV.A. explained, however, surrogate endpoints are not a panacea for the paradox. *First*, whether they are available depends on factors beyond a firm’s control, including the drug’s class and mechanism of action, the disease type and stage, the nature of the disease process itself, and any drug off-target effect.<sup>271</sup> *Second*, FDA has been very cautious about permitting *novel* surrogate endpoints. And *third*, novel surrogate endpoints result in a narrow scope of approval and labeling; the product is different.

### E. Other Factors Influencing Length

The dataset was also explored for possible trends with respect to therapeutic category, anticipated length of treatment, and pharmacologic class of the active ingredient.

#### 1. Therapeutic Category

The 570 drugs in the dataset (minus the five tested overseas) were sorted by therapeutic category.<sup>272</sup> Therapeutic categorization of drugs focuses on the disease or condition that the drug treats and tends to focus on its primary organ or outward signs and symptoms (“cardiovascular” versus “dermatological”).

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270. See discussion *supra* Part IV.A.

271. See discussion *supra* Part IV.A.

272. The methodology was crude. Some drugs in the dataset were withdrawn from the market years ago, and several were never launched in the United States. As a result, no commonly used database provides a therapeutic category for every drug in the dataset. An orthogonal approach was adopted. For each drug, four sources were consulted: the U.S. Pharmacopoeia (“USP”) Medicare Model Guidelines for CMS Version 6.0, the recently released draft of version 7.0 of the same guidelines, the CDC Long-Term Care Drug Database System, and the NIH National Library of Medicine Drug Portal. (Another possibility would have been the VA National Formulary, but it too lacks information for some of the drugs.) Based on the information from these four sources, each drug was placed into categories corresponding roughly to the USP categories. Twelve drugs were not categorized by any of the four sources and were left uncategorized.

Categories with fewer than five entries were dropped, which left 532 drugs in the database.

Figure 5 illustrates the length of clinical testing periods sorted by therapeutic category. At the high end, as the analysis in Part IV suggested might be the case, are the thirteen central nervous system agents, with an average clinical testing period of 9.30 years, followed by two categories of psychiatric drugs – antipsychotics (averaging 8.63 years) and antidepressants (8.49 years) – and two categories that arguably should be part of the central nervous system category – anticonvulsants (8.13 years) and anti-Parkinson’s agents (7.48 years). At the low end are six antimigraine agents, all serotonin receptor agonists, with an average clinical testing period of 2.99 years and a maximum clinical testing period of 4.75 years. Also at the low end are ophthalmic agents (averaging 4.38 years), sleep disorder drugs (4.47 years), antibacterials (4.59 years), antiviral drugs (4.68 years), imaging agents (5.05 years), antifungals (5.13 years), genitourinary (5.29 years), dermatological (5.38 years), anesthetics (5.57 years), metabolic bone disease (5.58 years), respiratory/pulmonary (5.73 years), blood glucose regulators (6.06 years), antidementia agents (6.08 years), cardiovascular drugs (6.12 years), hormonal (6.33 years), analgesics & anti-inflammatories (6.38 years), antineoplastics (6.39 years), antiemetics (6.58 years), blood products (6.70 years), gastrointestinal (6.72 years), immunological (6.77 years), antiparkinson's agents (7.48 years), anticonvulsants (8.13 years), antidepressants (8.49 years), antipsychotics (8.63 years), and central nervous system (9.30 years).

