

**BEYOND PATENTS:  
MITIGATING THE IMPACT OF THE HEALTH CARE CRISIS ON DRUG DEVELOPMENT**

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*We simply have invented and discovered more things to do to our aging bodies than our aging society can afford to pay for . . . . We have created a Faustian bargain where our aging bodies divert resources that our children and grandchildren need for their own families and that public policy needs for other important social goods.*<sup>1</sup>

Pharmaceuticals have provided the most compelling case for patents.<sup>2</sup> The special status of drug patents is being eroded, however, by spiraling health care costs, which put downward pressures on patent premiums, and scientific developments, which stand to erode the value of patents by shrinking markets for individual drugs and limiting entry of generic producers. These changes call for a reexamination of the role that patents play in promoting biomedical innovation and consideration of alternative policies.

The pharmaceutical and biotechnology industries are being upended by adverse market conditions and deepening scientific challenges.<sup>3</sup> Three primary factors are undercutting existing business models. Unsustainable increases in health care spending, which are spurring calls from the public and private sectors to contain costs.<sup>4</sup> Declining productivity of research and development—approvals of novel drugs hit a twenty-four-year low in 2007 despite a doubling of spending on research and development over the last decade.<sup>5</sup> And fragmentation of markets for drugs caused by scientific advances that have revealed the variation in drug efficacy and safety across patient populations. In short despite the major discoveries, biomedical science will, at least in the near term, shrink individual drug markets and magnify aggregate health care costs as multiple, personalized drugs are developed to treat subclasses of major diseases.<sup>6</sup>

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<sup>1</sup> David M. Cutler, *YOUR MONEY OR YOUR LIFE* 71 (2004) (quoting Richard Lamm former governor of Colorado).

<sup>2</sup> [cite to Levin, etc.].

<sup>3</sup> Jean-Pierr Garnier, *Rebuilding the R&D Engine in Big Pharma*, HARV. BUS. REV. 1, 1 (May 2008) (describing “the well-known perfect storm of trends—pricing pressures, regulatory requirements, legal entanglements, inroads by generics, and declining R&D productivity—that have increased the industry’s costs enormously and reduced its revenue and profit potential”).

<sup>4</sup> Henry J. Aaron, *Health Care Rationing: Inevitable but Impossible?*, 96 GEO. L. REV. 539, 543 (2008) (observing that “[t]otal health care spending [public and private] will absorb half of total increases in economic output by 2018 and all of it by 2044”).

<sup>5</sup> David Malakoff, *Spirally Costs Threaten Girdlock*, 322 SCIENCE 210, 210 (2008) (describing how drug testing costs have “skyrocketed”); Avery Johnson & Ron Winslow, *Drug Makers Say FDA Safety Focus Is Slowing New-Medicine Pipeline*, WALL ST. J., June 30, 2008, at A1 (observing that in 2007, “the FDA approved just 19 new medicines, the fewest in 24 years”); PriceWaterhouseCoopers, *Pharma 2020: The Vision Which Path Will You Take?* 1, 5-6 (2007) available at <<http://www.pwc.com/extweb/pwcpublishations.nsf/docid/91BF330647FFA402852572F2005ECC22>> (commenting that “the industry now spends far more on R&D and produces far fewer new molecules than it did 20 years ago”).

<sup>6</sup> Wesley Yin, *Market Incentives and Pharmaceutical Innovation*, 27 RES. POL. 1060, 1060 (2008) (concluding that “A model of pharmaceutical innovation founded on personalized therapeutic technologies . . . simply cannot be supported given the underlying cost parameters of drug innovation.”); Henry J Aaron & Joseph P. Newhouse, *Meeting the Challenge of Health Care Quality*, Brookings Opportunity 08 7 (2007) available at <[http://www.brookings.edu/papers/2007/0228useconomics\\_aaron\\_Opp08.aspx](http://www.brookings.edu/papers/2007/0228useconomics_aaron_Opp08.aspx)> (commenting that “A new

These trends are heightening tensions between promoting biomedical innovation and curbing health care spending. Contrary to the current focus on drug prices,<sup>7</sup> most health economists believe that expanded use of medical technologies is the primary driver of spiraling health care costs.<sup>8</sup> In fact advances in medical technologies have always increased *aggregate* health care spending, despite their capacity to reduce the costs of discrete treatments.<sup>9</sup> For many commentators, this association implies that “the control of technology [is] the most important factor in bringing costs down.”<sup>10</sup> Yet, rationing technology and controlling costs both erode demand-side market incentives. Health care policies designed to control costs consequently threaten to undermine incentives, particularly those that are patent-based, for companies to conduct costly biomedical research and development.<sup>11</sup>

This Article examines the impacts of shifting market conditions and scientific advances on patent incentives for developing new drugs. I will argue that patent incentives will weaken significantly and that complementary policies will be essential to sustaining robust research in the pharmaceutical and biotech sectors. Alternative policy instruments, some of which are already utilized modestly (e.g., research tax incentives, regulatory data exclusivity, accelerated regulatory approval), will become increasingly important. I will not assert, and do not believe, that patents are likely to become irrelevant any time soon, only that primary reliance on patents to stimulate innovation must be reevaluated. If there is a silver lining here, it is that alternative policy instruments may have the capacity to strike a more equitable balance between promoting drug development and ensuring access to new drug therapies.<sup>12</sup>

It would be difficult to overstate the magnitude of the fiscal crisis in U.S. health care, even absent the current global economic downturn. Spending in the United States on health care nearly tripled between 1985 and 2005,<sup>13</sup> while spending on prescription drugs alone increased

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approach to medical care—personalized medicine—promises both remarkable improvements in treatment and staggering increases in expenditures.”).

<sup>7</sup> Ernst R. Berndt, *The U.S. Pharmaceutical Industry: Why Major Growth in Times of Cost Containment*, 20 HEALTH AFFAIRS 100, 101 (2001) (while expenditures on drugs increased at double-digit rates from 1994 through 1999, almost eighty percent of these increases was from greater usage).

<sup>8</sup> Joseph P. Newhouse, *An Iconoclastic View of Health Cost Containment*, HEALTH AFFAIRS SUPP. 1993 152, 156 (1993); Thomas Bodenheimer, *High and Rising Health Care Costs. Part 2: Technologic Innovation*, 142 ANN. INTERN. MED. 932, 932 (2005) (“Most, if not all, economists and policy analysts believe that technologic advance is a key driver of health expenditure growth.”).

<sup>9</sup> Congressional Budget Office, *Technological Change and the Growth of Health Care Spending* 12 (Jan. 2008) available at <<http://www.cbo.gov/ftpdocs/89xx/doc8947/01-31-TechHealth.pdf>> (“advances in medicine and the changes in clinical practice that followed them have tended to raise spending.”).

<sup>10</sup> Daniel Callahan, *Health Care Costs and Medical Technology*, HASTING CENTER BIOETHICS BRIEFING BOOK 1 (2008) available at <<http://www.thehastingscenter.org/Publications/BriefingBook/Detail.aspx?id=2178>>. See also Paul Krugman & Robin Wells, *The Health Care Crisis and What to Do About It*, N.Y. REV. BOOKS \_\_, 2 (March 23, 2006) (quoting the a Congressional Budget Office report that observed “[t]he major factor associated with [the growth in health care spending] has been the development and increasing use of new medical technology”).

<sup>11</sup> Bruce Booth & Rodney Zimmel, *Prospect for Productivity*, 3 NATURE REV. DRUG DISCOVERY 451, 456 (2004) (observing that “as health care containment becomes an increasingly important issue for payers and governments, the pressure on the current R&D model will probably make it unsustainable for the industry”).

<sup>12</sup> John H. Barton & Ezekiel J. Emanuel, *The Patent-Based Pharmaceutical Development Process*, 294 JAMA 2075 2077 (2005) (creates tension between R&D and accessibility objectives).

<sup>13</sup> CBO, *supra* note 9, at 3.

*five-fold* between 1990 and 2006.<sup>14</sup> Projecting forward, if federal spending on health care (i.e., Medicare and Medicaid) continues to rise at the current rate, the costs will approach the combined revenue from federal income and payroll taxes by 2030.<sup>15</sup> Rising health care costs are also threatening private insurance—average insurance premiums in the United States for a family now almost equal the annual salary of a full-time, minimum-wage employee.<sup>16</sup> These statistics lead to the unavoidable conclusion that, although the net social benefits of medical technologies are clearly positive,<sup>17</sup> health care costs are outstripping both public and private capacities to absorb them.<sup>18</sup>

The stakes for drug development are equally great. Commentators have expressed increasing concern that private sector drug development could collapse as investors decide that the current business model is failing.<sup>19</sup> Even those health economists most vocal about the need for immediate action to reduce health care costs acknowledge that such policies would impede biomedical science.<sup>20</sup> Numerous economic studies have shown the negative impact of diminished market potential on investment in biomedical R&D,<sup>21</sup> and a recent simulation study suggests that investment rates could decline by as much as thirty percent.<sup>22</sup> These tensions are creating a severe rift in health care policy where, paradoxically, the most promising option for mitigating revenue losses from cost-containment policies is to reduce drug development costs, and the only means of reducing these costs is through costly R&D.<sup>23</sup>

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<sup>14</sup> “Spending in the U.S. for prescription drugs was \$216.7 billion in 2006, more than 5 times the \$40.3 billion spent in 1990.” (Kaiser, 1)

<sup>15</sup> Aaron, *supra* note 4, at 539-40. See also CBO, *supra* note 9, at 17 (“Current policies governing spending on Medicare and Medicaid will be unsustainable in the decades to come if historical patterns of rising health care costs continue.”).

<sup>16</sup> Henry J. Aaron and Joseph P. Newhouse, *Meeting the Dilemma of Health Care Access*, Brookings Opportunity 08 8 (2008) available at <[http://www.brookings.edu/papers/2007/0228useconomics\\_aaron02\\_Opp08.aspx](http://www.brookings.edu/papers/2007/0228useconomics_aaron02_Opp08.aspx)>. (observing that “the average annual health insurance premium for a family—\$10,880 in 2005—about equaled the earnings of a full-time, minimum-wage worker”).

<sup>17</sup> David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20 HEALTH AFFAIRS 11, 12-13 (2001) (concluding that, despite many acknowledged inefficiencies, “medical spending as a whole is clearly worth the cost” and that, in fact, “the quality-adjusted price of medical care is actually falling over time”); Alastair J.J. Wood, *A Proposal for Radical Change in the Drug-Approval Process*, 355 N. ENG. J. MED. 618, 618 (2006) (describing success of new drugs in reducing by about fifty-percent the number of deaths from heart disease and stroke over the past thirty years).

<sup>18</sup> Aaron, *supra* note 4, at 539-40; Krugman & Wells, *supra* note 10, at 2; CBO, *supra* note 9, at 3.

<sup>19</sup> Malakoff, *supra* note 5, at 210; Gary P. Pisano, 84 HARV. BUS. REV. 114, 114 (2006) (concluding that “[t]he global system of drug development and marketing is broken.”).

<sup>20</sup> Aaron, *supra* note 4, at 547 (acknowledging that “[b]y curtailing the size of the market for medical innovation, rationing would alter the financial incentives that guide investments in medical R&D”); Cutler & McClellan, *supra* note 17, at 25 (noting that “[p]olicies that eliminate waste and increase the incremental value of treatment may also directly or indirectly retard technological progress”).

<sup>21</sup> Daron Acemoglu & Joshua Linn, *Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry*, QUART. J. ECON. 1049, 1050-51 (Aug. 2004).

<sup>22</sup> Carmelo Giaccotto, et al., *Drug Prices and Research and Development Investment behavior in the Pharmaceutical Industry*, 48 J.L. ECON. 195, 212 (2005) (reporting a simulation study the predicted “the capitalized value of pharmaceutical R&D spending would have been about 30 percent lower if the federal government had limited drug price increases to the same rate of growth as the general CPI during the period 1980-2001”).

<sup>23</sup> Yin, *supra* note 6, at 1073 (arguing that the “the only way to increase innovation . . . [is to] lower[] fixed costs of drug development”); [refer to FDA Critical Path Initiative].

The prospects for neatly resolving these conflicting objectives through scientific advances is, at least for the time being, remote. In 2007 the journal *Science* announced that its pick for the scientific breakthrough of the year was “human genetic variation.”<sup>24</sup> The editors observed that researchers were for the first time “appreciate[ing] the extent to which our genomes differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.”<sup>25</sup> This recognition is consistent with recent observations that “scientific developments . . . are increasing uncertainty” in drug development.<sup>26</sup> It also highlights the extent to which broad human variation implies that few drugs will work for all or most people—the Achilles' heel of personalized medicine is that where a single drug once appeared sufficient, now multiple drugs will be necessary to treat many diseases.

These scientific insights have alarming implications for the pharmaceutical and biotech industries. Above all, they expose the depth of the scientific uncertainties and the inherent limitations of business models premised on discovering blockbuster drugs with huge markets.<sup>27</sup> Biological complexity is overshadowing the remarkable success of the Human Genome Project, recent discoveries of drugs targeted to specific genetic conditions (e.g. Herceptin, Type II diabetes), and the astonishing rate at which new targets for drugs are being identified. It is also a central reason that the massive infusions of funding over the last decade have not enhanced R&D productivity,<sup>28</sup> and that the pace of new drug development has been in decline for more than a decade.<sup>29</sup> The modest commercial success of the biotech sector, whose aggregate profits have hovered around zero or worse since it emerged in the mid-1970s, is a further testament to the magnitude of the scientific challenges.<sup>30</sup>

Growing scientific uncertainty is also impacting drug approval processes. The cost of drug development is inextricably tied to regulatory policies set by the Food and Drug Administration (“FDA”). The higher FDA standards are for drug approval and marketing, the greater the costs of drug development. As a general rule, heightened scientific uncertainty leads to more rigorous FDA review. The uncertainties and complexities exposed by recent scientific advances are also indirectly driving up the costs of drug development by adding to the costs of the FDA approval process. Human clinical trials are increasingly expensive and complicated, and the recruitment of patients is becoming increasingly difficult.<sup>31</sup> The scientific uncertainties

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<sup>24</sup> Elizabeth Pennisi, *Breakthrough of the Year: Human Genetic Variation*, 318 *Science* 1842, 1842 (2007).

<sup>25</sup> *Id.*

<sup>26</sup> Gary Pisano, *SCIENCE BUSINESS: THE PROMISE, THE REALITY, AND THE FUTURE OF BIOTECH* 64 (2006).

<sup>27</sup> Alison Abbott, *A Fiendish Puzzle*, 455 *NATURE* 1165, 1165 (2008) (observing that “the glory days of the blockbuster drug seem to be over”).

<sup>28</sup> Jeffrey Kindler, *Billion Dollar Pills*, *Economist*, Jan. 27, 2007, at \_\_\_ (“most years in the 1990s the industry spent roughly \$35 billion-40 billion on research and development and produced 35-40 new drugs. By 2004 spending had swept past \$50 billion, but the number of new drugs had fallen below 30, Now annual spending exceeds \$60 billion, but the number of new drugs has still to grow.”); Pedro Cuatrecasas, *Drug Discovery in Jeopardy*, 116 *J. CLINICAL INVESTIGATION* 2837, 2837 (2006) (R&D budget up 30-fold; aggregate R&D expenditures \$30 billion per year, greater than total NIH budget of \$28 billion).

<sup>29</sup> Barton & Emmanuel, *supra* note 12, at 2077; Pisano, *supra* note 26, at 188, 120-2 (2006) (commenting on the “crisis” in R&D productivity, particularly for new drug therapies, in the pharmaceutical industry, and noting that biotech does not have any higher R&D productivity).

<sup>30</sup> Pisano, *supra* note 26, at 65.

<sup>31</sup> Barton & Emanuel, *supra* note 29, at 2077 (noting that “research cost per new molecular entity approved is increasing 10.% per year”).

are particularly significant for new types of targeted drugs, for which FDA has required lengthier and more involved clinical testing.<sup>32</sup>

Collectively the trends in health care policy, market conditions, and scientific understanding pose fundamental challenges for new drug development. The sharpest conflict is between cost containment and providing adequate incentives for drug makers to invest in research and development. The rising costs of drug development and shrinking market-sizes for individual drugs exacerbate this central tension. Smaller markets and increased development costs will lead to either less R&D, and therefore fewer new drugs, or even higher costs as drug companies attempt to remain profitable by increasing price premiums. Evidence of extraordinary profit margins for high-value, patented therapies already exists, with some targeted drugs costing \$60,000 or more per year of treatment.<sup>33</sup>

Changes to patent doctrine cannot resolve these tensions. Notwithstanding the high premiums for specialized drugs, the incentives patents provide will shrink in response to health care reform and the changing landscape of drug development. This declining importance has two central sources. First, as is already evident in many countries outside the United States, the capacity of governments to bargain for lower drug prices limits patent premiums and thus incentives.<sup>34</sup> Second, insofar as the markets for individual drugs decline in size, aggregate market potential will also drop. Indeed, drug companies are already forced to make difficult choices between premium levels and market access. Evidence from foreign markets shows that where companies refuse to bargain and maintain high premiums, availability of such drugs is very limited—governments simply refuse to purchase them and access to valuable treatments is effectively cutoff.

