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#### Plan: The United States Federal Government should substantially increase prohibitions on anticompetitive business practices by the private sector by at least expanding the scope of its core antitrust laws to presume that biosimilar reverse payment settlements are anticompetitive

#### The Advantage is Pharma

#### **In 2013 the Supreme Court erred in *FTC v. Actavis*, forcing the FTC to pursue antitrust violations against “pay-for-delay” settlements in too narrow circumstances. District courts interpret *Actavis* as excluding next generation biologics, leading to runaway monopolization and skyrocketing healthcare costs**

Marmaro 21, Morgan Marmaro is the Editor in Chief of Columbia Journal of Law and Social Problems and has a JD from Columbia Law School, "Molecule Size Doesn't Matter: The Case for Harmonizing Antitrust Treatment of Pay-for-Delay Agreements," Columbia Journal of Law and Social Problems 54, no. 2 (Winter 2021): 169-218

It was not until 2013 that the U.S. Supreme Court addressed the legality and antitrust consequences of these agreements in FTC v. Actavis. 13 The Court held that these pay-for-delay agreements could have anticompetitive effects and were not shielded by patent law from antitrust scrutiny or justified by public policy favoring settlements. 14 Furthermore, it held the judicial standard of review for reverse payment agreements under federal antitrust law was the rule of reason. 15 It rejected the Federal Trade Commission's (FTC) argument that these settlements should be presumptively illegal or per se illegal because the Court could not conclude that these agreements would almost always be anticompetitive, noting that some might be justified for procompetitive reasons. 16

Since Actavis, the FTC has found the number of patent settlement agreements that on their face show pay-for-delay is decreasing, i.e., explicit cash settlement payments, but that the number of settlements with restrictions on generic entry that include other alleged forms of compensation have more than doubled from 2015 to 2016.17 Moreover, the FTC reports do not include every type of pharmaceutical agreement, and suggest that the form of pay-for delay has become more opaque and that any celebration of the demise of the pay-for-delay problem is premature. 18 The FTC only recently began requiring biologic companies to report their patent settlement agreements involving biologic drugs, and no FTC reports have yet been issued.1 9

Efforts to curb collusive pay-for-delay agreements are complicated by the different pharmaceutical manufacturing processes that enhance opportunities to game the system and by divergent regulatory and reporting regimes that can create undue confusion when interpreting and applying related case law. In large part, these differences are due to two different forms of pharmaceuticals - small and large molecule drugs - each with their own pathway to regulatory approval.2 0

Small molecule drugs are synthetic and have simpler, well-defined manufacturing processes. 21 Many of the drugs on the market, such as Aspirin, are small molecule drugs. 22 Large molecule drugs, also known as biologics, are generally produced using larger, complex molecules in living cells and are the fastest growing part of the drug market, often launched at eye-popping prices. 23 Not only do biologics offer some revolutionary advances in treating and curing previously incurable diseases, including some cancers, but also the biologics market is expected to increase from $239.2 billion in 2020 to $464.7 billion worldwide by 2023.24

Unlike small molecule drugs that can be replicated with relatively greater ease and confidence, large molecule biologics involve between dozens and hundreds of operating procedure controls to create the specific conditions that ensure an unexpected factor does not alter the resulting product.25 Not only must a manufacturer know what components to use, it must also know the precise sequence to assemble those pieces. 26 This also means that any attempts to make a "copycat" or "generic" version of a biologic drug - i.e., biosimilars - are more expensive. On average, some estimate that the cost of developing a generic is roughly $2 million, while developing a biosimilar may require $200 million or more. 27

Though biosimilars compete with biologics as generics compete with brands, biosimilars are subject to different regulations and state laws governing when and how they can be substituted or interchanged with the branded drug at the doctor and pharmacy level. 28 With small molecule drugs, the FDA determines whether the generic is a reliable copy or substitute for a brand drug (or an AB-rated generic); under many state laws, this FDA determination allows and often mandates a pharmacy to substitute a generic for a prescribed brand drug. 29 As a result, generics have an almost automatic path to competition in many situations.