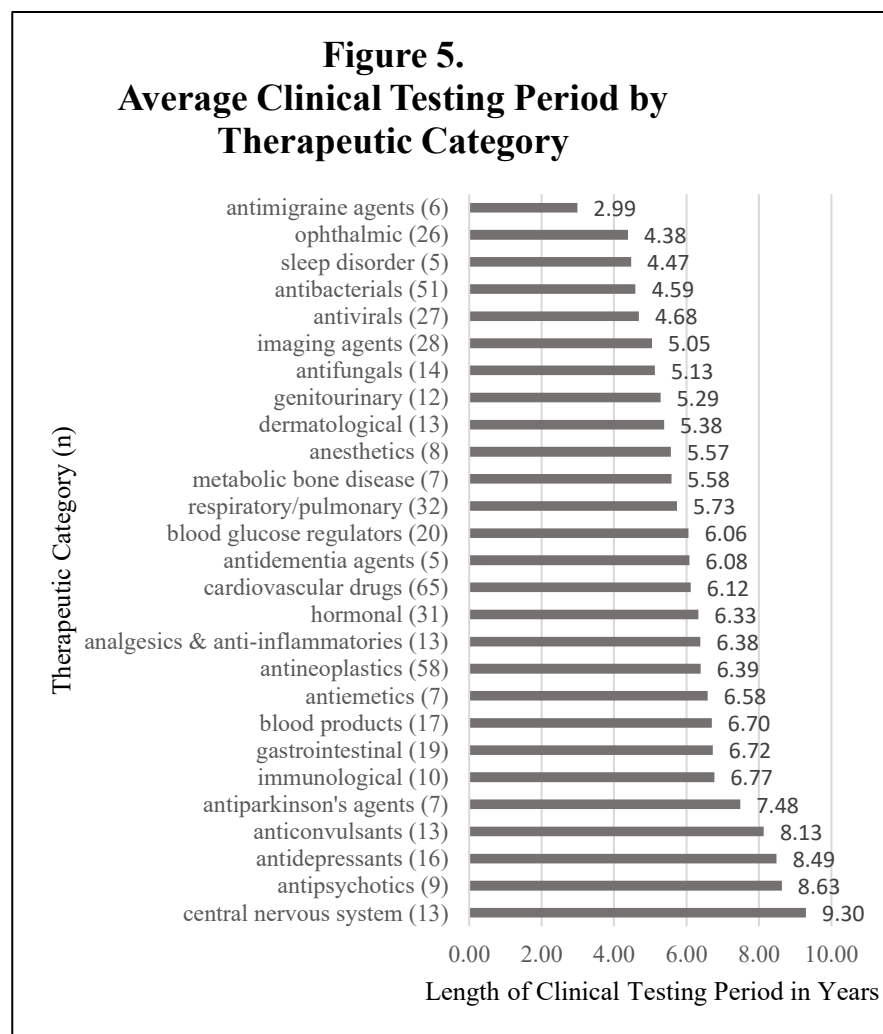


Table 3 provides summary statistics for average clinical testing period by therapeutic category. Whether one sorts by average or median, the ten categories with the longest clinical programs include the following nine: antipsychotics, central nervous system agents, antidepressants, anticonvulsants, anti-Parkinson's agents, immunological agents, blood products, antiemetics, and antineoplastic agents.

<b>Table 3. Average Clinical Testing Period in Years by Therapeutic Category</b>					
Category (n)	Average	Median	Min.	Max.	St. Dev.
antimigraine agents (6)	2.99	2.94	1.42	4.75	1.05
ophthalmic (26)	4.38	4.20	1.04	9.54	1.99
sleep disorder (5)	4.47	3.55	3.42	6.67	1.30
antibacterials (51)	4.59	4.39	1.35	17.25	2.89
antivirals (27)	4.68	4.84	1.84	8.03	1.47
imaging agents (28)	5.05	3.42	0.54	17.72	4.18
antifungals (14)	5.13	5.17	1.75	9.27	1.82
genitourinary (12)	5.29	4.55	2.47	9.26	2.19
dermatological (13)	5.38	5.42	1.18	8.92	2.20
anesthetics (8)	5.57	5.30	2.11	9.67	2.55
metabolic bone disease (7)	5.58	6.28	1.71	9.90	2.68
respiratory/pulmonary (32)	5.73	4.84	1.54	11.61	2.63
blood glucose regulators (20)	6.06	5.40	2.45	12.45	2.64
antidementia agents (5)	6.08	5.21	2.98	12.87	3.63
cardiovascular drugs (65)	6.12	5.11	1.88	15.63	3.33
hormonal (31)	6.33	5.29	1.34	14.32	3.44
analgesics & anti-inflam- matories (13)	6.38	5.69	2.95	11.06	2.42
antineoplastics (58)	6.39	5.95	1.93	13.31	2.69
antiemetics (7)	6.58	6.39	3.07	10.44	2.69
blood products (17)	6.70	6.71	1.97	13.07	2.53
gastrointestinal (19)	6.72	5.52	1.33	20.25	4.28
immunological (10)	6.77	6.49	2.83	12.61	2.92
anti-Parkinson's agents (7)	7.48	7.27	5.52	9.68	1.58
anticonvulsants (13)	8.13	8.13	4.52	15.07	3.23