Patents on new biotech drugs, which I will refer to as “biologics,” are already of secondary importance, but for a distinct set of reasons.<sup>35</sup> Unlike traditional prescription drugs, biologics are often subject to only nominal competition from generic producers. The origin of this market failure is scientific and regulatory. The primary reason is that establishing the biological equivalence of a generic biologic with the original requires elaborate and costly testing, while high manufacturing costs and technical challenges for biologics operate a second barrier to generic entry. These obstacles are compounded by the absence of an abbreviated FDA approval process for generic biologics, which for now (legislation is pending in Congress) effectively blocks marketing of generic biologics. Making matter worse, patent doctrines themselves, particularly disclosure requirements for patentability, limit the scope of patents on biologic compounds and make it relatively easy for competitors to design around them.

Global drug development, and biomedical innovation more generally, will be profoundly impacted by health care reform in the United States and recent scientific developments. The

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<sup>32</sup> Key drivers will be addition of costly screening test, earlier and broader therapeutic intervention, and increased per-drug costs due to “personalized drugs” whose costs cannot be spread (Aaron-Newhouse-Challenge, 8)

<sup>33</sup> Cuatrecasas, *supra* note 28, at 2840.

<sup>34</sup> PWC-09, 6 (concluding that “the days when pharmaceutical companies could dictate how much their medicines could fetch, without regard for the other stakeholders in the healthcare arena, are over”).

<sup>35</sup> Insulin was the first biologic to be commercialized and was quickly followed by other first-generation biologics that substituted for naturally produced proteins (e.g., insulin, human growth factor, Factor VIII); since the early 1980s, approximately sixty biologics have been commercialized. Pisano, 27.

diminished power of U.S. patents is globally significant because pharmaceutical companies, on average, draw about sixty-two percent of their profits from the U.S. market due to the high patent premiums it affords.<sup>36</sup> Further, a disproportionate (by population) amount of biomedical research and drug development is conducted by U.S. companies, and expenditures on private sector R&D are now more than double those of the public sector.<sup>37</sup> Health care policies in the U.S. and technical obstacles that erode incentives for companies to conduct costly R&D therefore stand to have widespread impacts on drug development in the absence of countervailing measures. I will argue that new policies will be needed to offset these effects and to ensure the continued vitality of the pharmaceutical and biotech industries.

This Article proceeds in three parts. Part I describes market conditions for the pharmaceutical and biotech sectors, with a focus on the likely rise of what is often referred to as “personalized medicine” and biologic compounds being developed using biotech methods. Part II discusses recent scientific developments that are affecting the costs of drug development, the size of markets for individual drugs, and regulatory approval processes for new drugs. Part III begins with an assessment of existing laws—beyond patent law—designed to promote innovation and then considers several policy options for offsetting the diminished incentives from lower (or lost) patent premiums that are likely to follow major health care reforms and emerging scientific developments.

## **I. Evolving Market Conditions for Pharmaceuticals and Biologics**

The emergence of the modern era of pharmaceutical development is a surprisingly recent phenomenon. The industry grew rapidly in the early 1980s with the introduction of new classes of drugs (e.g., antidepressants, high blood pressure medications, hormone therapies) that revolutionized the industry.<sup>38</sup> By the mid-1990s, the pharmaceutical industry was the most profitable economic sector in the U.S., and it has remained in the top five most-profitable industries ever since.<sup>39</sup>

The market growth in the pharmaceutical sector has been impressive even over the past decade. The number of prescription drugs purchased in the U.S. increased by seventy-two percent from 1997 through 2007, relative to a growth in population of just eleven percent.<sup>40</sup> Spending on direct-to-consumer advertising rose four-fold,<sup>41</sup> and despite worries that drug

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<sup>36</sup> Barton & Emanuel, *supra* note 29, at 2078; Kindler, *supra* note 28, at \_\_ (commenting that government in Europe, Japan, and Canada have demanded significant discounts in drug pricing, which have been offset by the U.S. market, “where most big drug firms earn half or more of their profits”).

<sup>37</sup> Kindler, *supra* note , at (describing the rapid increase in private sector R&D to more than \$60 billion per year); Cuatrecasas, *supra* note 28, at 2837 (noting that NIH budget is \$28 billion per year).

<sup>38</sup> Note, though, that the rise in FDA drug approvals during the mid-1990s was “part a statistical illusion, the result of unusually rapid backlog reduction as the FDA deployed the augmented staff hired under the PDHFA” (Scherer-07, 271)

<sup>39</sup> Kaiser, 3.

<sup>40</sup> Kaiser, 2.

<sup>41</sup> Kaiser, 3 (finding that spending on advertising directly to “consumers in 2007 was over 4 times the amount spent in 1996, while 2007 physician advertising was almost 2 times the 1996 amount”).

pipelines are drying up and many drugs going off patent, industry profits averaged almost sixteen percent in 2007, as opposed to less than six percent for the Fortune 500 firms.<sup>42</sup>

Expenditures on prescription drugs, as the preceding statistics suggest, are the fastest growing component of health care spending,<sup>43</sup> having risen, on average, eleven percent annually versus the seven percent for health care generally.<sup>44</sup> They are also a significant factor driving projections that Medicare will be bankrupt in nine years<sup>45</sup> and that health care costs will rise from the current \$2.1 trillion annually to \$4 trillion by 2018.<sup>46</sup> Spending on prescription drug alone is projected to increase from \$216.7 billion to \$515.7 billion over this period.<sup>47</sup>

Despite the abundance of data on health care expenditures, estimates of drug development costs have remained controversial, although they now appear to be converging.<sup>48</sup> The most cited studies highlight the up-front costs of R&D, which account for about seventy percent of pharmaceutical development expenses.<sup>49</sup> The aggregate costs of commercializing a drug, including capital costs that are borne over the fifteen-year average time for drug development, are estimated to be \$800 million to \$1.1 billion.<sup>50</sup> If post-approval R&D is

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<sup>42</sup> Kaiser, 3.

<sup>43</sup> Leslie Tucker, *Pharmacogenomics: A Primer for Policymakers*, National Health Policy Forum 3 (Jan. 2008) available at <[http://www.nhpf.org/pdfs\\_bp/BP\\_Pharmacogenomics\\_01-28-08.pdf](http://www.nhpf.org/pdfs_bp/BP_Pharmacogenomics_01-28-08.pdf)> (observing that “health insurers . . . spend more than \$250 billion per year on pharmaceuticals,” which over the past fifteen years have grown faster than any other category of health care spending).

<sup>44</sup> GAO-PD-07, 4. A similar study found that “retail prescription prices increased an average of 6.9% a year from 1997 to 2007, more than two and a half times the average annual inflation rate of 2.6%.” Kaiser, 2.

<sup>45</sup> Government Accountability Office, *Prescription Drugs: An Overview of Approaches to Negotiate Drug Prices Used by Other Countries and U.S. Private Payers and Federal Programs*, GAO-07-385T 1 (2007) available at <>.

<sup>46</sup> Callahan, 79.

<sup>47</sup> Kaiser Family Foundation, *Prescription Drug Trends* 1, 5 (Sept. 2008) available at <[http://www.kff.org/rxdrugs/upload/3057\\_07.pdf](http://www.kff.org/rxdrugs/upload/3057_07.pdf)>; F.M. Scherer, *Uncertainty and Choice: The Challenges of Pharmaceutical Efficacy, Safety, and Cost*, 28 *MANAGERIAL DECISION ECON.* 267, 267 (2007).

<sup>48</sup> Everyone agrees that the process is extremely expensive. As one commentator has put it, “Discovering and developing a new medicine takes at least 12 years, and the average cost is now more than \$1 billion—higher than NASA’s budget for sending a rocket to the moon.” Garnier-08, 2.

<sup>49</sup> John E. Calfee, et al., *An Exploratory Analysis of Pharmaceutical Price Disparities and Their Implications Among Six Developed Nations*, AEI-Brookings Joint Center for Regulatory Studies, Working Paper 06-07 2 (April 2006) available at <<http://www.aei-brookings.org/publications/abstract.php?pid=1062>> (manufacturing and other miscellaneous costs make up the remaining thirty-percent).

<sup>50</sup> Curtis R. Chong & David J. Sullivan, *New Uses for Old Drugs*, 448 *NATURE* 645, 645 (2007) (describing a study of 68 approved drugs finding “that it takes an average of 15 years and US\$800 million to bring a single drug to market”); Joseph A. DiMasi, et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 *J. HEALTH ECON.* 151, 180-81 (2003) (updating the authors’ earlier work assuming “that if growth continued and R&D was initiated in 2001 with approval 12 years later). Other studies have produced similar results, including a 2001 Boston Consulting Group study, which estimated drug development costs to be \$880 million, and one by Bain & Co., which estimated that they are about \$1.5 billion. Joseph A. DiMasi, et al., *Extraordinary Claims Require Extraordinary Evidence*, 24 *J. HEALTH ECON.* 1034, 1041 (2005). A more recent study estimated the clinical costs to be \$467 million and total capitalized expected cost per approved drug of \$868 million, with a range of \$521 million to \$2.1 billion. Christopher P. Adams & Van V. Brantner, *Estimating The Cost of New Drug Development: Is It Really \$802 Million?*, 25 *HEALTH AFFAIRS* 420, 422-23 (2006).

included the costs rise by about \$140 million.<sup>51</sup> Biotech-derived drugs, so called “biologics” or “biopharmaceuticals,” involve similar expenditures, with total capitalized costs that are estimated to average about \$1.2 billion.<sup>52</sup>

The availability of generic drugs is the only factor moderating the rising costs of prescription drugs.<sup>53</sup> A three- to five-fold difference exists between the prices of brand-name and generic drugs.<sup>54</sup> The importance of generic drugs in controlling costs is illustrated by the fact that although generic drugs constitute fifty-three percent of the unit volume of prescriptions in the U.S., they represent less than ten percent of the revenue.<sup>55</sup> However, the large divergence in costs and, as we will see, rising importance of biologics, suggest that the capacity for generics to stem cost growth much further may be limited.

### A. The Economics of Traditional Drug Development

The pharmaceutical sector is experiencing a fundamental challenge to its basic business model. Over the period from December 2000 to February 2008, the stock value of the fifteen leading pharmaceutical firms dropped by about \$850 billion, and their price-to-earnings ratio fell from an average of thirty-two to thirteen.<sup>56</sup> This dramatic downturn is prompting a shift away from relying solely on in-house development of new drugs.<sup>57</sup> The emerging model is based on R&D agreements between biotech startups, which have unique scientific knowledge, and major pharmaceutical companies that have the manufacturing and marketing resources.<sup>58</sup>

A primary driver of this reassessment is the declining productivity of the pharmaceutical industry.<sup>59</sup> Tellingly, while spending in the pharmaceutical sector on R&D has grown fifty-fold since 1970, the rate of new drug discovery has been essentially flat.<sup>60</sup> Currently, only five major pharmaceutical companies obtained more than ten percent of their sales from drugs approved within the preceding five years, and 2007 represented a low for new compounds with only eight

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<sup>51</sup> DiMasi-Hansen-03, 173 (estimating that “out-of-pocket cost per approved drug for post-approval R&D to be US \$140 million”).

<sup>52</sup> Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 *MANAGERIAL & DECISION ECON.* 469, 475 (2007). The authors note that one must be careful in making these comparisons, as biopharma data for a later period; if project pharmaceutical estimates to same time period costs very similar—biopharmaceuticals cost \$1241 million versus \$1318 million for pharmaceuticals. *Id.* at 476.

<sup>53</sup> Kaiser, at 1 (noting that “prescription spending growth slowed from 1999 to 2005 because of the increased use of generic drugs.”).

<sup>54</sup> Kaiser, 2 (noting that for drugs sold by a large number of generic producers, the generic price dropped to one fifth that of the brand name drug).

<sup>55</sup> Danzon-Furukawa, 226.

<sup>56</sup> Garnier-08, 1.

<sup>57</sup> Pisano, 85.

<sup>58</sup> Pisano, 85-86.

<sup>59</sup> Bruce Booth & Rodney Zimmel, *Prospect for Productivity*, 3 *NATURE REV. DRUG DISCOVERY* 451, 451 (2004); Scherer-07, 271 (highlight that fact that “Seven products out of ten failed to return average R&D costs”). The largest companies have been hit the hardest, as illustrated by the observation that “Top 10 drug companies had 25% of the industry’s pipeline in 1997 and [in 2004] have less than 15%.” Booth-Zimmel, 454.

<sup>60</sup> Booth-Zimmel, 451; *see also* Grabowski-Orphan, 5 (describing how R&D costs have grown “at an annual rate of 7.4% above general inflation when compared to the costs for new drug introductions of the 1980s, and that this rise has been driven by the size, number, and complexity of clinical trials).

out of twenty-seven drugs approved being “new molecular entities.”<sup>61</sup> The decline has been blamed on delays caused by overly burdensome FDA review,<sup>62</sup> undue focus on blockbuster drugs,<sup>63</sup> and a profusion of poorly characterized potential drug targets.<sup>64</sup> None of these explanations is entirely convincing. The optimists counter that it is just a matter of time before the benefits of new information and advanced methods begin to payoff.<sup>65</sup>

The economic troubles of the pharmaceutical sector have had surprisingly little impact on aggregate spending on R&D. Investment in drug development set a record in 2006 of \$55.2 billion, with pharmaceutical companies collectively investing \$42 billion.<sup>66</sup> Even taking into account inflation, the “industry is investing twice as much in R&D as it was a decade ago to produce two-fifths of the new medicines it then produced.”<sup>67</sup> At the same time, the blockbuster drug model is proving less and less economically viable.<sup>68</sup>

Declines in the pharmaceutical sector owe much to the technical challenges and economics of drug development.<sup>69</sup> On average, only 5 in 10,000 compounds makes it through drug discovery and preclinical testing, and just the earliest stages of drug development, target identification and validation, on average take 6.5 years.<sup>70</sup> Once a drug reaches clinical testing,<sup>71</sup> which is the most expensive stage of drug development, only one to two drugs out of ten tested on average will survive.<sup>72</sup> Failure rates in Phases II and III are still fifty percent,<sup>73</sup> implying that

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<sup>61</sup> PWC-09, 11.

<sup>62</sup> Booth-Zemmel, 452 (describing criticisms of FDA and countering that the FDA has not “made submissions disproportionately more challenging”).

<sup>63</sup> GAO-NDD, 28-29.

<sup>64</sup> Booth-Zemmel, 451 (arguing that the estimated 3,000 druggable targets are poorly characterized and thus increases failure rates, which are 50% higher than clinically validated targets).

<sup>65</sup> Booth-Zemmel, 454 (describing claims that the coming years will be far more productive with “lead-rich, target-rich environment” that recent scientific advances have created).

<sup>66</sup> PWC-2020, 5.

<sup>67</sup> PWC-2020, 6 (problem: there is 10+ year lag).

<sup>68</sup> Jim Gilbert, et al., *Rebuilding Big Pharma’s Business Model*, 21 IN VIVO 1, 2 (2003) (describing estimates that “the blockbuster drug model to deliver just 5% return on investment” going forward”).

<sup>69</sup> Booth-Zemmel, 451 (observing that the “most significant cause of the productivity decline has been the decrease in development survival rates, in particular the attrition rate in Phase II trials,” which “has dropped from near 50% to less than 30%”) According to at least one commentator, the problem is not only technical. He estimates that 25% of drugs in his experience were dropped for non-technical (i.e. marketing reassessments, management discontent) reasons before adequate data are available. Cuatrecasas, 2840.

<sup>70</sup> Government Accountability Office, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49 6-7 (Dec. 2006) available at <<http://www.gao.gov/new.items/d0749.pdf>>.