In contrast, the FDA only recently developed the regulations allowing it to determine that a biosimilar is "interchangeable" with a biologic.30 As of September 2020, the FDA has yet to designate a single biosimilar or biologic drug in the U.S as "interchangeable."3 1 Indeed, the FDA has been relatively slow to even approve biologic and biosimilar drugs for sale in the U.S., making biosimilar introduction relatively slow in the U.S compared to Europe. 32 While there are seventy-one biosimilar drugs approved in Europe as of January 2020, only twenty-six biosimilars had been approved in the U.S. 33

But even when the FDA actually approves a biosimilar as an "interchangeable" drug, most states do not have laws that permit or mandate the substitution of the "interchangeable" drug with the biologic. 34 The pharmaceutical industry successfully lobbied for laws requiring naming conventions for biosimilar drugs that make it difficult for pharmacists to identify similar biologic drugs.35 States, for their part, have generally not updated their laws to provide more substitution of biosimilars or those drugs with interchangeability designations.

However, with the end of the "golden age" for small-molecule brand drugs in sight and $200 billion in brand sales subject to generic competition by 2025, companies increasingly see biologics and biosimilars as the future of the pharmaceutical market.36 As explained infra, biologic drugs' large price tag derives, in part, from a lack of meaningful competition in the U.S. and few pricing constraints. 37 Some $67 billion of the biologic market is vulnerable to biosimilar competition as major patents are set to expire in 2020;38 the use of patents and pay-for-delay agreements by biologics companies remains a potent threat to any real competition.

For instance, Humira has been the top-selling rheumatoid arthritis and immunology drug in the U.S. for more than six years, generating over $20 billion in sales for 2018 alone.39 Popularity and high sales' volume alone do not explain the enormous revenues, which can be primarily attributed to its high price: in 2020, $72,000 per patient annually. 40 Yet, in 2018, AbbVie Humira's manufacturer - cut Humira's price by 80% in Europe once biosimilar versions became available. 41 Meanwhile, Humira has entered a number of settlement agreements with biosimilar competitors, two of whom had already received FDA-approval in 2016 and 2017.42 None of the biosimilar companies will enter the U.S. market until 2023, leaving U.S. consumers to pay up to 500% more than their European counterparts for the same drug. 43 In contrast, the same biosimilar companies received entry dates into European markets more than five years before entry in the U.S.44 In total, eight companies with Humira biosimilars have settled with AbbVie, extending Humira's U.S. monopoly, and its supracompetitive prices in the U.S., seven years past its main ingredient's patent expiry date. 45

A class action, In re Humira (Adalimumab) Antitrust Litigation,46 alleges that AbbVie's multiple agreements are actually market allocating agreements and settlements qualifying as reverse payments. As of this writing, the In re Humira litigation is undergoing appeal after a district court ruled in favor of AbbVie, noting that while the behaviors seem unsavory, they were legal "exploited advantages" derived from the current regulatory system.47 The court went further astray, finding that the agreements were not anticompetitive, and in contradiction with Actavis's rejection of the scope of the patent doctrine, did so by relying upon the alleged strength of AbbVie's Humira patents.48 But neither the parties nor the Court in In re Humira questioned the basic application of Actavis to the agreements in this case. Though the In re Humira district court dismissed the case in favor of defendants,49 this Note argues that the In re Humira district court was correct to engage in an Actavis analysis but did so incorrectly.

A constrictive reading of Actavis to not include biologics, despite similar economic incentives to game the system and collusively divide the markets, would undoubtedly result in the proliferation of collusive biologic settlement agreements that will increase the already staggering biologic prices. There is clear congressional intent that supports treating biologic and small molecule collusive agreements under the same standards.50 Further, using the ongoing In re Humira litigation as a framing device, an opportunity for courts to explicitly determine whether and how to apply the Actavis framework to biologic drug settlements, this Note will demonstrate how the reasoning and analysis of Actavis applies to qualifying settlements in the biologic sphere and is consistent with precedent, congressional intent, and public policy.