Category (n)	Average	Median	Min.	Max.	St. Dev.
antidepressants (16)	8.49	7.61	1.74	16.13	3.81
antipsychotics (9)	8.63	8.32	2.80	16.34	4.65
central nervous system (13)	9.30	7.13	1.48	26.22	6.44

Table 3 suggests there is considerable variability within many of the therapeutic categories. To begin with, in all but five categories (antivirals, antifungals, dermatological, metabolic bone disease, and blood products) the median clinical testing period is below the mean, indicating that in almost every category a few drugs with longer clinical testing periods skew the average. Moreover, drugs in nine categories have standard deviations exceeding three years: central nervous system drugs (6.44 years), antipsychotics (4.65), gastrointestinal drugs (4.28), imaging agents (4.18), antidepressants (3.81), antimentia drugs (3.63), hormonal drugs (3.44), cardiovascular drugs (3.33), and anticonvulsants (3.23). The least variable categories are the antimigraine drugs (1.05 years), sleep disorder drugs (1.30), antivirals (1.47), and anti-Parkinson's agents (1.58).

The apparent variability may be because therapeutic category is a poor proxy for the factors that actually determine the length of phase 3 trials. Categorizing research and development experiences based on the organ system, signs, and symptoms risks missing the scientific and regulatory considerations that have the most influence on the length of the premarket period. Part IV of this Article suggests these include the molecule itself and perhaps its mechanism of action and not only the disease but the disease stage and, most importantly, the outcome and use that the firm proposes to test and place in labeling.

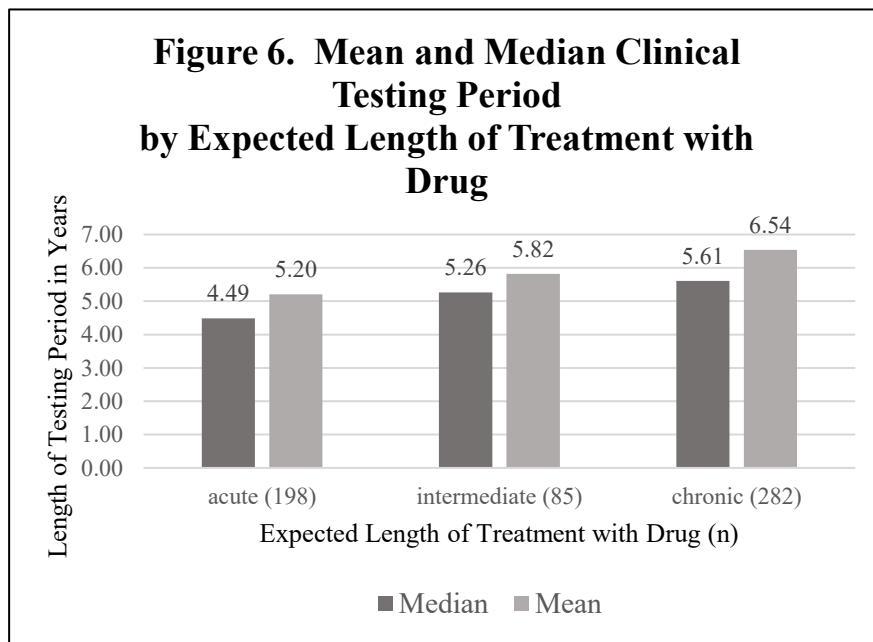
## 2. Other Factors Relevant to Length of Premarket Period