<sup>71</sup> There are three phases of clinical testing for drugs. Phase I involves small studies (i.e., 1-100 healthy volunteers) lasting about a year to test the safety of a drug that cost approximately \$10 million. Pisano, at 50. Phase II involves larger studies (50-500 healthy patients) lasting about one to two years that cost as much as \$40 million if multiple trials are involved. *Id.* Phase III involves the largest studies (\_\_\_ patients) lasting multiple years that cost on the order of \$ \_\_\_ million dollars. *Id.*

<sup>72</sup> Pisano, 56-57; Barton-E, 2076 (describes the success rate as comparable or about twenty-one percent). The high rate of attrition is compounded by the fact that “Pharmas will seldom out-license rejected compounds, even with generous buy-back provisions.” Cuatrecasas, 2840.

<sup>73</sup> Pisano, 56-57 (observing that the average failure rate for Phase I is 60%, for Phase II it is 50%, and for Phase III it is also about 50%).

the “vast majority” of expenditures on drug development are devoted to failed projects.<sup>74</sup> These high attrition rates have led some to despair that “Clinical trials are broken, just broken.”<sup>75</sup>

More ominously, the success rates at each stage of clinical testing are falling despite many recent scientific advances.<sup>76</sup> These trends may be attributable to the high “volume of drugs in clinical trials and the complexity of the diseases to be addressed have increased,”<sup>77</sup> which have caused clinical trials to become much more elaborate, costly, time consuming, and difficult to administer.<sup>78</sup> The duration of clinical trials increased by seventy percent between 1999 and 2006, and delays are costly because R&D costs must be capitalized for longer periods of time and because they reduce the effective lifetime of associated patents.<sup>79</sup>

## **B. The Economic Pitfalls of Personalized Medicine**

One of the central claims of personalized medicine is that it will make drugs more effective and thus potentially easier (and less costly) to get through FDA approval.<sup>80</sup> Commentators have argued that the new genomics methods, often referred to as “pharmacogenomics,” will allow companies to salvage drugs that failed clinical testing because of toxicity caused by genetic variants that affect only certain patients subpopulations.<sup>81</sup> Under this “personalized” approach, diagnostic tests would be used to identify appropriate drugs based on genetic predispositions and in doing so would enhance the overall efficacy of treatments.<sup>82</sup>

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<sup>74</sup> Pisano, 57.

<sup>75</sup> Malakoff, at 210; *see also* Cuatrecasas, 2841 (observing that “statistical theory and regulations drive trial design, under fundamentally faulty assumptions that human populations are homogeneous. As a result, an unnecessary number of very large, costly, and low-sensitivity trials are conducted or required by the FDA”).

<sup>76</sup> Jeffrey Mervis, *Productivity Counts—But the Definition Is Key*, 309 *SCIENCE* 726, 726 (2005) (describing a study of success rates in clinical trials showing that the success rate in Phase I has gone from 70% to ~62%, the success rate in Phase II from about 45% to less than 30%, and the success rate in Phase III from approximately 87% to less than 50%).

<sup>77</sup> GAO-NDD, 25-27, 31.

<sup>78</sup> David Malakoff, *Spirally Costs Threaten Girdlock*, 322 *SCIENCE* 210, 211 (2008); Kenneth Getz, *Protocol Design Trends and Their Effect on Clinical Trial Performance*, *RAJ Pharma* 315, 315 (May 2008) available at <[http://csdd.tufts.edu/\\_documents/www/Doc\\_233\\_7875\\_826.pdf](http://csdd.tufts.edu/_documents/www/Doc_233_7875_826.pdf)> (observing that “protocol designs are becoming more demanding and burdensome on investigative personnel and study volunteers. The combination of changes in the number, frequency, and type of unique procedures per protocol is driving higher levels of investigative site work burden. Growth in site work burden is, therefore, a function of both increasing complexity of protocol design and the rising administrative demand to execute these procedures”).

<sup>79</sup> Malakoff, 212.

<sup>80</sup> Ginsburg-05, 2333 (describing how “Proponents of pharmacogenomics have estimated potential reductions by 20% in the number of new compounds tested in phase 2 and 3 clinical trials, by 50% in the number of patients in phase 2 trials, by 10% in the number of patients in phase 3 trials, and by 20% in the length of phase 3 trials.” Could lead to “savings of up to \$500 million for each drug launched”).

<sup>81</sup> Geoffrey S. Ginsburg, et al., *Implications of Pharmacogenomics for Drug Development and Clinical Practice*, 165 *ARCH. INTERN. MED.* 2331, 2332 (2005) (asserting that pharmacogenomics could enable companies to “salvage” drugs that were abandoned because, for example, of “dose-related toxicity [that] is linked to a genetics variant in a drug metabolizing enzyme”).

<sup>82</sup> Ginsburg-05, 2333.

All of these claims are contested and subject to large uncertainties. It remains unclear whether new pharmacogenomic methods will lower the costs of clinical trials.<sup>83</sup> Indeed, some experts suggest that in the near term it is more likely to increase costs because it will increase the complexity of clinical testing, make it more difficult to obtain adequate patient samples, and add to the time it takes to conduct clinical testing.<sup>84</sup>

The often overlooked downside of personalized medicine is that it has the potential to shrink the markets for individual drugs while requiring a larger number of drugs to treat the same population.<sup>85</sup> This is unlikely to lead to aggregate cost savings, for while drugs may be more effective, they are very likely to be more expensive because larger investments in R&D will be required to serve a genetically differentiated population.<sup>86</sup> This exposes the critical “dilemma of personalized medicine—in order to make a return on far fewer patients, manufacturers have to increase prices.”<sup>87</sup> These predictions are already being realized, with many specialized drugs costing tens of thousands of, or even more than a hundred thousand, dollars per year.<sup>88</sup>

Some commentators have nevertheless argued that the markets for individual drugs could expand as new uses for them are identified.<sup>89</sup> Several drugs (e.g., Remacade, Herceptin, Rituxan) have proven this to be more than mere speculation, as each has been found to treat a range of conditions.<sup>90</sup> It remains unclear, however, how generalizable these claims are, as their confirmation requires a much better understanding of disease causality than we are likely to have in the near future.<sup>91</sup>

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<sup>83</sup> (observing that “whether pharmacogenomics will reduce the cost of clinical trials is still an open question”); Schmid-Smith, 1001.

<sup>84</sup> Tucker-08, 23; Horrobin-01, 1100 (arguing that patient recruitment likely to be a nightmare—must conduct genetic testing first and then, assuming works for 10% of population, must reject 90% of patients undergoing initial screens). Further, while the efficacy of drugs is likely to be high for certain subpopulations and easier to show (justifying smaller trials), safety issues will preclude lowering of costs of clinical trials because safety cannot be established using animal toxicology or small-scale clinical trials. Horrobin-01, 1100.

<sup>85</sup> Ginsburg-05, 2334 (arguing that “[a]s more products are brought to market for smaller subsets of patients, the cost of pharmaceutical therapy is likely to increase . . . the result is likely to be greater efficacy and safety at additional cost.”).

<sup>86</sup> David F. Horrobin, *Realism in Drug Discovery—Could Casandra be Right?*, 19 NATURE BIOTECH 1099, 1099 (2001).

<sup>87</sup> Schmid-Smith, 1001.

<sup>88</sup> Cuatrecasas, 2840 (describing examples including Rituxan for lymphoma, which costs \$13,000-\$25,000 per treatment cycle; Herceptin, which costs about \$3,200 per month; Avastin, which runs about \$60,000 per year; Erbitux (head neck cancer), which costs about \$110,000 per year; Cerezyme (Gaucher disease), which runs between \$200,000 (children) and \$600,000 (adults) per year); PWC-2020, 10 (discussing the costs of drugs Multiple Sclerosis, which range in price from \$19,289 (Betaseron) to \$28,400 (Tysabri) per year of treatment); John E. Calfee & Elizabeth DuPre, *The Emerging Market Dynamics of Targeted Therapeutics*, 25 HEALTH AFFAIRS 1302, 1302 (2006) (observing that targeted cancer drugs (e.g., Herceptin, Gleevec, Avastin, Erbitux) “have attracted attention for remarkable effectiveness, high prices, and, at least potentially, their impacts on overall health costs”).

<sup>89</sup> Ginsburg-05, 2333.

<sup>90</sup> Calfee-DuPre, 1303 (stating that a “narrow biological target does not imply a narrow therapeutic effect” and giving the examples of Remacade, which is now approved for Crohn’s disease, arthritis, colitis); Calfee-AEI-07, 4 (discussing how Rituxan was first approved for cancer, but later found to be useful for rheumatoid arthritis as well).

<sup>91</sup> Ginsburg-05, 2333 (describing, for example, how “market expansion may be limited by a lack of understanding of disease causality” as well as “financial and regulatory barriers”).

### C. The Anticompetitive Properties of Biologics

Biotech drugs are the “fastest growing and most expensive” class of prescription drugs,<sup>92</sup> and although still small relative to the pharmaceutical market, one of increasing importance. In absolute terms the \$50 billion it generates annually is significant,<sup>93</sup> and with biologics costing as much as ten to twenty times more per dose than traditional prescription drugs, there is every reason to believe that this sector will continue to grow rapidly.<sup>94</sup> Biologics are also attractive because they have proven resistant to efforts by countries with national health care systems to negotiate discounted prices.<sup>95</sup>

The distinctive characteristics of biologics markets are shaped by the complex chemical properties of the compounds.<sup>96</sup> These properties make it very difficult to establish that a generic version of a biologic is “bioequivalent” to the original brand-name drug. For similar reasons, the costs and technical challenges of producing a biologic drug are dramatically greater than for traditional drugs. Biologics also suffer from the same high attrition rates as traditional prescription drugs.<sup>97</sup>

These technical barriers have created a regulatory bottleneck because they preclude using the FDA’s abbreviated approval process for generic drugs.<sup>98</sup> Moreover, once a process is in place FDA is likely to require substantially more data for generic biologics than for generic version of tradition drugs.<sup>99</sup> This will substantially increase development times for and costs of commercializing generic biologics.<sup>100</sup> Collectively, these barriers stand to limit production of generic biologics to the largest firms, as only they will be in a position to absorb the large

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<sup>92</sup> Tucker-08, 11; *see also* Grabowski-08, 483 (commenting that “biotech drugs are the fastest growing segment of new therapeutics” and “more likely to be first in class or novel”); C. Thomas Caskey, *The Drug Development Crisis: Efficiency and Safety*, 58 ANN. REV. MED. 1, 2, (2007) (“biotech industry accounts for ~35% of new drug candidates”).

<sup>93</sup> John E. Calfee, *Facing Reality on Follow-On Biologics*, Health Policy Outlook 1 (April 2007) *available at* <[http://www.aei.org/publications/pubID.26010/pub\\_detail.asp](http://www.aei.org/publications/pubID.26010/pub_detail.asp)>. Profits from individual biologics, like those of biotech companies, are highly skewed. Twelve biologics have sales that exceed \$1 billion, and these compounds account for a disproportionate share of the total revenue from all biologics, while twenty-nine have sales that exceed \$250 million, which collectively constitutes ninety percent of the biologics market. Lanthier, 734.

<sup>94</sup> Michael Lanthier, et al., *Economic Issues with Follow-On Protein Products*, 7 NATURE REV DRUG DISCOVERY 733, 733 (2008).

<sup>95</sup> Calfee-DuPre, 1304 (observing that “biologic drugs were priced far higher abroad than nonbiotech drugs and were essentially at parity with U.S. in Canada and France”).

<sup>96</sup> Calfee-AEI-07, 2 (making that case that “The biologics market will likely never resemble the simple world of traditional generics”).

<sup>97</sup> Janice M. Reichert, *Trends in US Approvals: New Biopharmaceuticals and Vaccines*, 24 TRENDS BIOTECH. 293, 293 (2006). Note that biologics are not approved under an NDA, but under the Public Service Act pursuant to a Biologics Licensing Application. Harbour-FTC, 10.

<sup>98</sup> Calfee, 1303.

<sup>99</sup> Calfee-AEI-07, 3; Woodcock-07, 438 (commenting that the current FDA presumption is that data for generic biologic same as original, although FDA allows for certain exceptions). For some biologics (e.g., monoclonal antibodies, experts predict that “it will be many years before any sort of follow-ons for these drugs appear, regardless of patent expirations.” *Id.*

<sup>100</sup> Lanthier, 734, 736 (concluding that “follow-on proteins are likely to be significantly more costly to develop than are small-molecule generic drugs” and estimating that development times for generic are likely to be five to eight years versus one to two years for traditional small-molecule drugs); Grabowski-Biologics, 447 (predicting that generic biologics will require some testing in humans, which will dramatically increase fixed development costs).

upfront costs involved in manufacturing biologics.<sup>101</sup> Thus, even once a regulatory approval processes is established, it is unlikely to lead to entry of large numbers of generic producers.<sup>102</sup>

The high costs of biologics do not end with their development; manufacturing them is far more complex and costly than those for traditional drugs.<sup>103</sup> These technical challenges create two major obstacles to potential generic producers. First, the high cost of constructing a plant and running it create large barriers to market entry that do not exist for traditional drugs. Second, it is virtually impossible to replicate the processes used to make biologics, and in this sense “the process is the product.”<sup>104</sup> Regulatory approval is inextricably tied to manufacturing processes because subtle, but biologically significant, difference are difficult to detect.<sup>105</sup>

The obstacles to entry of generic biologics limit downward pressures on the pricing of biologics after patent protection lapses.<sup>106</sup> The smaller size of many of the markets for biologics will compound these problems, as smaller markets typically attract fewer generic entrants.<sup>107</sup> Recent studies have used models to estimate the number of generic producers and the drops in pricing for biologics once entry occurs. Using conservative R&D costs assumptions, one study estimated that the number of generic entrants would drop two, as opposed to nine for traditional drugs, and that the generic price would remain at eighty-two percent of the brand price.<sup>108</sup> Other

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<sup>101</sup> Harbour-FTC, 19.

<sup>102</sup> Calfee-AEI-07, 2 (arguing that establishing a path for FDA approval of biologics will increase generic entrants and “dramatically reduce drug prices . . . are wrong”). Evidence already exists that market entry will be limited. Conjugated hormonal contraceptives, which raise similar manufacturing challenges, have only two to three generic competitors despite the large size of the market. Grabowski-Biologics, 448.

<sup>103</sup> Pamela Jones Harbour, FTC Commissioner, *The Competitive Implications of Generic Biologics* (Jun. 2007) available at <<http://www.ftc.gov/speeches/harbour/070614genbio.pdf>> (observing that “biologics are expensive, in part, because they cost so much to develop and manufacture”); Calfee-Villarreal, 16 (commenting that “manufacturing costs are typically much higher for biotechnology drugs”); Manheim-06, 397.

<sup>104</sup> Harbour-FTC, 6 (describing how even slight changes, even of equipment or facilities, can have significant impacts of safety and efficacy, and these molecular changes may not be detectable using standard analytical methods); Calfee-AEI-07, 2 (“most biologics are highly complex proteins grown in living systems . . . [and] the final compound cannot be described in simple terms”).

<sup>105</sup> Harbour-FTC, 7 (concluding that “[a]t best, a follow-on biologic may be ‘biosimilar’ to an existing biologic”); Calfee-AEI-07, 2 (arguing that while methods will likely improve in the future, “subtleties such as protein folding, which can strongly alter a biologic’s effects in the body, will make that goal elusive for some time”); Manheim-06, 397 (concluding that because subtle process changes can lead to subtle structural changes that transform the functionality of a biologic, it is “virtually impossible for a follow-on company to show that its product is identical to an innovator’s [biologic] product”); Janet Woodcock, et al., *The FDA’s Assessment of Follow-On Protein Products: A Historical Perspective*, 6 NATURE REV DRUG DISCOVERY 437, 438 (2007)..

<sup>106</sup> Calfee-DuPre, 1303 (arguing that generic biologics “will exert no more than a modest effect on post patent prices of targeted large-molecule drugs” for the foreseeable future); Harbour-FTC, 19 (suggesting that “entry by follow-on biologics may not meaningfully bring prices”).

<sup>107</sup> Henry G. Grabowski, et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL DEC. ECON. 439, 440 (2007) (suggesting that large differences in levels of entry between large and small markets, with latter much less likely to have many entrants). It is important to recognize, however, that given the large aggregate size of these market that even small percentage drops collectively can lead to large drops in aggregate costs. One recent study estimated savings from generic biologics would be \$3.6 billion for federal government and \$71 billion for health insurers over the next 10 years. Lanthier, 736.