While differences between biologics and small molecule pharmaceutical production warrant different FDA manufacturing procedures, 51 recent and ongoing legislative proposals addressing pay-for-delay agreements apply the same legal standards to adjudication of agreements for biologic and small molecule drug manufacturers. 52 Some commentators, however, have advocated a narrow interpretation of Actavis to apply only to small molecule drugs53 because the Court only discusses the relevant regulatory framework for small molecule drugs in that case. 54 They argue that the Actavis result was founded and based on the language and intent of the Hatch-Waxman Act. 55 Just as the courts then spent years litigating whether Actavis only implicated cash-only "payments," 56 savvy pharmaceutical attorneys are likely to argue that Actavis should apply only to drugs covered by the Hatch-Waxman Act.

Part II will first discuss various forms of antitrust abuses that arise in the pharmaceutical space and are often utilized as part of or together with reverse payment agreements. It goes on to explain the legal and regulatory backgrounds of small and large molecule drugs, focusing on how the biologic regulatory regime differs. Part III then discusses the consequences of lax antitrust scrutiny on pharmaceuticals, and finishes with the allegations, arguments, and findings currently on appeal in In re Humira. Lastly, Part IV proposes a two-fold solution to the problems posed by Actavis's lack of legal clarity. First, there must be regulation or precedent that clearly indicates that for antitrust purposes, biologic settlement agreements should be subject to the same antitrust scrutiny as those concerning small molecule drugs. In re Humira provides the perfect opportunity; and as the Part IV analysis will show, applying Actavis to biologics is in the spirit of the law, aligns with public policy, and follows precedent - despite the In re Humira district court ruling in favor of the defendants. Second, this Note suggests a need for a corresponding legislative solution. This Note's purpose is to demonstrate that the way a drug is manufactured, approved, or allowed to compete does not alter the application of antitrust law seeking to rid the market of collusive agreements between rivals.

#### **Even individual pay for delay agreements cost consumers billions** of dollars in losses, only antitrust regulation makes healthcare accessible

Deb, 20

(Chaarushena, Yale Law School, and Gregory Curfman, MD, Deputy Editor, JAMA, “Relentless Prescription Drug Price Increases”, *JAMA 323*(9): 826-828, 03-03-2020, doi:10.1001/jama.2020.0359)\\JM