### a. Expected Length of Treatment

Many therapeutic categories combine drugs that are intended for immediate use with drugs that are intended for intermediate or even long-term use. For instance, the category of immunological agents includes Firazyr (icatibant acetate), approved for treatment of acute attacks of hereditary angioedema, as well as Torisel (temsirolimus), approved for treatment of advanced renal cell carcinoma, and Xeljanz (tofacitinib citrate), approved for treatment of rheumatoid arthritis. The 570 drugs in this dataset (minus the five tested overseas) were therefore categorized by the expected length of treatment for the use approved by FDA at the end of the regulatory review period. The categories were

acute use (less than one month), intermediate use (between one month and two years), and chronic use (greater than two years).<sup>273</sup>

Figure 6 shows that drugs intended for chronic use take an average of 6.54 years in clinical trials (twenty-six percent more time than drugs for acute use), while drugs intended for intermediate use take an average of 5.82 years, and drugs intended for acute use take an average of 5.20 years. The median clinical testing period follows the same pattern. But the standard deviations remain high: 3.42 years for chronic-use drugs, 2.74 years for intermediate-use drugs, and 3.15 years for acute-use drugs.



273. These category definitions were adopted from a study that examined the duration of the pivotal efficacy trials supporting approval of new molecular entity drugs and new biological products between 2005 and 2012. Nicholas Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 JAMA 368, 369 (2014). Categorization was based primarily on the first approved package insert, including the Indication statement and the Dosage and Administration instructions. The first approved package insert was obtained from Drugs@FDA. If not available from Drugs@FDA, the package insert was retrieved from the patent term restoration application or, failing that, the earliest edition of the PHYSICIAN'S DESK REFERENCE in which it appeared. Where none of these sources provided the first package insert, characterization of the first approved indication statement was taken from the text of the patent term restoration application, the FDA approval letter, or reporting in the PINK SHEET when the drug was first approved. Two individuals performed the categorization: the author, based on her expertise in pharmaceutical regulatory law, and an associate professor of family and community medicine at the University of Missouri, based on his training and expertise in the practice of medicine. Each was blinded to the other's work, and disagreements were resolved through discussion.

Without regard to therapeutic category, drugs tested, approved, and labeled for longer-term use consistently require longer clinical development programs. This is not because trials mimic real world use. Rather, the overall length of a clinical program reflects the speed and ease of progression from phase 1 through phase 2 to phase 3 and the duration of the phase 3 trials. The latter in turn reflects the trial size, the disease and disease stage, the hypothesized outcome, the trial endpoints, as well as perhaps the drug's mechanism of action, the nature of alternative treatments on the market, and various other considerations. The conditions targeted by the 282 drugs for chronic use in the dataset include common disorders of aging (such as osteoarthritis and hypertension) as well as serious psychiatric conditions (depression, anxiety, and schizophrenia) and life-threatening but ultimately chronic viral infections (HIV and hepatitis). They also include treatments for Alzheimer's disease, Parkinson's disease, multiple sclerosis, and fibromyalgia, as well as treatments for some slowly progressing cancers, such as prostate cancer. Again, these drugs are consistently associated with longer overall clinical testing periods.

#### b. Established Pharmacologic Class

In addition to grouping together drugs that are for acute use and drugs that are for chronic use, therapeutic categories group together drugs for diseases that have distinct molecular causes and divide drugs for diseases with common molecular cause.<sup>274</sup> They may group together some drugs with different mechanisms of action and separate some drugs with the same basic mechanism of action.<sup>275</sup> Although there does not appear to be a publicly available database that categorizes all of the drugs in this dataset by mechanism of action or the molecular cause of the disease in question, FDA captures some of the same considerations when it assigns an "established pharmacologic class" to approved drugs. A "pharmacological class" is defined by reference to three attributes of the active moieties that fall within it: mechanism of action, physiological effect, and chemical structure.<sup>276</sup> FDA designates a pharmacological class as the "established pharmacologic class" for an approved indication of a specific active moiety if the class is both scientifically valid and clinically meaningful with respect to that moiety and indication.<sup>277</sup>

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274. PAVING THE WAY, *supra* note 225, at 17.