<sup>108</sup> Grabowski-Biologics, 440.

studies have predicted price drops for biologics of just ten to thirty percent from the brand-name prices.<sup>109</sup>

These regulatory and market dynamics have led a number of commentators to conclude that markets for biologics will be far less competitive than those of traditional prescription drugs.<sup>110</sup> Put another way, patents will not limit the effective duration of market exclusivity for biologics.<sup>111</sup> Further, because biologics often do not have competitive substitutes,<sup>112</sup> the absence of generic competition means that biologics producers will be in a much stronger position to charge premium prices for their products indefinitely.

Two countervailing factors may partially offset this anticompetitive state of affairs. First, it gives producers strong incentives to continue to conduct R&D on alternative uses of a biologic, as there is little risk of competition limiting their ability to recoup these expenses.<sup>113</sup> Aggressive follow-on investment is already being observed for a number of biologics.<sup>114</sup> Second, the insensitivity of biologics to patent rights also immunizes them against the relatively narrow scope of rights that large biomolecules receive under existing patent doctrines.<sup>115</sup> Design-around competition is also potentially easier for biologics, as once a given pathway is identified, competitors can select other targets associated with it.<sup>116</sup> Thus, while patents may present a modest obstacle to market entry by generic producers,<sup>117</sup> the regulatory and technical barriers appear to more than offset these doctrinal shortcomings.

The market conditions for biologics therefore differs substantially from that of traditional prescription drugs. Direct competition with generic competitors is likely to be far less than that for traditional drugs, affording biologic producers effectively indefinite periods of market exclusivity. One might expect, as we are already seeing, that biologics will have high price premiums, and that this will be especially true when they have both high efficacy and no

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<sup>109</sup> Alexis Ahlstrom, et al., *Modeling Federal Cost Savings from Follow-On Biologics*, Avalere 9 (April 2007) available at <[http://www.avalerehealth.net/research/docs/Modeling\\_Budgetary\\_Impact\\_of\\_FOBs.pdf](http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf)>.

<sup>110</sup> Grabowski-Biologics, 448-49; Calfee, 1303 (concluding that “for the foreseeable future, biosimilar drugs will exert no more than a modest effect on postpatent prices of targeted large-molecule drugs”).

<sup>111</sup> Wood-06, 619 (“because of lack of a path for FDA approval of generic biologic products (“biogenerics”), these products have an effectively unlimited period of exclusivity even when their patent life is exhausted”).

<sup>112</sup> Calfee-Villarreal, 16 (observing that biologics also “usually have no close substitutes”).

<sup>113</sup> Calfee-DuPre, 1305 (arguing that “without the prospect of generic entry, research investment on a pioneer drug does not face a natural end-point. Absent overwhelming inventing-around . . . we can expect research to continue almost indefinitely”).

<sup>114</sup> For example, Avastin, which was originally approved for colorectal cancer, is being aggressively studied for its effectiveness against twenty other cancers. Calfee-AEI-07, 4; Calfee-DuPre, 1303, 1306. Similarly, Remicade is now approved for treatment of Crohn’s disease, arthritis, and colitis. Calfee-DuPre, 1303.

<sup>115</sup> Rebecca S. Eisenberg, *The Shape of Things to Come: Pharma’s Nonobviousness Problem*, 12 LEWIS & CLARK L. REV. 375, 376-78 (2008); Editorial, *Risks, Returns and Reassurance*, 7 NATURE REV. DRUG DISCOVERY 545, 545 (2008) (“it seems that the patents for biologics could be considerably more vulnerable to challenges or circumvention. For this reason, data exclusivity [may be an attractive alternative]”). [need cites to law review articles on limited scope of biotech patents].

<sup>116</sup> Grabowski-08, 484; Calfee-DuPre, 1306 (arguing that once a pathway is identified as relevant, research will evaluate all potential targets associated with it to develop competing drugs).

<sup>117</sup> Harbour-FTC, at 14 (suggesting that “for many biologics, patents may not be an obstacle to generic entry”).

substitutes.<sup>118</sup> This should not be read to imply that biologics will be free of competitors. Where the potential markets are large, competitors will seek out other closely related targets to develop competing drugs. This is precisely what has occurred with the specialized breast cancer drug Herceptin, which must now compete with the drugs Iressa and Tarceva, both of which target a different receptor in the Herceptin pathway.<sup>119</sup> Where alternative targets or therapies are not readily discoverable, however, biologics will have few if any competitors.

## II. Emerging Scientific Challenges and Opportunities

It is difficult to appreciate the significance of the recent advances in drug development. One relatively simple measure is the growth in potential drug targets identified using genomics technologies. Genomics methods have revealed that the number of potential drug targets is likely six to eight thousand.<sup>120</sup> To put this in context, as of 2006 scientists estimated that approved drugs in the United States were based on 266 molecular targets.<sup>121</sup> Screening methods have also become far more powerful—scientists can now screen one million compounds in a week, whereas twenty years ago the number was one hundred.<sup>122</sup> At this point, the number of targets being identified is outpacing scientific capacity to study them systematically.<sup>123</sup>

The biomedical sciences are also changing at a deeper level.<sup>124</sup> Originally, genes were understood purely functionally as the source of heritable traits, and genes were believed to code for specific traits according simple Mendelian principles. Once Watson and Crick discovered the structure of DNA, this simple model began to break down. By the 1980s, a revolution in scientific understanding was occurring and this process was accelerated with the advent of genomics technologies during the 1990s.<sup>125</sup>

Scientists are now reconsidering earlier theories about genes,<sup>126</sup> grasping that most genetic conditions are highly complex and influenced by environmental factors,<sup>127</sup> and struggling

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<sup>118</sup> Calfee, 1307 (predicting that “we can expect rapid accretion of what might be called QALY-driven drugs: drugs that provide large benefits, especially for previously poorly treated conditions, but at high prices and, often, significant total expenditures”).

<sup>119</sup> Calfee-DuPre, 1306.

<sup>120</sup> Yves Landry & Jean-Pierre Gies, *Drugs and Their Molecular Targets: An Updated Overview*, 22 *FUNDAMENTAL & CLINICAL PHARMA.* 1, 1 (2008); Peter Imming, et al., *Drugs, Their Targets and the Nature and Number of Drug Targets*, 5 *NATURE REV. DRUG DISCOVERY* 821, 821 (2007) (estimated that 5000 could be targeted by traditional drugs, 2,400 by antibodies, and about 800 by protein therapeutics).

<sup>121</sup> Landry-Gies, 1; *but see* Pisano, 31 (suggesting that all of the drugs currently commercialized are based on just 500 targets).

<sup>122</sup> Pisano, 38. Screening of 100,000 to 300,000 compounds typically reveals 100-200 drug candidates, which upon further testing reduce down to one to two compounds worth more extensive analysis. *Id.*

<sup>123</sup> Pisano, 68 (discussing how the number of scientific papers per potential drug target has dropped from one hundred in 1993 to eight in 2002).

<sup>124</sup> Thomas R. Gingeras, *Origin of Phenotypes: Genes and Transcripts*, 17 *Genome Res.* 682, 682 (2007) *available at* <<http://genome.cshlp.org/content/17/6/682.abstract>>.

<sup>125</sup> PWC-2020, 5 (concluding that “the human genome has proved more complex and less amenable to mechanistic analysis than many scientists anticipated”).

<sup>126</sup> Gerstein-07, 669 (“The discrepancy between our previous protein-centric view of the gene and one that is revealed by the extensive transcriptional activity of the genome prompts us to reconsider now what a gene is.”)

to understand a new class of “epigenetic” heritable traits that control gene regulation.<sup>128</sup> To give one example, only about 1.2 percent of the human genome codes directly for proteins (i.e., biologically active compounds), but almost five percent of it is subject to natural selection, which means that so called non-coding sections of the genome must have some functional significance for an organism’s survival.<sup>129</sup> These purely regulatory segments of the genome reflect a level of complexity that is only now being factored into biomedical research.

### A. The Complexity of the Human Genome

Recent scientific developments, while undeniably exciting, are raising concerns among scientists that understanding is not keeping pace with the welter of information that is being produced.<sup>130</sup> According to one prominent critic of the genomics revolution, “we might be making bigger haystacks as opposed to finding more needles.”<sup>131</sup> The identification of specific genetic risk factors for complex diseases like Alzheimers, which has been linked to a genetic mutation for over twelve years, have not led to any therapeutic advances.<sup>132</sup> Most forms of cancer also display a high degree of genetic complexity—multiple associated genetic mutations and wide variability between patients in their health impacts.<sup>133</sup>

Accordingly, while genomic studies have identified genetic associations for many diseases, from about one hundred in the 1980s to more than 2200 in 2008, the significance of these genetic variants remains highly uncertain.<sup>134</sup> A primary reason for this persistent

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<sup>127</sup> David Altshuler, et al., *Genetic Mapping in Human Disease*, 322 SCIENCE 881, 881 (2008) (“Despite great hopes, [to find simple Mendelian traits] for common forms of human disease—such as diabetes, heart disease, and cancer—that show complex inheritance in the general population.”); David F. Horrobin, *Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality?*, 2 NATURE REV. DRUG DISCOVERY 151, 154 (2003) (describing studies of twins that suggest environmental factors may account for forty to ninety percent of diseases susceptibility).

<sup>128</sup> Romulo M. Brena, et al., *Toward a Human Epigenome*, 38 NATURE GENETICS 1359, 1359 (2006) (describing these processes, referred to “epigenetic,” as involving “interplay of DNA methylation, histone modifications and expression of noncoding RNAs, in the regulation of gene expression patterns from early development to adulthood”).

<sup>129</sup> Gerstein-07, 673. A recent study found that “a vast amount of DNA, not annotated as known genes, is transcribed into RNA . . . . While the majority of the genome appears to be transcribed at the level of primary transcripts, only about half of the processed (spliced) transcripts detected across all the cell lines and conditions mapped is currently annotated as genes.” *Id.*

<sup>130</sup> Imming-Sinning, 830 (observing that “The recent progress made in our understanding of biochemical pathways and their interactions with drugs is impressive. However, it may be that ‘the more you know, the harder it gets’”).

<sup>131</sup> Horrobin-00, 342.

<sup>132</sup> Anna C. Need, et al., *Priorities and Standards in Pharmacogenetic Research*, 37 NATURE GENETICS 671, 671 (2005) (observing that “the ε4 allele of the gene APOE has been known for 12 years to be a risk factor for Alzheimer disease, [but] its identification has not yet helped to create effective medicines or prevention strategies”).

<sup>133</sup> Laura J. van’t Veer & Rene Bernards, *Enabling Personalized Cancer Medicine Through Analysis of Gene-Expression Patterns*, 452 NATURE 564, 564 (2008) (concluding that “it has become clear that that cancer develops as a result of multiple genetic defects and that individuals with the same type of cancer often have dissimilar genetic defects in their tumors. This findings explains why patients who seem to have similar cancers respond in a heterogeneous manner to anticancer agents and shows clearly the huge obstacle to providing effective treatments for cancer.”).

<sup>134</sup> Alshuler-Daly, 881 (concluding that “it remains unclear how much of the heritability of common disease [genetics] explain”).

uncertainty is that complex diseases often “involve dozens, if not hundreds, of contributing genes, combined with an unknown number of environmental factors.”<sup>135</sup> This makes detecting enhanced disease susceptibility exceedingly difficult, as it involves rare genetic variants that cannot be resolved from standard background variation.<sup>136</sup>

Even putatively simple genetic conditions are proving to have a large array of genetic variants.<sup>137</sup> Metabolic proteins important to drug metabolism, and implicated in many adverse drug reactions, are illustrative of this complexity. In one case prominent case, scientists found that seventy-eight percent of the adverse drug reactions tied the TPMT enzyme were not associated with the primary mutation believed to deactivate it.<sup>138</sup> Similarly, although more than seventy mutations have been identified for a related metabolic enzyme (CYP2D6), no genetic test exists for predicting its activity despite the enzyme’s sixty-fold variance in activity.<sup>139</sup>

Similar findings are emerging for other genetic conditions assumed to be simple. The now famous BRCA1 and BRCA2 genes associated with breast cancer, upon closer study, reveal much more genetic variation than previously thought.<sup>140</sup> The primary gene associated with Cystic Fibrosis, which was originally believed to be a simple Mendelian trait, has more than one thousand genetic mutations.<sup>141</sup> Finally, the metabolic condition PKU, for which every infant in the U.S. is tested at birth, was also thought to be simple, but is now associated with five hundred mutations in the primary protein as well as mutations in other related enzymes.<sup>142</sup>

These findings are leading scientists to conclude that “most, if not all, human genes have about 3 to 10 major [mutations], and dozens or hundreds, of rare [ones].”<sup>143</sup> An important corollary of these findings, however, is that individuals with rare detrimental mutations (i.e., a population frequency of less than a one percent) are unlikely to be discovered or protected.<sup>144</sup> In essence, the high degree of human genetic variability that exists will circumscribe, if not all but precludes, clinical uses of genetics tests for many complex diseases.<sup>145</sup>

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<sup>135</sup> Nebert-Zhang, 197.

<sup>136</sup> Alshuler-Daly, 885 (“the universe of rare structural changes contributing to each disease may be as large and diverse as the common [single-nucleotide variants]” found in the human genome (i.e., in the millions)). Yet, the state-of-the-art genomic maps do not have the resolution to cover genetic mutations with frequencies below five percent, but it is these variants that may be of particular significance because “[genetic variants] with strong deleterious effects are constrained by natural selection from becoming too common.” *Id.*; Need-Motulsky, 679 (haplotype tagging is only effective for common variants of alleles (>5%), but not for polymorphisms with a minor or rare frequency).

<sup>137</sup> Nebert-Vesell-04, 272 (commenting that “virtually no examples can be cited in which a single DNA variant site (genotype) is always associated with a particular trait (phenotype)—in all subjects within all human populations”).

<sup>138</sup> Nebert-Vesell-04, 268.

<sup>139</sup> Nebert-Vesell-04, 268 (although the authors caution that this may be overly optimistic, scientists predict that “predictive genotyping for CYP genes will improve clinical efficacy for all drug therapy by 15% to 25%, thereby decreasing adverse drug reactions by 10-20%”).

<sup>140</sup> Nebert-Zhang, 195.

<sup>141</sup> Esther F. Schmid & Dennis A. Smith, *Pharmaceutical R&D in the Spotlight: Why is There Still Unmet Medical Need?*, 12 DRUG DISCOVERY TODAY 998, 1000 (2007); Nebert-Zhang, 190.

<sup>142</sup> Daniel W. Nebert, *From Human Genetics and Genomics to Pharmacogenetics and Pharmacogenomics: Past Lessons, Future Directions*, 40 DRUG METABOLISM 187, 190 (2008).

<sup>143</sup> Nebert-Vesell-04, 268.

<sup>144</sup> Nebert-Vesell-04, 268.

<sup>145</sup> Nebert-Vesell-04, 272.

Epigenetics, which concerns heritable changes gene regulation that do not involve changes in DNA sequences, adds a further layer of complexity.<sup>146</sup> These heritable traits typically involve modifications to chemicals closely associated with DNA, such as chemicals associated with its translation or the chemical scaffolding on which DNA is organized.<sup>147</sup> However, “unlike the genome, the epigenome is highly variable between cells and fluctuates in time according to conditions even within a single cell.”<sup>148</sup> Thus, while epigenetic traits are stable, they can be readily affected by environment conditions over the course of an organism’s life.<sup>149</sup>

The critical role of epigenetic factors is now well established in cancer, asthma, and developmental processes.<sup>150</sup> The implications for cancer have been particularly important, as it has been shown that epigenetic factors are critical “in all stages of cancer development.”<sup>151</sup> Work on epigenomics has led to a number of striking findings, such as the discoveries that “cigarette smoking by a grandmother increases the risk of asthma in the granddaughter” and that poor nutrition in a male at the time of puberty is correlated with a four-fold reduced risk of type-2 diabetes in his grandson.<sup>152</sup> All of these findings challenge deterministic views of genetic susceptibility and human disease.

While the field of epigenetic is still in an infancy, it is already generating results that are challenging established scientific theories. Among the most important, and surprising, results is the finding from a recent high-resolution map of a segment of the human genome that only sixty percent of actively translated DNA subsequences coded for proteins.<sup>153</sup> This result demonstrates that many gene regulatory elements are completely uncharacterized. The study also found that arrangement of and mechanisms for regulating genes is far more complex and spread out across the genome than scientists had previously assumed.<sup>154</sup>

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<sup>146</sup> Jones-Baylin, 683.