One in 4 people in the US has difficulty paying the cost of their prescription medications. This stark fact was recently reported in a 2019 Kaiser Family Foundation public opinion poll among a nationally representative random sample of 1205 adults.1 Persons who reported having the greatest difficulty affording their prescription drugs were those who most needed them, including those who took 4 or more prescription drugs, spent $100 or more per month on their drugs, and reported being in fair or poor health. In response to relentless increases in prescription drug prices and the burden they place on consumers, the federal government has begun to take some action. The House of Representatives passed H.R.3, The Elijah E. Cummings Lower Drug Costs Now Act, which would allow Medicare to negotiate the price of 250 drugs per year; cap payments for drugs in the US at 120% of the average prices in 6 other countries; prohibit drug price increases beyond the rate of inflation; allow private insurers to purchase drugs at Medicare’s negotiated price; and cap out-of-pocket drug spending for older adults at $2000 annually. But this comprehensive legislation is very unlikely to pass in the Senate, as Majority Leader Mitch McConnell, referring to drug price negotiation as “socialist price controls,”2 has made it clear that he will not take it up. Meanwhile, Senators Chuck Grassley (R-IA) and Ron Wyden (D-OR) have introduced bipartisan drug pricing legislation that, like the House bill, would place penalties on pharmaceutical companies if they raise prices faster than inflation. However, this provision in the bill, considered crucial by the sponsors, is also its greatest obstacle to passage, as many Republican senators oppose the idea as a form of government price setting. Thus, without substantial compromise, the prospects for passage of this bill in a Republican Senate are not bright. The Trump administration has proffered its own proposal to control the prices of prescription drugs, which is focused primarily on facilitating importation of prescription drugs from Canada. Senator Bernie Sanders (I-VT) has introduced drug importation legislation in the Senate, the Affordable and Safe Prescription Drug Importation Act, which the Congressional Budget Office estimates would save $7 billion over the next decade. However, both Canadian officials and the pharmaceutical industry are strongly opposed to these importation proposals, creating major hurdles for passage. With the fate of federal initiatives to control drug prices uncertain, individual states have begun to focus on this issue. Since 2015, a total of 35 bills have been passed in 22 states that include provisions requiring drug price transparency to aid consumers in purchasing prescription drugs.3 However, these state actions generally do not help patients because they do not require the disclosure of real transaction prices at each stage of the drug distribution process. The Trump administration has also proposed a price transparency rule, whereby pharmaceutical companies would be required to include their wholesale acquisition (list) prices in drug advertisements. This proposal, however, is unlikely to survive a legal challenge by the industry. In another state-level proposal, Governor Gavin Newsom of California recently signed into law a bill, Preserving Access to Affordable Drugs, banning pay-for-delay deals. Such tactics involve payments from brand-name companies to generic companies to keep lower-cost generic drugs off the market, and both brand-name and generic companies profit from these arrangements. These arrangements are commonplace, and with the elimination of market competition, brand-name companies are at liberty to keep their prices high—as high as the market will bear. Although the Supreme Court ruled in Federal Trade Commission v Actavis (2013)4 that such deals may be challenged as anticompetitive, California has been sued on constitutional grounds that the state law banning pay-for-delay interferes with interstate commerce. For now, pending the outcome of the lawsuit, the law remains in effect, but it is uncertain if it will ultimately survive legal challenge. Governor Newsom also recently announced another novel development, in which California will explore manufacturing its own generic drugs as a way of controlling costs to consumers. Exactly how such an ambitious plan would be implemented, however, remains to be determined. In the current presidential election year, the high cost of prescription drugs has emerged as a major campaign issue for all the candidates. In this issue of JAMA, 3 original research articles address different aspects of the prescription drug price quandary. Also relevant to this discussion is a fourth article, published simultaneously in JAMA Internal Medicine, that describes the substantial expenditures by the pharmaceutical industry on political donations and lobbying between 1999 and 2018.5 The pharmaceutical industry often points to the high costs of research and development (R&D) required for the creation of innovative therapies as justification for high pricing, and in the Kaiser Family Foundation opinion poll, 69% of respondents believed that R&D costs were an important contributing factor to high prescription drug costs.1 A previous study of large pharmaceutical companies reported that the estimated R&D cost to bring a new drug to market was $2.87 billion.6 This study came under sharp criticism because the data on which it was based were considered to be “proprietary” and, therefore, were not provided in the published article.7 A new analysis by Wouters and colleagues8 in this issue of JAMA relied only on publicly available data, which were made available primarily by smaller biotechnology companies. Examining 63 of 355 new drugs approved by the US Food and Drug Administration between 2009 and 2018, the authors reported an estimated median R&D cost to bring a new drug to market of $985 million. Although this figure is substantially lower than the previously reported R&D cost for larger companies, it is still a considerable amount for smaller, start-up biotechnology companies to recoup from a new product. In a second article in this issue, Ledley and colleagues9 examined the profitability of 35 large pharmaceutical companies, as compared with 357 nonpharmaceutical companies, listed among Standard & Poor 500 companies between 2000 and 2018. During this period, the median profit margin for large pharmaceutical companies was nearly double that of nonpharmaceutical companies. Specifically, the median net income (earnings) expressed as a fraction of revenue was 13.8% for pharmaceutical companies compared with 7.7% for nonpharmaceutical companies. Although the difference narrowed over the last 5 years, pharmaceutical companies still remained more profitable than nonpharmaceutical companies. The authors also noted that the median annual net income margins of Apple, Alphabet, and Microsoft, technology giants that are increasingly involved in health care, were 19.2%, 21.9%, and 27.6%, respectively, compared with 13.8% for pharmaceutical companies. In the Kaiser Family Foundation opinion poll, 4 of 5 respondents believed that drug company profits are a major factor contributing to the high cost of prescription drugs.1 Thus, most US residents perceive that pharmaceutical companies maintain their high profit margins by keeping prices high. In a third article in this issue, Hernandez and colleagues10 reported on trends in both list prices (defined as the wholesale acquisition price) and net prices (the price after discounts and rebates) for 602 brand-name drugs from 2007 to 2018. Inflation-adjusted list prices increased by 159%, and net prices increased by 60%. Increases in discounts offset 62% of increases in list prices, but there was wide variability among different classes of drugs. Pharmaceutical companies offer discounts to payers to secure a favorable position for their drugs on the payers’ formularies and to stave off competition. Some companies that manufacture brand-name biologic products, for instance, may provide discounts to keep biosimilar products off formularies or to improve the positioning of their other drugs. For example, attempting to establish another robust income stream, biologics manufacturer AbbVie now discounts Humira, which accounts for more than half of its revenue, to secure better formulary positioning of its new biologic for plaque psoriasis, Skyrizi. The financial strategy for some products of some pharmaceutical companies follows this scenario: increase list prices; offer discounts to partially offset the list price increases; restrain competition and enhance market share through optimal formulary placement; and increase volume of sales. It is noteworthy that patients do not receive discounts, and patients who are uninsured, covered by high-deductible plans, or are in the deductible phase of their coverage, must pay list prices. Also, coinsurance payments, which may be required for some more expensive specialty drugs, are determined based on a percentage of the list price. The pharmaceutical industry just announced prescription drug price increases for 2020. According to the health care research firm 3 Axis Advisors, prices were increased for nearly 500 drugs, with an average price increase of 5.17%.11 To mitigate public criticism, most of the price increases were kept below 10%. The list price of the world’s best-selling drug, adalimumab (Humira), was increased by AbbVie by 7.4% for 2020, which adds to a 19.1% increase in list price for years 2018 and 2019. The 2018 price increase alone was estimated to have added $1 billion to US health care costs. In a recent analysis, the Institute for Clinical and Economic Review determined there was insufficient clinical evidence to justify such a large price increase.12 Humira serves as a prime example of the aggressive tactics that may be used by some pharmaceutical companies to maintain high drug prices. In response to these price hikes for Humira, AbbVie has recently been the subject of a series of groundbreaking class-action lawsuits. Insurance payers and workers’ unions allege that AbbVie created a “patent thicket” around the monoclonal antibody therapy, thereby acting in bad faith to quash competition from Humira biosimilars.13 The original Humira patent expired in 2016, but AbbVie has been able to stave off biosimilar market entry by filing more than 100 follow-on patents that extend AbbVie’s monopoly beyond 2030. It is not uncommon for drugs to be protected by multiple patents, but the Humira patent thicket is extreme and allows AbbVie to aggressively extend its high monopoly pricing. A second claim in the lawsuits against AbbVie is that the company allegedly used “pay-for-delay” tactics to negotiate later market entry dates with biosimilar competitors. Pay-for-delay agreements in the pharmaceutical industry have been controversial for years, but the notion of a “patent thicket” greatly exacerbates the issue because the normal route for generics and biosimilars to enter the market is through patent litigation. Typically, a generic or biosimilar drug maker will try to enter the market prior to the patent term expiration date by asserting that the patents they would be infringing are, in fact, invalid. AbbVie contended it would continue to sue biosimilar manufacturers for infringement using its full complement of patents, pushing market entry dates well into the 2030s, leading the biosimilar companies to simply give up and settle the litigation. These settlements will likely allow AbbVie to continue instituting price increases for Humira. The pioneering class-action lawsuits, filed on behalf of the people who actually bear the burden of increasing drug prices, represents a novel way of challenging the drug industry with the aim of increasing access to expensive medicine for all patients. When legislative solutions are unsettled, this innovative lawsuit could establish a new legal pathway for curtailing relentless price increases for expensive prescription drugs. Collectively, the articles in the current issues of JAMA and JAMA Internal Medicine, along with the illustrated cover of JAMA, paint a concerning picture about the relationships among rising drug prices, pharmaceutical industry profits, uncertainty about pharmaceutical R&D costs, and lobbying and political donations to gain influence with legislators. We anticipate that publication of this information will further stimulate the ongoing national debate on prescription drugs and help rein in increasing drug prices while sustaining innovation in drug development, which is so critical to the health of individuals both in the US and around the world.