275. *E.g.*, Littman, *supra* note 203, at 22.

276. OFFICE OF NEW DRUGS, U.S. FOOD & DRUG ADMIN., DETERMINING THE ESTABLISHED PHARMACOLOGIC CLASS FOR USE IN THE HIGHLIGHTS OF PRESCRIBING INFORMATION 1 (July 18, 2013), <https://www.fda.gov/downloads/AboutFDA/Center-of-Offices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM361380.pdf>.

277. *Id.* at 2. The class is scientifically valid if evidence shows that it is known (not merely assumed), relevant, and specific to the indication. It is clinically meaningful if understanding the pharmacological effect enhances the ability of healthcare professionals to understand the physiologic basis of the indication or their ability to anticipate

The 570 drugs in the dataset (minus the five tested overseas) were sorted by established pharmacologic class, and the seventy-five drugs that lacked an assigned class were dropped.<sup>278</sup> FDA placed twenty-three of the remaining 490 drugs into more than one class; the nine that contained more than one active ingredient were dropped, and the remaining fourteen were considered in each category assigned. Table 4 provides the summary statistics for any classes containing more than four drugs.

<b>Table 4. Length of Testing Period by Established Pharmacologic Class</b>			
<b>Established Pharmacologic Class (n)</b>	<b>Mean</b>	<b>Median</b>	<b>St. Dev.</b>
radioactive diagnostic agents and contrast agents (11)	2.95	2.97	1.04
serotonin-1b and serotonin-1d receptor agonist (6)	2.99	2.94	1.05
histamine-1 (H1) and histamine-2 (H2) receptor antagonist (8)	3.05	2.88	1.49
quinolone antimicrobial (7)	3.68	3.57	1.23
cephalosporin antibacterial (13)	3.96	3.30	1.66
corticosteroid (7)	4.17	3.97	2.14
HMG-CoA reductase inhibitor (6)	4.21	3.07	2.12
cholinesterase inhibitor (4)	4.38	4.10	1.45
topoisomerase inhibitor (6)	4.59	5.17	1.91
cholinergic muscarinic antagonist (4)	4.62	3.79	2.26
proton pump inhibitor (7)	4.74	4.45	2.04
retinoid (4)	4.79	4.94	0.65
beta-2 adrenergic agonist (4)	5.00	5.01	2.04
dihydropyridine calcium channel blocker (6)	5.04	4.06	2.79

undesirable effects that may be associated with the active moiety or pharmacologic class.

278. FDA regulations state that if a product belongs to an established pharmacologic class, the approved labeling must identify the class. 21 C.F.R. § 201.57(a)(6) (2017) (requiring a statement under Indications and Usage that “(Drug) is a (name of class) indicated for (indication(s))”). FDA has also issued a forty-five-page guidance document listing active moieties by their established pharmacological class. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., FDA ESTABLISHED PHARMACOLOGIC CLASS (EPC) TEXT PHASE, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf> (last visited Mar. 5, 2018) (listing active moieties by established pharmacological class).

<b>Table 4. Length of Testing Period by Established Pharmacologic Class</b>			
<b>Established Pharmacologic Class (n)</b>	<b>Mean</b>	<b>Median</b>	<b>St. Dev.</b>
human immunodeficiency virus 1 non-nucleoside analog reverse transcriptase inhibitor (5)	5.05	4.96	0.62
prostaglandin analog (5)	5.16	4.16	2.25
estrogen and progestin (4)	5.22	3.48	4.01
azole antifungal (9)	5.22	5.20	1.65
angiotensin converting enzyme inhibitor (7)	5.34	4.80	1.33
bisphosphonate (5)	5.49	6.28	1.83
gonadotropin releasing hormone receptor agonist (4)	5.78	6.23	1.71
alpha-adrenergic blocker (7)	5.92	5.07	2.37
nonsteroidal anti-inflammatory (10)	5.99	5.31	2.50
serotonin-3 receptor antagonist (5)	6.10	4.74	2.80
kinase inhibitor (15)	6.54	6.20	2.47
anti-coagulant (4)	6.73	7.41	2.97
nucleoside metabolic inhibitor (5)	6.84	6.91	2.52
anti-epileptic agent (10)	6.98	6.49	2.51
beta-adrenergic blocker (9)	7.39	6.66	3.48
serotonin reuptake inhibitor (13)	8.33	7.44	3.93
atypical antipsychotic (10)	8.55	8.05	4.42
anti-arrhythmic (7)	8.88	9.64	2.35
norepinephrine reuptake inhibitor (6)	9.16	7.76	5.39
radioactive diagnostic agents and contrast agents (11)	2.95	2.97	1.04
serotonin-1b and serotonin-1d receptor agonist (6)	2.99	2.94	1.05
atypical antipsychotic (10)	8.55	8.05	4.42
anti-arrhythmic (7)	8.88	9.64	2.35
norepinephrine reuptake inhibitor (6)	9.16	7.76	5.39