<sup>147</sup> Jones-Baylin, 683 (describing how epigenomic “gene silencing at the level of chromatin . . . is particularly important in orchestrating key biological processes, including differentiation, imprinting, and silencing of large chromosomal domains such as the X chromosome”). Types of epigenetic mechanisms include histone modification, positioning of histone variants, nucleosome remodeling, DNA methylation, small and non-coding RNAs; these modifications “interact with transcription factors and other DNA-binding proteins” to alter rates of transcription. Peter A. Jones, et al., *Moving Ahead with an International Human Epigenome Project*, 454 NATURE 711, 711 (2008).

<sup>148</sup> Miho M. Suzuki & Adrian Bird, *DNA Methylation Landscapes: Provocative Insights from Epigenomics*, 9 NATURE REV. GENETICS 465, 465 (2008); Florian Eckhardt, *DNA Methylation Profiling of Human Chromosomes 6, 20, and 22*, 38 NATURE GENETICS 1378, 1381 (2006) (DNA methylation patterns have been to differ significantly between different cell types).

<sup>149</sup> Adrian Bird, *Perceptions of Epigenetics*, 447 NATURE 396, 396 (2007); Jones-Baylin, 683.

<sup>150</sup> Suzuki-Bird, 474 (“Aberrant DNA methylation in cancer has been persuasively argued”); Nebert-Zhang, 199.

<sup>151</sup> Peter A. Jones & Stephen B. Baylin, *The Epigenomics of Cancer*, 128 CELL 683, 683 (2007); Editorial, *Between Genotype and Phenotype*, 38 NATURE GENETICS 1355, 1355 (2006) (describing studies showing that certain colon cancers in humans correlated with specific patterns of DNA methylation (GpG island methylation).

<sup>152</sup> Nebert-Zhang, 198; Bird-07, 396 (“Mouse agouti locus, which affects coat color, is the best-studied example [in animals], being affected by the extent of DNA methylation at an upstream transposon”).

<sup>153</sup> George M. Weinstock, *ENCODE: More Genomic Empowerment*, 17 GENOME RES. 667, 667 (2007) available at <<http://genome.cshlp.org/content/17/6/667.full>>.

<sup>154</sup> Nebert-Zhang, 202 (discussing how scientists found “many new transcription start-sites, with an arrangement of far more complex regulatory sequences and binding of transcription factors than heretofore

## B. Implications for Drug Development

Mitigating or avoiding adverse effects associated with drugs is a primary of motivation for genetic testing and “personalized” approaches to drug prescription and development. A third of the visits to hospital emergency rooms by seniors in 2005 and 2006 were attributable to adverse effects from three drugs.<sup>155</sup> In 1992, “2 million hospitalized patients experienced serious adverse drug reactions, and more than 100,000 fatalities occur as a result—ranking adverse drug reactions as the fifth leading cause of death in the U.S” at the time.<sup>156</sup> Human genetic variation also affects the efficacy of drugs and, in combination with environmental influences, causes drugs to be ineffective in more than fifty percent of the individuals taking them.<sup>157</sup>

Drug metabolism exemplifies this variability.<sup>158</sup> The blood-thinning drug Warfarin, which is currently taken by more than 2.1 million Americans, is a model example.<sup>159</sup> Dosing of Warfarin requires very careful calibration. Dosage levels vary by a factor of 120 due variable patient response, and the adverse effects (dangerous internal bleeding) are potentially life threatening.<sup>160</sup> Warfarin dosing nevertheless relies largely on trial and error, despite there being a well-established genetic association. As is the case with most drugs, this association does not allow precise dosing because only about a third of the variation in response is attributable to genetics and just seventeen to twenty-one percent to established clinical indicators.<sup>161</sup> The existing tests simply do not eliminate enough of the uncertainty to be relied on.

The clinical difficulties associated with Warfarin highlight the complex genetic interactions that influence drug safety and efficacy.<sup>162</sup> It is the exceedingly rare case in which the biochemistry and genetics of a drug are fully understood,<sup>163</sup> and the analytical challenges alone create a major stumbling block to predictive testing.<sup>164</sup> A potential saving grace may be that because the use of drugs is a recent occurrence from an evolutionary perspective, genetic variants that lead to adverse responses may exist at relatively high frequencies in the human

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imagined”); see also Mark B. Gerstein, *What is a Gene, Post-ENCODE? History and Updated Definition*, 17 GENOME RES. 669, 669 (2007) available at <<http://genome.cshlp.org/content/17/6/669.full>>.

<sup>155</sup> Lesko-08, 301.

<sup>156</sup> Kathleen M. Giacomini, et al., *When Good Drugs Go Bad*, 446 NATURE 975, 975 (2007); Daniel W. Nebert & Elliot S. Vesell, *Advances in Pharmacogenomics and Individualizing Drug Therapy: Exciting Challenges that Lie Ahead*, 500 EUROPEAN J. PHARMA. 267, 268 (2004); Tucker-08, 3 (describing how “adverse drug reactions are the 6<sup>th</sup> leading cause of hospitalization and death in the U.S”).

<sup>157</sup> Tucker-08, 3.

<sup>158</sup> Goldstein-05, 1571 (describing how 34 variants of genes described in the literature involve “genes that are either the target of the drug or are enzymes that are involved in metabolizing the drug (or in the relevant pathway) or one of its metabolites”).

<sup>159</sup> Evans-06, 757.

<sup>160</sup> Robert F. Service, *Going From Genome to Pill*, 308 SCIENCE 1858, 1859 (2005).

<sup>161</sup> L. J. Lesko, *The Critical Path of Warfarin Dosing: Finding an Optimal Dosing Strategy Using Pharmacogenetics*, 84 CLINICAL PHARMA. & THERAPEUTICS 301, 3010 (2008).

<sup>162</sup> Need-Motulsky, 678 (stating that “in general [drug] response is a product of interacting polymorphisms in multiple genes”).

<sup>163</sup> Need-Motulsky, 679 (describing an examples in which of “the 124 genes associated with response to common leukemia drugs, only 3 had been implicated in previous candidate gene studies”).

<sup>164</sup> Need-Motulsky, 678 (challenge is that “the huge number of comparisons involved when interactions among polymorphisms are considered creates serious difficulties for power, statistical design and interpretation).

population, which could make detecting them viable.<sup>165</sup> Some initial data suggesting relatively high frequencies (i.e. greater than ten percent) support this intuition, but even under the likely best-case scenario the technical obstacles are sobering.<sup>166</sup>

These realities are leading to a growing consensus that application of genomics methods will take more time to develop and that the promise of personalized medicine is more tenuous than initially understood.<sup>167</sup> They also have important ramifications for FDA regulation. Not only does the recognition of this increased complexity exacerbate the uncertainties endemic to FDA regulatory decision making, it also exposes the potentially difficult tradeoffs that FDA will have to make between different groups of patients.<sup>168</sup> Scientists, for example, are already aware that patient subpopulations can be at heightened risk from certain drugs (e.g., twenty to thirty percent of patients taking anti-psychotics experience serious adverse effects),<sup>169</sup> and that some cancer drugs work only in certain patient subpopulations (e.g., Herceptin, Gleevec).<sup>170</sup>

This variability presents a significant problem because many drugs fail in late-stage clinical trials because of adverse effects in patient subpopulations.<sup>171</sup> Such failures could be mitigated if reliable testing, genetic or otherwise, were available to identify the patient population for which a candidate drug has high safety and efficacy.<sup>172</sup> Similarly, the costs of drug development could be markedly lowered if the size and duration of clinical trials could be reduced based on this information, and the failure rate of drugs (particularly in Phase III testing) could be diminished.<sup>173</sup> Some scientists have even argued that diagnostic testing could aid in identifying commonalities between different diseases to expand that range of diseases that a drug

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<sup>165</sup> Goldstein-05, 1572.

<sup>166</sup> Goldstein-05, 1572 (describing results “of 42 genetic variants associated with drug response in at least two studies, a majority of them have minor allele frequencies greater than 10%”).

<sup>167</sup> Barbara J. Evans, *What Will It Take to Reap Clinical Benefits of Pharmacogenomics?*, 61 FOOD & DRUG L.J. 753, 754 (2006) (“progress will be much slower than was first hoped”); Nebert-Zhang, 208 (concluding that “*individualized drug therapy*, will be most challenging to achieve in the near future”).

<sup>168</sup> Evans-06, 766 (suggesting that the “FDA is now entering a difficult decisional terrain where its approval decisions may entail interpersonal trade-offs among respective subgroups of its statutorily protected class, i.e., patients”).

<sup>169</sup> Need-Motulsky, 671.

<sup>170</sup> Need-Motulsky, 672.

<sup>171</sup> Evans-06, 758 (“discovery of genetic variability of drug response late in clinical trials often leads to drug development failure”).

<sup>172</sup> van’t Veer-08, 569 (arguing that “[i]ncreasingly, drugs will be developed together with a dedicated companion diagnostic test that identifies responders to the drug in question”); Alshuler-Daly, 886 (arguing that “[g]enetics may also increase the efficiency of outcome trials by focusing on patients at higher-than-average risk.”). This may not be a stretch scientifically, as “the genetics of drug response is generally a more tractable phenotype than common disease predispositions.” David B. Goldstein, *The Genetics of Human Drug Response*, 360 PHIL. TRANS. R. SOC. B 1571, 1571 (2005).

<sup>173</sup> Need-Motulsky, 676, 680 (suggesting that pharmacogenetics could reduce the costs of drug development by identifying patient groups for which a drug is highly effective and reduce failure rates during clinical trials); Tate-Goldstein, S439 (suggesting that “early identification of a marker for drug response could lead to smaller phase 3 trials involving those individuals who are more likely to respond”); Nebert-Zhang, 206 (arguing that “[d]ividing a large population into more valuable subsets can enhance the statistical power of a study, while reducing the number of individuals studies”).

is effective against.<sup>174</sup> None of this will be viable, however, until scientists gain a much better understanding of the complex genetic, and epigenetic, determinants of disease susceptibility, and the costs will be considerable in terms of failed drug development and lost treatment options.

### III. Tensions Between Health Care Reform and Biomedical Innovation

The successes of biomedical innovation are paradoxically at the root of the health care crisis.<sup>175</sup> The better technologies become, the more people want access to them and the more total health care costs grow.<sup>176</sup> If we as a society treat access to health care as a presumptive right, technological advances in the number and efficacy of treatments will inexorably lead to rising health care spending.<sup>177</sup>

The costs of health care in the United States are approaching the outer bounds of what is sustainable. Health care spending was projected to reach \$2.4 trillion in 2008, or about sixteen percent of U.S. gross domestic product.<sup>178</sup> Federal spending on Medicare and Medicaid are projected to double by 2024 and triple 2036, and these two programs “account for the entire projected long-term gap between federal revenues and federal spending.”<sup>179</sup> The system of private health insurance is not fairing any better, as annual premiums have risen to the equivalent of the annual salary of a minimum-wage worker.<sup>180</sup> And yet, the percentage of health care costs directly borne by individuals has remained stable, further highlighting the degree to which the crisis is driven by escalating costs as opposed to reallocation of the burden to individuals.<sup>181</sup>

For an increasing number of commentators the only option for pulling out of this downward spiral is some form of health care rationing.<sup>182</sup> This will certainly require denial of

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<sup>174</sup> van't Veer-08, 569 (suggesting that while diagnostic testing may reduce the market size for a drug for a specific use, “it may uncover commonalities between seemingly different tumors, potentially expanding the market for a drug candidate”).

<sup>175</sup> James J. Mongan, et al., *Options for Slowing the Growth of Health Care Costs*, 358 N. ENGL. J. MED. 1509, 1509 (2008) (“the primary driver of cost increases is technological progress,” and yet “we want cost control, but we also want broad access to health care and continued innovation in medical science”); Thomas Bodenheimer, *High and Rising Health Care Costs. Part 2: Technologic Innovation*, 142 ANN. INTERN. MED. 932, 932 (2005) (“Most, if not all, economists and policy analysts believe that technologic advance is a key driver of health expenditure growth.”).

<sup>176</sup> Annetine C. Gelijns, et al., *Evidence, Politics, and Technological Change*, 24 HEALTH AFFAIRS 29, 32 (2005) (“Because technological change often reduces cost per patient and improves quality, thereby expanding demand, improvements in efficiency do not necessarily yield global cost savings”).

<sup>177</sup> Roger Lowenstein, *The Quality Cure*, N.Y. TIMES, \_\_, 8 (March 13, 2005) (arguing that “the drive to keep spending down will forever be challenged by technology’s efforts to overcome it”).

<sup>178</sup> Henry J. Aaron and Joseph P. Newhouse, *Meeting the Dilemma of Health Care Access*, Brookings Opportunity 08 1 (2008) available at <[http://www.brookings.edu/papers/2007/0228useconomics\\_aaron02\\_Opp08.aspx](http://www.brookings.edu/papers/2007/0228useconomics_aaron02_Opp08.aspx)>.

<sup>179</sup> Aaron-Newhouse, 1, 3. The two program also account for close to 50% of total health care spending. Aaron-Newhouse, 5-6.

<sup>180</sup> Aaron-Newhouse, 8.

<sup>181</sup> Aaron-Newhouse, 8; CBO, 9 (reporting that patient out-of-pocket costs have fallen dramatically since 1965 from fifty-percent to fifteen percent in 2005).

<sup>182</sup> Aaron-04, 2-3 (“lowering Medicare and Medicaid costs *significantly* means limiting care for everyone—that is, rationing for all. The alternative—the *only* alternative—will be not only higher taxes but dedication of

coverage of services deemed not to be cost effective, but it could go beyond this if such cuts are not deep enough.<sup>183</sup> As President Obama has stated publicly, failing to address the systemic problems with the U.S. health care system is simply not an option.<sup>184</sup> This is particularly true given the huge federal budget deficits:

“The fact is that government expenditures under current law are almost certain to grow much faster than national income. The principal reason is rapid projected growth of government spending on Medicare and Medicaid. Projected increases in health care spending are so large that cuts in other government programs could not possibly close the projected gap between taxes and spending.”<sup>185</sup>

With tightening federal budget for the foreseeable future, the pressure and need to reduce health care costs is only becoming more acute.

If the U.S. cannot absorb current rates of biomedical innovation, difficult choices, explicitly or implicitly, will have to be made regarding what to support. Private investment in biomedical research and development will unavoidably be affected by government cutbacks—smaller markets for products will reduce incentives to invest.<sup>186</sup> Insofar as federal policies go beyond increasing the efficiency of health care delivery, health care reform will shrink the markets for medical technologies and realign them with federal spending priorities.

The government intervention that the health care crisis demands—failure to take affirmative steps will lead only to fiscal constraints taking the place of considered policy—provides an opportunity to reevaluate the prevailing focus on patents to stimulate investment in drug development. Many commentators predict that the pharmaceutical industry will no longer be able to control what it charges for its products irrespective of whether or not they are patented; prices instead will be set based on their efficacy and safety, which will be closely scrutinized.<sup>187</sup> Significant signs of this movement are beginning to emerge with decisions by drug makers to adopt differential pricing in middle-income countries and novel pricing regimes (e.g., compensation conditional on performance) in developed countries.<sup>188</sup>

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much—and eventually of all—of the growth in total income to health care”; estimates that in 2049, “growth of health care spending would equal total economic growth”).

<sup>183</sup> Aaron-Newhouse, 12 (“to rein in health care spending will require rationing—the elimination of health care services that are not worth what they cost”).

<sup>184</sup> [need cite].

<sup>185</sup> Henry J. Aaron, *The Rising Cost of Health Care: Is it a Problem?*, Remarks to the 2004 Annual Meeting, Institute of Medicine 1 (2004) available at <[http://www.brookings.edu/speeches/2004/1019healthcare\\_aaron.aspx](http://www.brookings.edu/speeches/2004/1019healthcare_aaron.aspx)>.

<sup>186</sup> Aaron-Geo, 547 (“By curtailing the size of the market for medical innovation, rationing would alter the financial incentives that guide investments in medical R&D”); Cutler-McClellan-01, 13 (arguing that even “waste reduction must be balanced against the potential for less rapid technical innovation”).

<sup>187</sup> PWC-09, 4 (“For many years, pharmaceutical companies decided what their products were worth, and priced them accordingly. But healthcare policy-makers, payers and patient groups are now playing an increasingly important role in the valuation process—and this trend will accelerate, as healthcare expenditure everywhere continues to soar.”)

<sup>188</sup> PWC-09, 19 (describing how GSK started using variable pricing within and between middle-income countries in March 2008; “reimbursement for Velcade, Johnson & Johnson’s new cancer treatment, is contingent on proof of a measurable reduction in the size of a patient’s tumor”).