#### Pay-for-delay raises costs, reduces access, and slows innovation

Shabbir, 21

(Ruqayyah, Ivey Business School at Western University, “The Delay of Competition in the Pharmaceutical Industry: A Closer Look at the Pharmaceutical Giants”, *Western Undergraduate Economics Review,* 20, (2021), https://ojs.lib.uwo.ca/index.php/wuer/article/view/14025)\\JM

Lastly, one of the most controversial and recent acquisitions in the pharmaceutical industry was AbbVie’s purchase of Allergan. In 2019, the American biopharmaceutical company, AbbVie, officially acquired Allergan, an Irish pharmaceutical company. Prior to the official acquisition, there was significant concern regarding how drug prices and future drug innovation would be affected as a result. This concern was substantial enough to bring together 17 consumer advocacy groups. This collective group expressed their worries to the Federal Trade Commission (FTC), based on historical information about AbbVie and the broader pharmaceutical industry. Specifically, the group noted that between 2006 and 2017, AbbVie had tripled its price for Humira (generic name: adalimumab), and “neither inflation, nor higher manufacturing costs could explain these price increases” (Mogin, 2019). Based on these voiced concerns, it would have been important to question what AbbVie would be capable of once it acquired Allergan’s drug portfolio. In addition to expressing concern, the group presented data on recent trends in the pharmaceutical industry. Among data on price increases, there was also concern that AbbVie’s acquisition would hamper innovation, reducing how much firms spend on research and development (R&D). It has been noted that “the share of new drugs coming from the top twenty big pharma firms has dropped every year since 2013, from over 60% to just above 30% in 2018”(Mogin, 2019). Simply stated, large firms are acquiring smaller firms to increase their drug portfolio, rather than working to benefit consumers through increased innovation and R&D. With a focus on mergers and acquisitions (M&A), innovation has become a secondary goal. This directly impacts consumers as it has taken firms longer to introduce new drugs and when these new drugs come to market, they come much later. Firms are simply taking the “easy route” to becoming pharma giants, once again at the detriment of consumers. With discussion concentrated around the time delay in bringing affordable and innovative drugs to market, it is important to introduce the role of pay-for-delay schemes. The previous three case analyses illustrate how certain strategies can still harm consumers through hindered competition, even if there is no overall “lessening of competition” according to the respective country’s competition law. Unlike the tactics used by the firms discussed above, the pay-for-delay tactic is a way for patent-holders (“brands”) to stifle competition in a much more direct way. The pay-for-delay scheme involves brands offering settlements to generics, deterring them from developing and marketing generic versions of their patented drugs once the patent expires. Pay-for-delay deals have “cost consumers and taxpayers $3.5 billion in higher drug costs every year” (Federal Trade Commission, 2019). Recognizing this, the United States’ FTC has made it its priority to prevent these schemes from injuring competition. The controversy surrounding each of the cases discussed above highlights the need for a deeper analysis of competition cases, specifically with respect to how the actions of firms directly and indirectly affect consumers. Although it was found that these firms did not lessen competition, the difficulties they caused other firms and potential entrants resulted in delayed entry of competitors. In the case of Celgene, generics were repeatedly denied access to CRPs, which hindered their ability to validate their drugs and bring them to market. Pfizer engaged in various exclusive dealing arrangements to deter the entry of generics, impeding their ability to sell appropriate quantities once they enter. Finally, AbbVie’s acquisition of Allergan caused great concern among consumers, as past data has shown higher prices, less competition, and slowed innovation as a likely result. With generics entering the industry later than expected and with higher costs due to the strategies pursued by major pharma brands, consumers cannot access cheap drugs in a timely manner. Unfortunately, a population that desperately requires medicine, but can only afford generic versions, will always exist. Therefore, even if competition eventually builds, this does not necessarily mean that consumers will no longer be affected during the period of delay. According to a paper addressed by the NCBI, “1 in 5 Americans do not fill prescription drugs because of prohibitive costs” (Carrier et al., 2016). From a global perspective, this statistic reflects the staggering reality of many other countries. Competition law is often designed in a generalized manner, such that every firm in every industry is subject to the same laws. This helps in promoting fairness and ensuring justice. However, it is important to note that medicine is unlike many other consumer goods. Although the nuanced nature of the medical industry is being increasingly recognized and competition law has recently evolved in the pharmaceutical industry, there must be greater discipline. The three cases discussed in this paper are just a handful of the many cases that do not lessen competition per se, but surely delay competition and the introduction of affordable drugs to consumers in a timely manner.