The consistently smaller standard deviations in this chart (as compared to the standard deviations when sorting drugs by therapeutic categorization or duration of treatment) invites the hypothesis that the pharmacologic class of a new drug – which combines its mechanism of action, physiological effect, chemical structure – directly influences the length of the clinical testing period.

This is consistent with the discussion in Part IV, which suggested that the length of any particular premarket research and development process is likely to depend on factors like the disease and its biological process, the chemical structure of the drug and its mechanism of action, and the possible outcomes (physiological effects) to be tested.

This interpretation is important because it suggests the length of any particular program will depend on factors generally outside the sponsor's control. This is key to understanding the *problem* with the innovation paradox in the field of medicine. If longer premarket programs are associated with shorter post-market exclusivity, and if sponsors have limited control over the time that will be needed to bring a particular product (active ingredient, product features, disease, outcome) to market, the paradox may lead rational companies to select different products – with shorter timelines – in the first instance. Companies may avoid important areas of medical need. Many of the drugs in the dataset were not included in this analysis of established pharmacologic class, however, and more data points would be helpful to explore this correlation.

#### *F. Scope of These Findings*

The goal of this Article is to describe the premarket research and development program for new medicines in order to better understand the innovation paradox. It focuses on approved new drugs with new active ingredients because FDA has published the regulatory milestones for most of those drugs. The agency has not, however, calculated a regulatory review period for all new medicines that might be of interest, and the dataset includes some drugs that may skew the results.

*First*, the analysis does not reflect many new active ingredient drugs that started clinical trials in the mid to late 2000s. The dataset includes data for 221 drugs that started trials in the 1990s but data for only 100 drugs that started trials in the 2000s. When this Article was being written, there were more than seventy pending patent term restoration requests for approved new drugs for which FDA had not yet calculated a regulatory review period. All of these drugs were approved in 2012 or later, and presumably all were in clinical trials in the mid to late 2000s. As a result, the analysis does not fully reflect changes in the premarket research and development paradigm – including statutory and regulatory changes, evolution in clinical trial and statistical methodologies, advances in computer-assisted data analysis, scientific discoveries and opportunities, and changes in the regulatory culture – in the 2000s.

*Second*, the analysis does not capture new active ingredient drugs for which FDA did not calculate a regulatory review period. This includes any for which a request was not timely filed at PTO, any requests abandoned or withdrawn before FDA calculated the regulatory review period, and any for which the NDA holders neglected to seek restoration to which they were entitled. The original spreadsheet from PTO indicates that the first two groups are small (in the single digits). The third group is surprisingly large. A review of historical editions of the *Orange Book* identified more than 100 drugs approved in the

time period covered by this dataset that were awarded new chemical entity exclusivity but were *not* in the patent term restoration dataset. Most appear to have listed patents, and it is unclear why the NDA holders did not request patent term restoration. One possibility is mistake. Another possibility is that these companies were already slated to enjoy fourteen or more years of effective patent life on any patents they might have sought to restore (listed or not).<sup>279</sup> Where the second explanation is true, it would be important to learn more. Some could be instances where a particularly long research and development period eliminated all effective patent life on the active ingredient patent, leaving only later-expiring patents on formulation and the like. In these cases, fourteen years of effective patent life might not translate to fourteen years of effective market exclusivity. In the alternative, some could be instances where a swift premarket program led to approval with fourteen years remaining on the active ingredient patent. In such a case, the firm might well have enjoyed fourteen years of effective market exclusivity.