The challenge will be to contain costs without unduly slowing innovation.<sup>189</sup> It is important to be cautious about focusing exclusively on access, for without innovation there is nothing to gain access to and the increasing costs of drug development and fragmenting of drug markets are already putting serious economic strains on the drug sector.<sup>190</sup> Further, innovation, even with the premiums that patents enable, has been empirically shown to generate social returns that are often several times that of the private return.<sup>191</sup>

The interplay between progressive health care policies and innovation is also complex. Even policies designed to improve the performance of the health care system, such as managed care, have been found in some cases to slow the rate of adoption of new technologies, which in turn can reduce incentives to invest in research and development.<sup>192</sup> Recent economic modeling results have suggested that the impacts on investments in R&D could be dramatic. One study calculated that the “decline in R&D intensity [could be] between 23.4 and 32.7%,”<sup>193</sup> while another estimated that a one percent drop in potential market size would result in a four percent drop in new drugs commercialized.<sup>194</sup> The authors concluded that their results “suggest a strong link between market size and innovation.”<sup>195</sup> Health care policies therefore unavoidably implicate biomedical innovation and drug development in particular.

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<sup>189</sup> Carl Nathan, *Aligning Pharmaceutical Innovation with Medical Need*, 13 NATURE MED. 304, 304 (2007); Reed-06, 1315 (arguing the innovation, incentives, and access must be carefully balanced); “reductions in drug industry profits, achieved through price controls, could have a sizeable impact on R&D investment, leading to fewer breakthrough therapies in the future”); Richard G. Frank & Joseph P. Newhouse, *Should Drug Prices Be Negotiated Under part D of Medicare? And If So, How?*, 27 HEALTH AFFAIRS 33, 39 (2008) (arguing that “Any proposal to alter approaches to setting prices for prescription drugs must recognize the threat posed to research and development incentives and the industry’s ability to attract capital if prices are set ‘too low’ or even if there is merely a threat that they may be set too low”).

<sup>190</sup> Joseph A. DiMasi & Henry G. Grabowski, *Economics of New Oncology Drug Development*, 25 J. CLINICAL ONCOLOGY 209, 209 (2007) (arguing that market growth “uncertain because sponsors may face increasing resistance to what are perceived to be high and unsustainable prices, increasing competition if a substantial number of new therapies enter the market, and smaller market sizes for highly targeted therapies”).

<sup>191</sup> Lawrence H. Goulder & Ian W.H. Parry, *Instrument Choice in Environmental Policy*, RFF DP 08-07 20 (April 2008) (stating that “Numerous empirical studies suggest that the (marginal) social return to innovative activity in general might be several times the (marginal) private return”); Frank-Newhouse-08, 39 (stating that “Pharmaceutical R&D has produced enormous value in recent decades”).

<sup>192</sup> Cutler-McClellan-01, 25 (describing “recent evidence [suggesting] that managed care has slowed the rate of diffusion of new medical technologies,” but acknowledging that “less evidence [is available] on the effects of managed care and other policy influences”). Although the estimates are all over the map, twenty percent is a representative estimate of the proportion of health care spending that is unnecessary.” Acemoglu-Linn, 1082.

<sup>193</sup> John A. Vernon, *Examining the Link Between Price Regulation and Pharmaceutical R&D Investment*, 14 HEALTH ECON. 1, 9 (2005). Another study found that if drug prices were limited by the growth in the cost-price index, R&D spending would have been thirty percent lower and 38% fewer drugs would have been developed. Carmelo Giaccotto, et al., *Drug Prices and Research and Development Investment behavior in the Pharmaceutical Industry*, 48 J.L. ECON. 195, 212 (2005).

<sup>194</sup> Daron Acemoglu & Joshua Linn, *Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry*, QUART. J. ECON. 1049, 1051 (Aug. 2004). This study also found that “a 1 percent increase in the size of the potential market for a drug category leads to a 6 percent increase in the total number of new drugs entering the U.S. market. Much of this response comes from the entry of generics.” *Id.*

<sup>195</sup> Acemoglu-Linn, 1082.

## A. Shifting Market Conditions

The pharmaceutical industry is under intense pressure to alter its basic business model. Health care expenditures in every OECD country increased as a percentage of GDP from 2000 to 2006.<sup>196</sup> In the United States, expenditures on health care are more than \$2 trillion, and the country cannot be relied on to generate more than sixty percent of the industry's profits.<sup>197</sup> If current trends were to continue, OECD countries other than the United States would spend the equivalent of sixteen percent of their GDPs on health care (the current number is less than two percent), and the United States would spend an even more shocking twenty-one percent of its GDP on health care.<sup>198</sup> The private sector is reeling as well, with companies like GM and Ford spending billions on health care that undermines their already shaky economic status.<sup>199</sup>

The formidable marketing machine that has made the pharmaceutical industry so successful is also threatened if not obsolete. Spending on marketing almost tripled between 1996 and 2005, rising from \$11.4 to 29.9 billion annually, and was associated with substantial growth until recently.<sup>200</sup> However, in the years 2004 and 2005, the industry saw its return on marketing investments fall by twenty-three percent, suggesting that it had reached the limits of the growth it could achieve through these methods.<sup>201</sup> At the same time new technologies, particularly e-prescribing and automated systems for dispensing generic versions of prescription drugs, are undermining the industry's capacity to influence physicians prescribing habits. Equally important, newer biologic drugs cannot be marketed in the same manner as traditional drugs because they are much more expensive to manufacture, typically cannot be administered in pill form, and are much more fragile and costly to store on site.<sup>202</sup>

The industry is thus experiencing unprecedented pressures to lower the costs of its products and, in many respects, is in a relatively weak position to resist them. Government and payer policies once believed unthinkable are beginning to gain traction. It now appears inevitable that the federal government will be empowered to negotiate lower prices for prescription drugs under Medicare Part D (this alone could reduce revenues by \$260 million between 2007 and 2017), that payers will place strict limits on what doctors can prescribe, and that drug pricing will be increasingly based on performance.<sup>203</sup> The capacity of the pharmaceutical industry to dictate the prices of its products and to expand the size of the markets for them is now clearly in decline.

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<sup>196</sup> PWC-09, 4.

<sup>197</sup> PWC-2020, 27.

<sup>198</sup> PWC-2020, 11.

<sup>199</sup> PWC-2020, 12 (discussing how in 2006 GM spent \$5.9 and Ford \$2.9 billion on health care, which adds \$1,380 to the cost of producing each car).

<sup>200</sup> PWC-09, 2 (also pointing out that at least one estimate found that expenditures may have risen to \$57.5 billion).

<sup>201</sup> PWC-09, 3.

<sup>202</sup> PWC-09, 20.

<sup>203</sup> PriceWaterhouseCoopers, *Pharma 2020: Virtual R&D 1*, 13-14 (2008) *available at* <<http://www.pwc.com/extweb/pwcpublishations.nsf/docid/9367E5486347EA278025746A006029B1>> (observing that, "by January 2010 feds will cover 37% of the costs for prescription drugs in the U.S. and private insurance will cover 39%," suggesting that both the public and private sector will be able put the pharmaceutical industry under intense pressure to reduce its prices).

Several recent developments suggest that change is already occurring. Pricing in Europe began to move toward pay-for-performance in 2006 when the pricing of two new prescription drugs were based on drug efficacy, and adoption of this pricing model has continued progress since then.<sup>204</sup> At the same time, several countries (i.e., Australia, Canada, Finland, New Zealand, United Kingdom) are in the process of establishing agencies dedicated to conducting cost-effectiveness evaluations of prescription drugs, and the U.S. Senate has pending legislation that would establish a similar program titled “Health Care Comparative Effectiveness Research Institute.”<sup>205</sup> These policy initiatives implicate approximately \$82 billion dollars in revenue and possible eighty-five of the top selling drugs.<sup>206</sup>

Such developments are being reinforced by electronic records and prescribing programs. The confluence of electronic patients records, electronic prescribing, and remote monitoring will permit collection of treatment outcome data on a scale previously unimaginable. These systems will enable the safety and efficacy of prescription drugs to be assessed much more accurately and rapidly, including differential effects on patient subpopulations.<sup>207</sup> Electronic prescribing also stands to alter doctor’s judgments about what to prescribe a patient, as it will be used to supply them with extensive clinical and cost data. Preliminary studies suggest that this information will dramatically increase their prescription of generic drugs.<sup>208</sup> In recognition of the fiscal benefits, Congress recently passed a law that provides significant incentives for physicians to use electronic prescription systems.<sup>209</sup>

Pharmaceutical companies are responding to these changes in a variety of ways, but one of the most significant is their redirection of R&D investments towards development of biologics. According to a recent estimate, approximately 400 of the 2,000 potential prescription drugs in development are biologics, and fifty-five of the blockbuster drugs in 2005 were targeted biologic compounds (an increase from just twelve in 2001).<sup>210</sup> Despite estimates that biologics will be used to treat just three percent of the global population, this class of compounds could generate forty-four percent of global revenue from prescription drugs in 2008.<sup>211</sup> These numbers highlight the dilemma created by the small markets for biologics, namely, that they require companies to charge super-premium prices to cover their manufacturing and development costs, which leads to heightened scrutiny, if not outright rejection, of their utilization.<sup>212</sup>

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<sup>204</sup> PWC-2020, 17; PWC-09, 7-8 (concluding that “by 2020, we think that all new medicines will be paid for on the basis of the outcomes they deliver”).

<sup>205</sup> PWC-09, 5.

<sup>206</sup> PWC-2020, 17.

<sup>207</sup> PWC-09, 7.

<sup>208</sup> PWC-09, 5 (describing a study finding that two-thirds of the doctors in an e-prescribing initiative said that they were more likely to prescribe generic with the information provided).

<sup>209</sup> PWC-09, 5 (describing the law as giving eligible doctors a two percent bonus for writing electronic prescriptions in 2009-10, a one percent bonus in 2011-12, and a half percent bonus in 2013, with penalties imposed on those who do not use e-prescribing by 2012).

<sup>210</sup> PWC-09, 13.

<sup>211</sup> PWC-09, 13-14.

<sup>212</sup> PWC-09, 14-15 (enumerating the obstacles to broad adoption of biologics, including their high costs, the heightened scrutiny to show safety and efficacy to which they will be subjected, the added costs for diagnostic testing that might be required, and the added costs and logistical hurdles associated with have to deliver them by injection or infusion).

The economics of small markets is presumably offset in the eyes of the industry by the open-ended exclusivity that biologics enjoy.<sup>213</sup> As discussed above, the difficulty of demonstrating the bioequivalence of generic versions of biologics creates a major impediment to market entry of generic manufacturers, and this barrier is exacerbated by the high costs and technical challenges of producing biologics.<sup>214</sup> Some commentators have suggested that patients may be more reluctant to switch to generic versions of biologics because their sensitivity to process changes, and that pharmaceutical companies will be in a position to exploit these fears by bundling sales with patient services, which could generate additional revenue.<sup>215</sup>

## **B. The Impact of Technological Change on Health Care Costs**

One must be careful in making inferences about the impacts of new drugs, and technologies more generally, on aggregate health care costs. Much depends on whether a new technology replaces an existing treatment regime or expands the range of people being treated. If it is the former, there is at least the chance that aggregate costs could be lower, assuming that the new treatment option is cheaper or more efficacious.<sup>216</sup> By contrast, treatment expansion, whether by making a treatment more broadly available or through providing wholly new treatment options, necessarily increases costs.<sup>217</sup> A new drug, for example, could replace much more expensive existing treatments, thereby reducing per treatment costs, but could increase aggregate expenditures if it is used much more broadly.<sup>218</sup>

Treatments of cardiovascular disease and depression illustrate this point well. New treatments for heart attacks have added a full year of life for patients and for every dollar spent led to benefits estimated to be seven dollars; the benefits are so large that the net positive social value of the treatment is unambiguous.<sup>219</sup> The introduction of these treatments led to a dramatic increase in expenditures on treating heart attacks and the intensity of the treatment patients received.<sup>220</sup> By contrast, the use of antidepressants (particularly SSRIs) to treat depression was accomplished with virtually no net increase in costs.<sup>221</sup> In this latter case, the estimated benefits from enhanced efficacy exceeded costs by about a factor six.<sup>222</sup>

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<sup>213</sup> PWC-09, 24 (asserting that “specialist medicines will provide new commercial opportunities and reduce the risk of generic erosion”).

<sup>214</sup> PWC-09, 22.

<sup>215</sup> PWC-09, 15.

<sup>216</sup> David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?*, 20 HEALTH AFFAIRS 11, 12 (2001) (describing how replacing older technologies may be more or less costly, but may bring significant health improvements, which are highly valued).

<sup>217</sup> Cutler-McClellan-01, 12 (describing how diagnosis rate for depression doubled after the introduction of SSRNs and how cataract surgery was performed much more as procedures and outcomes improved).

<sup>218</sup> Aaron-Newhouse, 4 (arguing that “Technological advances usually result in lower prices, but increased total spending, as the technology is widely adopted.”); Aaron-Geo, 548 (“blaming drug companies for increasing health care spending is not justified. First, careful studies have found that increasing drug outlays have reduced other forms of health care spending, notably on hospitalizations and physician services”).

<sup>219</sup> Cutler-McClellan-01, 17 (describing how the benefits of the treatment “dwarfed” the uncertainties in the cost-benefit analysis performed).

<sup>220</sup> Cutler-McClellan-01, 16.

<sup>221</sup> Cutler-McClellan-01, 20-21.

<sup>222</sup> *Id.*

These examples highlight a central dilemma presented by health care policy. Per-person medical spending in the United States increased by \$35,000 between 1950 and 1990.<sup>223</sup> This represents a huge rise in aggregate costs, but the benefits have far exceeded even this number—the lifespan of the average American increased by seven years over this time, which according to conservative assumptions for valuing life has a net present value of \$130,000 per person.<sup>224</sup> By implication, if medical technologies and patient care account for a little more than a quarter of this increase, the rise in health care expenditures would be cost justified.

Aggregate numbers, however, obscure the variation in the benefits of medical treatments. The benefits from lower infant mortality and improved treatment of heart disease alone “about equal to the entire cost increase for medical [since 1950].”<sup>225</sup> Put differently, 4.88 years of the seven-year increase in life expectancy (70% of total) is attributable to reduced rates of cardiovascular disease.<sup>226</sup> Perhaps more importantly, the costs per year of life gained through medical interventions has increased from \$7,400 in the 1970s to \$36,300 in the 1990s, and this rise is being driven disproportionately by the treatment of individuals sixty-five years and older.<sup>227</sup> Whereas the cost per year of life was, on average, \$53,000 for a forty-five year old person in 2000, the cost was \$145,000 for someone sixty-five years old and older.<sup>228</sup> These trends may signal that some areas of health care are reaching a point of diminishing returns.<sup>229</sup>

Higher costs of treatment correlate with higher levels of acute care generally. For example, despite the impressive benefits of cardiac care, there is strong evidence that intensive cardiac interventions are being overused. Heart patients in the U.S. receive high-cost procedures like bypass surgery and angioplasty at far greater rates than patients in Canada, but the survival rates in both countries are essentially the same.<sup>230</sup> In large part because it is reimbursed at higher rates, acute care involving sophisticated technologies is disproportionately overused in the United States, which in turn inflates the markets and incentives for new medical technologies to be developed.<sup>231</sup> Medical reimbursement policy is therefore integral to the rapid growth in new technologies that are fueling health care spending in the United States.

One can gain a qualitative sense of the potential implications of cost containment policies by analyzing the impacts of health care policies in other countries. With the exception of Japan, health care expenditures in other developed countries are about thirty to fifty percent lower than

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<sup>223</sup> Cutler-McClellan-01, 24.

<sup>224</sup> *Id.*

<sup>225</sup> Cutler-McClellan-01, 12.

<sup>226</sup> Cutler-Rosen-06, 923.

<sup>227</sup> David M. Cutler, et al., *The Value of Medical Spending in the United States, 1960—2000*, 355 N. ENGL. J. MED. 920, 920 (2006); *see also* Cutler-Rosen-06, 921 (stating that “Adjust for inflation, annual medical spending per has increased from approximately \$700 in 1960 to more than \$6,000 today, tripling as a share of the gross domestic product”).

<sup>228</sup> *Id.*

<sup>229</sup> Cutler-Rosen-06, 926 (acknowledging that the “temporal trends suggest that the value of health care spending is decreasing over time, particularly for older age groups”).

<sup>230</sup> David M. Cutler, *YOUR MONEY OR YOUR LIFE* 58 (2004).