#### Early clarity is key---companies are watching this litigation. If not reversed, biologic companies will copy AbbVie’s strategy. That crushes innovation.

Balto, 21

(David, leading expert on healthcare competition and regulation and an antitrust attorney as well as the Former Assistant Director of Policy and Evaluation at the FTC, Brief Of Amici Curiae Consumer Action And U.S. Public Interest Research Group In Support Of Plaintiffs-Appellants, Ufcw Local 1500 Welfare Fund, et al., v. Abbvie Inc., et al, In The United States Court Of Appeals For The Seventh Circuit, Filed 10/14/20, WestLaw)

The District Court’s dismissal will only embolden other drug manufacturers to use the patent process, along with the courts and reverse settlement payments, as tools to delay the entry of rivals.6 The District Court’s decision incentivizes drug manufacturers not to innovate but rather to focus on tweaking their patent estates to extend the life of their monopolies and then suing rivals for alleged patent infringement and seeking reverse payments.7 Indeed, one of the most effective ways for a brand manufacturer to maintain market power is through the abuse of government processes.8 The cost to the brand manufacturer engaging in such abuse typically is minimal, while the anticompetitive effects resulting from such abuse often are significant.9 Approximately 40 years ago, then-Circuit Court Judge Robert Bork observed that “[p]redation by abuse of governmental procedures, including administrative and judicial processes, presents an increasingly dangerous threat to competition.”10 Anticompetitive conduct through regulatory and judicial abuse can be especially pernicious. In a healthy market, when a company obtains a dominant position through competition in the marketplace, we can expect other competitors to arise and possibly displace them. But no natural competitive force can displace dominance acquired through abuse of the regulatory and judicial processes. That is especially the case in the pharmaceutical industry where litigation and regulatory approval are necessities to market entry. Here, AbbVie’s successful extension of its Humira monopoly along with the reverse settlements kept biosimilars out of the U.S. market in exchange for an early entry in Europe. If this strategy is found to be legal under the antitrust laws, it will have serious ramifications for the cost of prescription drugs going forward. Biologics such as AbbVie’s Humira are essential for the treatment of serious debilitating and life-threatening diseases. While fewer than 2% of all U.S. prescriptions are for biologic drugs, they account for almost 40% of all U.S. drug spending.11 In other words, biologics are extremely expensive, and they are the fastest-growing segment of drug spending in the United States. When Congress passed the Biologics Price Competition and Innovation Act ten years ago, the expectation was that a robust biosimilar market would substantially lower the price of biologic drugs. Indeed, there were estimates indicating that the cost savings to the U.S. healthcare system from the use of biosimilars could have been up to hundreds of billions of dollars over a decade.12 One study suggests that there may be a significant uptick in the rate of biosimilar approvals over the next few years which have the potential to generate nearly $100 billion in cost savings.13 However, a number of obstacles including anticompetitive patent thicket strategies and reverse settlement agreements have delayed and may in the future delay many biosimilars from entering and competing in the United States. Unfortunately, from 2010 to 2019, biosimilars have only saved U.S. patients about $1.8 billion.14 If Americans could have bought FDA-approved biosimilars over the past four years, they could have saved over $9 billion.15 Thus, patients’ access to biosimilar drugs is critically important to lowering overall drug spending and costs to patients in the United States. Disputes between branded biologics and biosimilars will continue as patent thickets prevent biosimilar entry after the expiration of the original patents on a drug. A recent report analyzing the twelve best selling drugs in the United States revealed that pharmaceutical manufacturers of the brand drugs filed on average 125 patent applications to extend their monopolies “far beyond the twenty years of protection intended under U.S. patent law” in an effort to preserve their monopoly pricing.16 As if to add insult to injury, drug manufacturers are also increasing prescription drug prices even as they extend the life of their monopolies.17 Make no mistake the District Court’s decision with respect to AbbVie’s conduct will have huge ramifications going forward. AbbVie is the most egregious violator of the patent thicket strategy that resulted in a reverse settlement and the harm caused to U.S. payors and consumers is clear. AbbVie’s economic incentive is to prolong the life of Humira, the world’s number one selling drug for as long as it can. Humira’s list price in the United States more than tripled from 2006 to 2017, with the list price soaring from $16,636 to $58,612 for a one-year supply;18 and from 2012 to 2018, Humira’s price increased by 144%.19 Neither inflation nor higher manufacturing costs explain these price increases. As the record demonstrates, most of Humira’s U.S. patents were set to expire in 2016, but AbbVie engaged in a patent thicket strategy that allowed the company to prolong its Humira monopoly for years beyond what Congress intended. And while biosimilar manufacturers challenged AbbVie’s patent estate, they all eventually agreed to delay their entry into the U.S. market until 2023 in exchange for entering the European market much sooner. The predictable result is that in Europe, where biosimilars have entered the market without obstacles, biologics such as AbbVie’s branded blockbuster Humira has been discounted as much as 80%.20 AbbVie offered these discounts to maintain its sales in the face of biosimilar competition. In the United States, however, the price of Humira has continued to climb due to the lack of biosimilars. Biologic drug manufacturers are watching this appeal closely and if the District Court’s opinion is not reversed, they will have every incentive to copy AbbVie’s strategy. If the District Court’s opinion is not reversed, their incentive to copy AbbVie’s strategy which will result in widespread harm as well as higher drug prices for payors and patients. The price differential for Humira in Europe versus the United States makes one thing startingly clear: patent thickets and pay for delay strategies harm payors and patients who are effectively forced to use more expensive biologics when more affordable medicines should be available – indeed are available for payors and patients that happen to be on the winning land-mass of AbbVie’s devil bargain. In addition, the federal government as well as taxpayers are harmed as well because government programs such as Medicare suffer as they must pay artificially inflated monopoly prices. There is also harm to manufacturers of biosimilars. They suffer loss of sales, loss of investment, damage to brand and reputation, and loss of business opportunity. Finally, there could be a real impact on the research and development of more affordable medicines. If drug manufacturers use AbbVie’s anticompetitive strategy, it will affect the decisions of biosimilar manufacturers to launch new products into new markets going forward despite already investing heavily into research and development and some biosimilar manufacturers may decide not to continue with any R&D efforts or to launch new biosimilar products. These decisions to abandon R&D efforts or to hold back the launch of biosimilars unquestionably harm competition, payors, and patients.