*Third*, the dataset does not include biological medicines, which are licensed under a different statute, the Public Health Service Act.<sup>280</sup> Neither the *Orange Book* nor the newly established *Purple Book* for biologics lists patents claiming these products, and there was therefore no proxy for the beginning of the preclinical period for purposes of the analysis in Part V.B. FDA has published the regulatory review period for these products, however, and it would have been possible to conduct the analyses in Parts V.C. through V.E.

Although this analysis was not performed, there is good reason to think the results would have been similar. Although biologics are licensed under a different statute, as a scientific and regulatory matter the premarket schemes are mostly harmonized.<sup>281</sup> Therapeutic biologics have been regulated by the

279. One example is Actonel (risedronate sodium), approved in March 1998 with five years of NCE exclusivity. Letter from James Bilstad, Dir., Office of Drug Evaluation II, to Hina Wu, Senior Scientist (Mar. 27, 1998) (on file with FDA). The NDA holder listed three patents, and the earliest to expire (U.S. Patent No. 5,583,122) was slated to expire in December 2013 – more than fourteen years after NDA approval. There was no point seeking patent term restoration.

280. At the time this Article was drafted, FDA's website listed 143 therapeutic biological products with approved biologics license applications. Ctr. for Drug Evaluation & Research, U.S. Food & Drug Admin., *List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date*, <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf> (last visited Mar. 5, 2018).

281. See Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 Food & Drug. L.J. 671, 687 (2010); see Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 123(f), 111 Stat. 2296, 2324 (directing FDA to “take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the [PHSA] and products required to have approved new drug applications under section 505(b)(1) of the [FDCA]”).

unit at FDA responsible for drugs – not the unit responsible for other biologics like vaccines – since 2003.<sup>282</sup> The same clinical trial regulations apply to both new drugs and therapeutic biologics, and FDA’s guidance documents on pre-market research and development – such as the exploratory IND guidance, the statistical methodology guidance, the cancer endpoints guidance, and the early Alzheimer’s guidance – apply equally to both. FDA generally does not differentiate, and the statutory and regulatory paradigm does not provide any reason to think that the findings in this Article would not also apply to therapeutic biological medicines.

*Fourth*, the dataset includes forty-five new drugs that did not receive new chemical entity exclusivity. FDA denies NCE status when a drug contains the same active moiety as a previously approved drug.<sup>283</sup> The standard for patent term restoration is different and more forgiving.<sup>284</sup> The inclusion of non-NCE drugs may have skewed the results of the analysis because the premarket programs for these drugs may have been reduced if the same firm had developed the earlier drug that received exclusivity. If the firm owned the application for the prior drug (or was willing to pay for the right to reference it), relevant data from the first application could be used. In this situation, the firm might have performed only a phase 2 dose-ranging study and the phase 3 pivotal trials. Excluding the five drugs studied overseas and the thirty-three drugs approved under the antibiotic provisions prior to 1997 (because they were not eligible for NCE status), the average clinical period for the non-NCE drugs in the dataset is 4.59 years, noticeably shorter than the average for the NCE drugs, which is 6.18 years. It is unclear whether approval of non-NCE drugs with shorter premarket timelines affects some therapeutic categories or established pharmacologic classes in the dataset more than others. The correlation between pharmacologic class and length of clinical program might be more clear if one excluded the new drugs that were not NCEs and if it were possible to obtain the regulatory review period information for *all* NCEs.

*Finally*, the dataset does not include new drugs that are not new active ingredients. This includes new drugs for which patent term restoration requests were submitted and rejected, as well as new drugs for which patent term restoration requests were never submitted. Companies could face an innovation paradox when engaging in incremental innovation with old, established molecules, but the nature of the innovation is different, and a different analysis – beyond the scope of this Article – would need to be performed.