<sup>231</sup> Cutler-YMYL, 67 (making the case that “services that are reimbursed very generously are overused, while services that are reimbursed less well are not”).

those in the United States.<sup>232</sup> Several impacts have been associated with these cost differentials, most notably either a lag in the introduction of new prescription drugs or no introduction at all of certain high-cost drugs.<sup>233</sup> These delays and absences are evident in the larger quantity of older, lower-priced brands purchased in other developed countries.<sup>234</sup>

The United States, perhaps surprisingly, has the most competitive market for generic drugs in the world. It has the most drugs available in a generic form at the lowest prices.<sup>235</sup> Two factors account for the slower entry of generics in other countries: first, the markets are smaller and therefore there is less incentive for generic firms to enter them; second, the regulatory hurdles tend to be greater and the time delays from regulatory review longer.<sup>236</sup> The larger proportion of generic drugs in the U.S. is of great economic significance, as they constitute to great majority of prescriptions dispensed but a modest fraction (i.e., about a third) of the costs incurred.<sup>237</sup> Limiting the proportion of on-patent branded drugs sold consequently avoids much larger aggregate expenditures.

The international markets for biologics do not fit the typical patterns. Prices for biologics in developed countries, including the U.S., vary only nominally (i.e., less than ten percent).<sup>238</sup> This apparent parity is misleading, however, because biologics are simply not available in many countries.<sup>239</sup> Producers of biologics appear to have made the decision to forego markets in which governments are unwilling to pay high prices.<sup>240</sup> One reason for this might be the absence of substitutes for many biologics, which means that companies can holdout without any risk of competition.<sup>241</sup> The end result is less “free riding” on the U.S. market, but at the cost of fewer people benefiting from potentially valuable therapies.<sup>242</sup>

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<sup>232</sup> Calfee-Villarreal, 5 (noting that “the disparities have grown over the past fifteen years and have come to substantially exceed disparities in per capita GDP”).

<sup>233</sup> Calfee-Villarreal, 7 (describing evidence that “price controls in several advanced economies reduce profits and cash flow sufficiently to reduce the introduction of new chemical entities by approximately 2.7 to 4.1 entities per year”); Patricia M. Danzon & Michael F. Furukawa, *International Prices and Availability of Pharmaceuticals in 2005*, 27 HEALTH AFFAIRS 221, 225 (2008) (discussing “several recent studies [that] have shown that countries with strict price regulation tend to experience launch lags or nonlaunch of new drugs”). Consistent with these findings, for period 1995-2005, the “U.S. had the shortest average launch lag and the highest percentage of new drugs available.” Danzon-Furukawa, 225.

<sup>234</sup> Calfee-Villarreal, 9 (pointing out that “foreign nations consume relatively larger quantities of lower-priced brands”); Danzon-Furukawa, 222, 224-25, 230 (noting that the U.S. ranks first in total spending on pharmaceuticals, but ranks second to last in terms of number of doses per capita).

<sup>235</sup> Danzon-Furukawa, 226 (highlighting that the “U.S. leads all other countries with generic availability for almost 74 percent of these potentially off-patent molecules”).

<sup>236</sup> Danzon-Furukawa, 226.

<sup>237</sup> Danzon-Furukawa, 226 (disclosing that on-patent branded drugs account for less than one-fourth of the unit volume sold in all developed countries, whereas they make up 43-56% of the total sales revenue”).

<sup>238</sup> Calfee-Villarreal, 16 (describing “anecdotal evidence suggest[ing] that some biotech drug manufacturers maintain a single world price in developed nations regardless of national price controls”).

<sup>239</sup> Calfee-Villarreal, 16, 19, 21, 24 (arguing that revenues from biotech drugs are disproportionately low given price parities with U.S., implying that there is much lower usage of biologics in other countries).

<sup>240</sup> Calfee-Villarreal, 25 (suggesting that given the high prices charged for biologics, “firms may conclude that sacrificing a substantial portion of foreign profits is a price worth paying to forestall price controls in the much larger U.S. market”).

<sup>241</sup> Calfee-Villarreal, 22-23.

<sup>242</sup> Calfee-Villarreal, 27.

#### IV. Developing Complementary Policies to Promote Biomedical Innovation

Regulation of prescription drugs is inseparable from the policies designed to spur their development. More stringent regulatory hurdles, or scientific uncertainties that demand more elaborate testing, place greater economic and technical burdens on innovators that counteract innovation policies. The interactions between regulatory, health, and innovation policies must therefore be considered together in order to assess their impacts in each area.

The 1962 amendments to the Food Drug and Cosmetics Act provide a clear example of the impact that enhanced regulation can have on innovation. The 1962 amendments shifted the burden to drug producers to demonstrate the safety and efficacy of their products and, in doing so, required an unprecedented level of testing to be conducted. Drug development post-1962 through mid-1970s was marketed “by a dramatic decline in new drug introductions together with relatively stagnant growth in R&D expenditures”<sup>243</sup> Economists have estimated that the added delay in returns on R&D significantly reduced investment in the industry.<sup>244</sup> However, by the late 1970s, the industry—and investor expectations—adjusted to the new regulatory climate, and with this normalization R&D expenditures have grown steadily ever since.<sup>245</sup>

The close interplay between rigorous FDA regulation and the costs of drug development have led to a proliferation of hybrid legal policies. These either mitigate the cost increases associated with FDA regulatory standards or offset them using enhanced patent terms or regulatory market exclusivity. The Hatch-Waxman amendments to the FDCA are the best-known example of this strategy. Under the law, producers of new drugs are eligible for up to a five-year period of “data exclusivity,” which means that no other company can rely on their clinical studies to obtain FDA approval of generic versions of a brand-name drug.<sup>246</sup> At the same time, the law makes it easier for generic producers to obtain FDA approval by allowing them to submit applications while the relevant patent(s) are still enforceable.<sup>247</sup>

Hatch-Waxman has led to dramatic growth in the availability of generic drugs and the number of generic companies. As noted above, the entry of generic drugs has an enormous impact on pricing, such that the cost of drugs with large markets drop by ninety percent within several months of generic entry.<sup>248</sup> The net impact of the law on incentives to produce new drugs is less clear, although the primary source of criticism has been concern that it overcompensates brand-name producers, not that it undercuts their incentives.

This section begins by surveying existing laws—beyond patent law—designed to promote innovation. It then evaluates several policies that could be utilized to offset the likely impacts of health care reform on incentives for investing in drug development. I tentatively

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<sup>243</sup> Henry Grabowski & John Vernon, *The Determinants of Pharmaceutical Research and Development Expenditures*, 10 J. EVOLUTIONARY ECON. 201, 201-02 (2000).

<sup>244</sup> Grabowski-Vernon, 201-02.

<sup>245</sup> Grabowski-Vernon, 202.

<sup>246</sup> Manheim-06, 397. The period of data exclusivity is calculated using “a formula that extends the patent by up to half the time spent on human clinical trials, and for the full amount of time spend by the FDA in its review of the application.” *Id.*

<sup>247</sup> Manheim-06, 396.

<sup>248</sup> Grabowski-Moe, 86.

argue for the adoption of several complementary policies, drawing on some recent economic studies of complementary approaches used in the energy sector.

## A. Federal Policies for Promoting Innovation

### 1. *Small-Market Policies*

Market characteristics have obvious impacts on drug development and policy. This subsection examines two statutes designed to address the problem of small product markets. The Orphan Drug Act (“ODA”), by most accounts, has been a highly successful response to the problem of small markets. Its focus is rare diseases (i.e., those that affect fewer than 200,000 people in the U.S.) that are of insufficient size to justify the large costs of drug development. At base, the passage of the ODA was driven by the limitations of a patent-based system for incentivising drug development, which is premised on minimal market sizes to be effective. Prior to passage of the ODA,<sup>249</sup> few drugs for rare illnesses were available, only thirty-four were produced over the decade preceding its passage.<sup>250</sup> By contrast, 229 orphan drugs have been commercialized over the subsequent twenty years,<sup>251</sup> based on 1566 products awarded orphan drug status (out of 2255 applications).<sup>252</sup>

The ODA incorporates an eclectic mix of policies that range from regulatory streamlining to more traditional market-based incentives. The Act establishes a streamlined drug approval process that is facilitated by technical support from FDA scientists for development of clinical testing regimes.<sup>253</sup> This collaborative approach has resulted in a fifty percent reduction in the time for FDA approval of new orphan drugs (i.e., “new molecular entities”), adding one to two years to the effective duration of patent protection.<sup>254</sup> In addition, the clinical trials have, on average, been shorter and smaller than those for drugs serving larger markets and therefore substantially cheaper.<sup>255</sup>

The ODA also gives a fifty-percent tax credit for the costs of clinical trials, which amounts to a rebate of millions of dollars for the up-front costs associated with drug

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<sup>249</sup> ODA passed in 1982, took effect in 1983 and was amended in 1984, 1985, and 1988 (Loughnot, 368).

<sup>250</sup> Loughnot, 367.

<sup>251</sup> Loughnot, 370; Paul D. Maher & Marlene Haffner, *Orphan Drug Designation and Pharmacogenomics*, 20 *BIODRUGS* 71, 71 (2006) (find that only ten orphan drugs commercialized in the decade prior to passage of the ODA, whereas 269 orphan drugs had been commercialized by 2006).

<sup>252</sup> Maher-Haffner, 71.

<sup>253</sup> Loughnot, 374. FDA provides directing funding for OD R&D and clinical trials amounting to about \$25 million annually. Loughnot, 369. To combat misuse, critics have proposed amending the ODA to cap total revenues as a condition on the duration of market exclusivity. Loughnot, 377.

<sup>254</sup> Loughnot, 368 (the time for drug approval was reduced to 12.4 months versus 25.6 months for NMEs granted outside the ODA program).

<sup>255</sup> Henry Grabowski, *Increased R&D Incentives for Neglected Diseases—Lessons From the Orphan Drug Act*, 16 (July 2003) available at <[http://www.econ.duke.edu/Papers/Other/Grabowski/Orphan\\_Drug.pdf](http://www.econ.duke.edu/Papers/Other/Grabowski/Orphan_Drug.pdf)>. Grabowski-Orphan, 16 (find that the number of subjects in clinical trials for orphan drugs was much smaller than the average for all drugs and that “the representative orphan drug has R&D costs that are significantly lower than non-orphan compounds”); Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards* 71 (1993) (observing that orphan drugs “may have a different cost structure from other NCEs, not only because of the tax credit but also because they may involve smaller and shorter clinical trials than other drugs”).

development.<sup>256</sup> The aggregate value of this tax credit is significant—through 2007 it cost nearly \$2 billion, and it is projected to cost \$1.9 billion between 2008 and 2012.<sup>257</sup> The tax credit may be the tail of the dog, though, as its effectiveness is bounded by the size of the potential market size for the drug.<sup>258</sup> This limit can be overcome, however, insofar as the ODA can be gamed by use one indication for a drug to gain orphan status and another indication to achieve blockbuster status. This susceptibility is the most controversial aspect of the ODA, as high-profile examples exist of this occurring (e.g., Amgen’s blockbuster anemia drugs).<sup>259</sup> Fortunately, despite the controversy that they have inspired, these cases appear to be the exception to the rule. The average peak annual sales of orphan drugs is about \$100 million, versus \$500 million for standard drugs, and the annual sales of most orphan drugs do not exceed \$10 million.<sup>260</sup>

Economists estimate that the ODA has led to a sixty-nine percent increase in the number of clinical trials conducted on drugs for rare diseases, and the number of drugs for rare diseases increased relative to that common diseases.<sup>261</sup> The social benefits also appear to be quite high. Although direct causal links are difficult to establish, the percentages of individuals dying from rare illnesses fell from twenty-two percent in 1979 to sixteen percent in 1998, whereas the drop for common diseases was from thirteen to eleven percent, and the greatest declines were for rare diseases with newly available drugs to treat them.<sup>262</sup> Moreover, as genetic testing improves, the number of orphan diseases is likely to increase, which could further enhance the social value of the ODA.<sup>263</sup>

Testing of drug safety and efficacy for use by children has, for a variety of legal and ethical reasons, been relatively rare. To promote studies on pediatric uses of drugs, Congress included a provision (Section 505A) in the 1997 U.S. Food and Drug Administration Modernization Act, which provides an additional 6 months of patent protection, or marketing exclusivity, in return for performing pediatric studies specified by the FDA.<sup>264</sup> The program is credited with substantially increasing the number of pediatric studies (estimated to be more than 300), and has resulted in new labeling of about 115 drugs for pediatric use.<sup>265</sup>

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<sup>256</sup> Loughnot, 369.

<sup>257</sup> Yin, 1062.

<sup>258</sup> Yin, 1061 (concluding that “the effectiveness of tax credits on pharmaceutical R&D depends in part on revenue potential”).

<sup>259</sup> David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses*, 31 AM. J.L. & MED. 365, 365, 370 (2005).

<sup>260</sup> Grabowski-Orphan, 16.

<sup>261</sup> Yin, 1061; F. Lichtenberg & J. Waldfogel, *Does Misery Love Company? Evidence from Pharmaceutical Markets Before and After the Orphan Drug Act*, NBER working paper No. 9750 (2003) (finding that “after the ODA, the increase in the variety of drugs was higher for rare diseases than for non-rare diseases”). However the increase in clinical trials was much more dramatic, about 230 percent, for “more prevalent rare diseases.” Yin, 1070.

<sup>262</sup> Grabowski-Orphan, 18.

<sup>263</sup> Maher-Haffner, 77 (arguing that “with therapies becoming increasingly guided by a more complete understanding of both genomics and proteomics, the number of potential orphan diseases should be expected to increase”).

<sup>264</sup> Jennifer S. Li, et al., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 JAMA 480, 480 (2007). The program was extended under the Best Pharmaceuticals for Children Act of 2002), but was set to expire in 2007. *Id.*

<sup>265</sup> Li-07, at 480.

Critics have focused their attention, similar to the ODA, on what they view as windfall profits for the pharmaceutical industry. They argue that the estimated economic benefits of the added patent exclusivity far exceed the costs of conducting the pediatric studies.<sup>266</sup> For example, the median costs for standard studies ranged from about \$900,000 to \$2.3 million for pharmacokinetic studies and about \$6.5 million for studies of drug efficacy, whereas the median economic benefit of the six-month exclusivity period was \$134 million.<sup>267</sup> The variance in the economic value of the exclusivity period was dramatic, though, with blockbuster drugs receiving large windfalls while products with relatively small markets received only modest returns.<sup>268</sup>

Although not necessarily limited to drugs with small markets, legislation is pending in Congress that would establish a distinctive pathway for generic biologics incorporates some the mechanisms described above.<sup>269</sup> Several bills have been introduced in the House and the Senate, and all to varying degrees establish separate standards and processes for biologics.<sup>270</sup> One of the leading bills, H.R. 1038, delegates broad authority to FDA to establish a standard for evaluating generic version of biologic drugs, but also includes a default option where an applicant can meet specified data requirements for “comparability” and “interchangeability.”<sup>271</sup> However, by giving FDA broad discretion to request more data, the bill could nullify the streamlining that the default options seeks to achieve.<sup>272</sup> The bills also contain market-exclusivity terms extending up to twelve years,<sup>273</sup> as well as extensive expert counseling from FDA scientists on “biosimilarity” testing, FDA priority review, and federal vouchers for purchasing.<sup>274</sup>

## 2. *General Policies for Promoting Research and Development*

The federal government has provided tax incentives for research and development since 1981.<sup>275</sup> The R&D tax credit has been extended twelve times over this period, most recently in the \$700 billion dollar economic rescue package this past fall.<sup>276</sup> When first adopted, the law gave a twenty percent tax credit for new research and development spending based on research

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<sup>266</sup> Li-07, 480.

<sup>267</sup> Li-07, 482-84.

<sup>268</sup> Li-07, at 484 (concluding that the “program overcompensates blockbuster products for performing clinical trials, while other products have more modest returns on investment under this programs”).

<sup>269</sup> All interested parties agree that the system and standards for traditional small-molecule drugs is not appropriate for biologics because of the many biochemical differences between these two class of compounds. Bruce S. Manheim, et al., *Follow-On Biologics’: Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFAIRS 394, 395 (2006) (observing that the key distinction between proposed legislation and Hatch-Waxman is that “bioequivalence” (and identity of the molecular entities) is replaced by the term “biosimilarity,” which could allow for structural differences that avoid the patent claims of NME).

<sup>270</sup> The primary legislation in 2007 was H.R. 1038 and S. 623 (1695), but new bills were introduced in 2008, including H.R. 6376 and H.R. 5629.

<sup>271</sup> Calfee-AEI-07, 2.