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282. Drug and Biological Product Consolidation, 68 Fed. Reg. 38,067 (June 26, 2003).

283. See discussion *supra* Part III.A.

284. See discussion *supra* Part III.A.



## VI. CONCLUSION

The problem explored in this Article is the paradoxical relationship between drug innovation and its reward. The reward shrinks (or, at best, stays flat) when premarket innovation takes longer. On the whole this should lead to post-invention efficiency, minimizing the impact of any endogenous factors contributing to the premarket program length.<sup>285</sup> It also means that companies are unlikely to make choices specifically to delay market entry. With the clock ticking on post-approval market exclusivity, there is no benefit to doing so.<sup>286</sup>

The historical and empirical work in this Article leads to three important insights about the paradoxical relationship between drug innovation and its reward.

*First*, the length of any particular drug's premarket research and development program may depend heavily on factors like the disease and its therapeutic category, our current understanding of the causal pathways of the disease, the proposed therapeutic outcome, the chemical structure of the active ingredient, its mechanism of action, its physiological effect, and FDA's innate conservatism. These exogenous factors are beyond the sponsor's control in the sense that any seasoned firm with qualified personnel picking one premarket program instead of another would face the same issues.<sup>287</sup>

*Second*, certain drugs are simply going to take longer to develop. These will include some drugs for some early stage cancers that have a longer time to progression and mortality, for instance, as well as drugs for use in the earliest

285. For instance, Bristol-Myers Squibb historically required eight months "to produce and activate a new study protocol" but has made "efforts to improve the review cycle" and reduce the internal process to five months. REBECCA A. ENGLISH ET AL., TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES: CHALLENGES AND OPPORTUNITIES 34 (2010).

286. According to Professor Roin, the product-development management literature reveals an "accepted wisdom" that because time to market "is . . . the most important factor affecting the internal rate of return" on investment, "most firms work hard to get their inventions onto the market as quickly as possible." Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672, 713 (2014). He found five explanations in the literature, one of which seems particularly salient here: that "delays diminish the innovator's window of opportunity to earn a profit from its invention." *Id.* at 714.

287. Other exogenous factors may contribute to the length of a particular premarket testing program, including raw materials that are difficult to find, the fact that studies must be performed where experts are available to serve as investigators rather than where patients may be located, and bureaucratic delays at academic institutions providing clinical trial workforces. ENGLISH ET AL., *supra* note 285, at 31, 35–36 ("U.S. academic institutions typically take longer to navigate the approval process (i.e., from budget/contract to IRB approval) compared to private or academic institutions abroad.") (citing Dr. Woodcock for proposition that "[w]hen patient recruitment is impeded, the trial is delayed, sometimes by years, until the number of patients required by the study protocol can be enrolled").

stages of neurodegenerative diseases if the therapeutic goal is delay or prevention of the ultimate outcome. They will include drugs for long-term use for conditions (such as diabetes mellitus) that significantly precede clinical events of interest (such as heart disease, stroke, and kidney damage). They will include drugs intended for less well understood body systems, like the central nervous system, where even novel surrogate markers may be years off.

*Third*, the choices faced by a company in the new drug paradigm are generally *not* choices among more and less efficient routes to the same end result. A new drug in the federal drug scheme is a particular combination of active ingredient, product features, and the labeling (disease and outcome). The research performed by a drug's sponsor thus *defines* the product approved by FDA at the end of the day. This means the sponsor's choices during the research and development period are tantamount to choices about the product to be pursued. The Paraplatin example illustrates why it may generally be more rational to select a short runway with a limited approval than a long runway with a broader approval. This decision may be due to the time value of money, but the innovation paradox suggests that it may also result from the price paid in lost effective patent life when clinical programs run longer.

As a matter of public policy we may prefer that companies facing this choice select the product with the shorter runway. But in some cases a company will not have that option. If a company must choose between a long runway and a different product altogether, the innovation paradox may mean whole areas of medicine remain underdeveloped. The implication for social welfare is that we may have a profound interest in breaking the paradox – in ensuring that *longer* research programs no longer lead to *shorter* rewards.