<sup>272</sup> Calfee-AEI-07, 2.

<sup>273</sup> Kingham-Lietzan, 635. Note that process/method patents will be of little value because pharmacists can substitute generics even if they are not approved for the same indication. *Id.*

<sup>274</sup> Grabowski-07, 699.

<sup>275</sup> Note that only two supply-side federal policies exist for promoting innovation: the Research and Experimentation Tax credit and the Orphan Drug Act. Yin-08, 1060.

<sup>276</sup> Jeffrey Mervis, *Tax Credit Is Silver Lining for Science*, 322 SCIENCE 181, 181 (2008) (noting that the new provision is retroactive to December 31, 2007, and extends through the end of 2009, with an estimated to cost U.S. budget of \$8.3 billion in 2009).

as a share of overall sales. By 2006, most companies obtained a twelve to fourteen percent tax credit through a simplified provision that is based on demonstrated increases in R&D spending.<sup>277</sup> In the pharmaceutical sector, the economic value of the law has provided tax credits equal to approximately two percent of the industry's R&D expenditures.<sup>278</sup> Given their large expenditures on R&D, it is the large pharmaceutical companies that have benefited most from this policy.<sup>279</sup>

Economists have traditionally been opposed to R&D tax credits, as they have assumed that investments in R&D are insensitive to savings on after-tax costs.<sup>280</sup> Despite this widespread skepticism, recent studies have found that they are costs justified, with estimates suggesting that a ten percent reduction in R&D costs leads to about a one percent rise in R&D expenditures in the short-run and almost a ten percent rise in R&D over the long-run.<sup>281</sup>

The virtue of a broad R&D tax credit is that it does not dictate the type of research conducted; the downside is that this means it is poorly targeted and therefore likely to go disproportionately to R&D in fields that already provide significant market-based incentives.<sup>282</sup> Poor targeting presents particularly difficult problems but it not unique to a tax-based approach; knowledge deficiencies and asymmetries that make targeting difficult apply equally to all supply-side policy instruments.<sup>283</sup> The other major risk, namely, that a tax credit could induce too much R&D, appears low given that social returns of R&D are believed to be much greater than the private returns.<sup>284</sup> Further, a potentially offsetting virtue of tax credits is that they can reduce the pressure to maximize sales, especially by shifting from investment in R&D to marketing, that reliance on patents can encourage.<sup>285</sup>

A wide variety of federal programs provide grants and direct subsidies for various stages of drug development. The primary concern about direct public subsidies is whether they substitute or complement private funding for R&D.<sup>286</sup> While still subject to debate, it appears that there is little evidence of direct substitution, but nor is there clear evidence that government subsidies stimulate additional investment in R&D beyond what would have occurred without a subsidy.<sup>287</sup> Ultimately only a weak case can be made for direct government subsidies to promote private investment in R&D.

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<sup>277</sup> Mervis, 181.

<sup>278</sup> DiMasi-05, 1036.

<sup>279</sup> DiMasi-Hansen-03, 175.

<sup>280</sup> Dick Bloom, et al., *Do R&D Tax Credits Work? Evidence from a Panel of Countries 1979-1997*, 85 J. PUB. ECON. 1, 1, 2 (2002).

<sup>281</sup> *Id.* at 21-22; Hall-Reenen, 462 (finding that “the R&D tax credit produces roughly a dollar-for-dollar increase in reported R&D spending on the margin”). Moreover, these results are not inconsistent with earlier studies, which were influenced by the lag time in company's adaptation to the credits. *Id.*

<sup>282</sup> Bronwyn Hall & John Van Reenen, *How Effective are Fiscal Incentives for R&D? A Review of the Evidence*, 29 RESEARCH POL. 449, 449 (2000).

<sup>283</sup> Hall-Reenen, 449-50.

<sup>284</sup> Hall-Reenen, 457.

<sup>285</sup> Hall-Reenen, 449-50.

<sup>286</sup> Xulia Gonzales & Consuelo Pazo, *Do Public Subsidies Stimulate R&D Spending?*, 37 RESEARCH POL. 371, 372 (2008).

<sup>287</sup> Gonzales-08, 373-74, 384.

Some critics have also raised concerns about the impact of information deficiencies and asymmetries in government subsidy programs as well. They worry that the most knowledgeable individuals, academic and venture capitalists, do not have adequate funds on their own, while those entities, particularly federal agencies, with sufficient resources lack the relevant knowledge.<sup>288</sup> An interesting, though problematic, model they propose involves government providing funding for R&D that would be overseen by a group of academics and venture capitalists.<sup>289</sup>

On the demand-side, guaranteed purchase agreements are being used as effective technology-pull policies. The federal government incorporated a provision for guaranteed purchase agreements in the 2004 Project Bioshield Act to create an incentive for firms to invest in R&D related to combating bioterrorism threats (e.g., anthrax, ebola, smallpox).<sup>290</sup> The statute appropriates \$5.6 billion over ten years for the federal government to purchase vaccines and drugs, and it allows the government to enter into agreements up to eight years prior to the expected FDA approval of a candidate drug.<sup>291</sup> By establishing a ready and well-defined market for such drugs, these agreements reduce the commercial risk of drug development and enhance incentives to invest in costly R&D. They are not without their limitations, though, as pricing, product specifications, liability issues, unrecognized blocking patents, and opportunity costs make such early-stage contracting difficult to negotiate and subject to large uncertainties.<sup>292</sup>

[need a section on innovation prizes]

## B. Promising Policy Options

Innovation policies fall into one of two camps, either supply-side “technology-push” measures or revenue-side “technology-pull” incentives. Supply-side measures reduce effective development costs, e.g., through tax benefits or direct subsidies, at the time when investments in research and development are being made.<sup>293</sup> Unless targeted like the ODA, these mechanisms have a limited capacity to promote research on drugs with small markets because they cannot affect revenues.<sup>294</sup> By contrast, revenue-side policies (e.g., patents, prizes, prescribing guidelines, future purchase agreements) affect revenues, but they are vulnerable to political pressures to reduce drug expenditures and to renegeing, which can be especially problematic given the high upfront costs associated with drug development.<sup>295</sup> The two types of strategies

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<sup>288</sup> Klausner, 1218.

<sup>289</sup> Klausner, 1218.

<sup>290</sup> Henry Grabowski, *Encouraging the Development of New Vaccines*, 24 HEALTH AFFAIRS 697, 699 (2005).

<sup>291</sup> Grabowski-05, 699.

<sup>292</sup> Grabowski-07, 699.

<sup>293</sup> Yin, 1073 (noting that if this is done through a tax, it lowers the marginal development cost, whereas a subsidy simply reduces bulk costs); Grabowski-Moe, 88-89 (describing supply-side measures as including tax credits, research grants, and accelerated FDA drug approval processes).

<sup>294</sup> Yin, 1073 (arguing that “small revenues simply cannot justify large capital investments (even if fully subsidized) from an opportunity cost perspective. For these markets, innovation policy must also operate on revenue margins.”). Tax policies (or direct subsidies) could be calibrated to disease incidence, or possibly, prevalence markers to scale incentives to social needs. *Id.* at 1074.

<sup>295</sup> *Id.*; Grabowski-Orphan, 27-29 (acknowledging concerns potential for renegeing on commitments).

thus have complementary attributes, suggesting that hybrid policies that combine both types of measures may be the most effective approach.<sup>296</sup>

A variety of hybrid supply-revenue approaches are currently being advocated in the health care context.<sup>297</sup> I will focus on two quasi-regulatory measures, FDA data exclusivity and regulatory fast-track processes, that have received only modest attention. As described above, data exclusivity limits the use of data generated by an original drug maker in obtaining FDA approval for the marketing of a generic version of a brand-name drug.<sup>298</sup> The key point to appreciate here is that without access to the original discoverer's data, the cost of obtaining FDA approval for a generic is prohibitive.<sup>299</sup>

The Hatch-Waxman amendments to the FDCA, as discussed above, include mechanisms for extending FDA data exclusivity.<sup>300</sup> Similarly, the European Union recently created a ten-year period of data exclusivity for new molecular entities and biologics.<sup>301</sup> Health economists have been strong advocates of these measures, and have singled out the class of newer biologic compounds as being particularly well suited to them, in part because of concerns about the inadequacy of biotech patents under Federal Circuit precedent.<sup>302</sup>

A revenue-side policy measure based on data exclusivity has the advantage that it can be calibrated to serve other social goals. The duration of data exclusivity, for example, could be tied to the social value of the drug (e.g., number of people affected, severity of the condition, novelty of the drug), such that the exclusivity might turn on the specific disease (as opposed to the compound) to encourage follow-on R&D for use against other conditions.<sup>303</sup> In addition, the FDA could be permitted to grant extensions on the default term of exclusivity to encourage drug producers to conduct additional safety or comparative efficacy studies that are not required under the standard FDA approval process.<sup>304</sup>

Accelerating the FDA approval process is likely the least costly option, at least in direct monetary terms, available to reduce the costs of drug development and thereby counteract any negative effects on biomedical innovation. According to a recent economic assessment, “a reduction of one year in FDA review time would be worth approximately \$300 million in increased present value for the average product in the top decile of compounds and more than

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<sup>296</sup> Yin, at 1073.

<sup>297</sup> Grabowski-Moe, 89 (arguing for a mix of policies, including FDA data exclusivity, tax incentives, and direct subsidies or grants).

<sup>298</sup> Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISC. 479, 479 (2008).

<sup>299</sup> Data exclusivity has the added virtue that it circumvents the risks of patent challenges. Grabowski-08, 479.

<sup>300</sup> Grabowski-08, 479.

<sup>301</sup> Grabowski-08, 479; Grabowski-Moe, 88 (arguing for a data exclusivity period of ten to fourteen years).

<sup>302</sup> Editorial, *Risks, Returns and Reassurance*, 7 NATURE REV. DRUG DISCOVERY 545, 545 (2008).

<sup>303</sup> Wood-06, 622 (arguing that derivative “me too” drugs should have short exclusivity periods, unless they have some meaningful advantage over the existing drugs); PWC-2020, 8 (making the argument for the virtues of variable patent terms for me-too drugs (short) and new molecular entities (long), which applies equally to data exclusivity terms); GAO-NDD, 36 (also making the case for variable patent terms).

<sup>304</sup> Wood-06, 620; Manheim-06, 401 (arguing that the “weak patent protection” for biologics undercurrent Federal Circuit legal doctrines (i.e., written description and enablement) necessitates the creation of backstop measures to ensure a minimum period of market exclusivity).

\$100 million for a product in the second decile.”<sup>305</sup> The risk, of course, is that this would lead to higher rates of adverse drug reactions. The studies are mixed on this account. While evidence exists that rapid review of novel drugs increases rates of adverse reactions, the volume of a drug’s sales is the strongest predictor of rates of adverse reactions.<sup>306</sup> More importantly, rates of adverse reactions did not increase after the passage of the 1992 Prescription Drug User Fee Act reduce the length of FDA review processes.<sup>307</sup>

More radical departures from binary drug approval processes offer a different approach altogether. A promising approach being advocated involves creating a form of conditional approval, such as an initial license to market a drug on a limited basis, that would be combined with much more elaborate post-marketing review.<sup>308</sup> Insofar as this model lowers the initial standard for regulatory approval, this system would be far less costly than one based solely on pre-market testing, as much of the costs associated with drug testing would arise after revenue is being generated under the initial marketing license.<sup>309</sup> Further, by spreading out the high up-front costs of clinical testing, this system would prove especially beneficial for capital-limited biotech firms that are reliant on smaller niche markets for their new products.<sup>310</sup>

Precedent exists for this approach in the U.S. under the Orphan Drug Act, which provides for both accelerated FDA review and enhanced post-marketing clinical studies (so called Phase IV studies), as well as significant movement in Europe in this direction.<sup>311</sup> Moreover, under the FDA Amendments Act of 2007, Congress’ renewal of the user-fee program provides dedicated user fees for new post-market safety initiatives.<sup>312</sup> The challenge to implementing this approach

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<sup>305</sup> Grabowski-Orphan, 26. A complementary study found that “each twenty-percentage point increase in costs [from Phase II trials] results in an additional \$3.4 million reduction in net present value in year 1,” while “each one-month increase beyond three years [for Phase III trials] lowers the net present value in year 1 by approximately \$2.9 million.” Reed-06, 1314.

<sup>306</sup> Henry Grabowski & Y. Richard Wang, *Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patients Safety? An Analysis of the 1992 Prescription Drug User Fee Act*, 51 J.L. ECON. 377, 394, 396 (2008). This correlation is consistent with the observation that “the adverse side effects that have typically attracted public debate are intrinsically small-numbers events, with occurrence probabilities too low to yield significant indications of user risk with the clinical trial sample sizes customarily required by the FDA.” Scherer-07, 279.

<sup>307</sup> Grabowski-Wang, 401.

<sup>308</sup> Alan M. Garber, *Is Having More Preapproval Data the Best Way to Assure Drug Safety?*, 27 Health Affairs w371, w373 (Aug. 2008) (arguing that an “optimal information strategy for new drugs will likely consist of a shifting balance of pre- and post-approval data collection,” as post-approval studies are less expensive, gets drugs to market sooner, and allow costs of a study to be offset by revenue from drug sales); PWC-09, 18 (arguing that “the current “all-or-nothing” approach to the approval of new medicines may be replaced by a cumulative process, based on the gradual accretion of data. In other words, all newly approved therapies would receive “live licenses” conditional on further in-life testing to substantiate their safety and efficacy in larger populations”)Shelby D. Reed, *How Changes in Drug-Safety Regulations Affect the Way Drug and Biotech Companies Invest in Innovation*, 25 HEALTH AFFAIRS 1309, 1310 (2006).

<sup>309</sup> PWC-09, 18 (observing that this approach has “the great merit of enabling companies to start capitalizing on their R&D expenditure much more rapidly, although sales would peak more slowly”); Reed-06, 1314 (arguing that “sizeable increases in spending for postmarketing safety evaluations are likely to have a much less detrimental economic impact on manufacturers” than pre-marketing requirements).

<sup>310</sup> Reed-06, 1315.

<sup>311</sup> PWC-2020, 34 (describing how “the European Medicines Agency and FDA are both open to granting “conditional marketing approvals for some therapies, subject to certain obligations, including the completion of in-life testing”).

<sup>312</sup> Grabowski-Wang, 3404.

will be ensuring the adequacy of the post-marketing testing, as the track record for Phase IV testing so far has been disappointing.<sup>313</sup> Prior experience suggests that the system will fail unless physicians are given adequate incentives to take part in Phase IV testing, such as awards for doctors who are the first to identify adverse drug reactions.<sup>314</sup>

#### Other Potential Policies:

- Transferable patent or exclusivity rights could be established; to avoid temporal uncertainties, should make it for a fixed term perhaps with a market cap on additional earnings; burden shifted to a different set of consumers (Grabowski-Orphan, 25)
- “Progressive Blockbusters”: “first target a limited segment of potential patients and then expand to other segments over time”; could substantially reduce costs of clinical trials “by limiting the clinical trials to a highly uniform segment of patients” (i.e., with certain genetic profiles) (Garnier-08, 7)
- Tradeoff changes in burden of persuasion for greater transparency; biopharma must disclose all clinical studies and in-life testing; take advantage of electronic data systems to enable independent analysis, or auditing, of data (PWC-2020, 35)
- Nathan argues for (1) fee-for-service components of drug companies, which would work in conjunction with academics and small biotech companies, (2) patent track that rewards innovation in proportion to its impact on the global burden of disease (Nathan-07, 304)
  - Patentees could choose track II is thought would make more money by receiving \$\$ from a global fund that would pay based on disease impact ; give up exclusive rights for direct payments; drugs sold competitively (essentially at generic prices early on) (Nathan-07, 307)

Virtues of small markets: Clinical trials for drugs with smaller markets could be cheaper, as the smaller markets imply that higher rates of problems will be much harder to detect—in essence the size of the clinical trials could be calibrated to the annual rates of usage. Moderately higher levels of adverse effects will be far less detectable in smaller patient populations, which may partially explain why trials for orphan drugs can be less costly, smaller, and quicker.

## V. Conclusions

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<sup>313</sup> Wood-06, 621 (describing how Phase IV commitments are often ignored and the results of a recent study in which “of 1191 open post-marketing commitments, only 114 (9.6%) had been met, yet none of these drugs has been withdrawn from the market”).

<sup>314</sup> Scherer-07, 280. Alternatively, FDA could require simple, large-scale randomized studies of people taking drugs to try to detect ADRs (i.e., a sample size of 100,000). *Id.*