#### Pharmaceutical innovation is crucial to solving global threats from infectious diseases and bioterror. Alternatives to market-based incentives are guaranteed to fail.

Marjanovic, 20

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We need to ensure scalable and sustainable approaches for pharmaceutical innovation in response to infectious disease threats to public health As key actors in the healthcare innovation landscape, pharmaceutical and life sciences companies have been called on to develop medicines, vaccines and diagnostics for pressing public health challenges. The COVID-19 crisis is one such challenge, but there are many others. For example, MERS, SARS, Ebola, Zika and avian and swine flu are also infectious diseases that represent public health threats. Infectious agents such as anthrax, smallpox and tularemia could present threats in a bioterrorism context.1 The general threat to public health that is posed by antimicrobial resistance is also well-recognised as an area in need of pharmaceutical innovation. Innovating in response to these challenges does not always align well with pharmaceutical industry commercial models, shareholder expectations and competition within the industry. However, the expertise, networks and infrastructure that industry has within its reach, as well as public expectations and the moral imperative, make pharmaceutical companies and the wider life sciences sector an indispensable partner in the search for solutions that save lives. This perspective argues for the need to establish more sustainable and scalable ways of incentivising pharmaceutical innovation in response to infectious disease threats to public health. It considers both past and current examples of efforts to mobilise pharmaceutical innovation in high commercial risk areas, including in the context of current efforts to respond to the COVID-19 pandemic. In global pandemic crises like COVID-19, the urgency and scale of the crisis – as well as the spotlight placed on pharmaceutical companies – mean that contributing to the search for effective medicines, vaccines or diagnostics is essential for socially responsible companies in the sector. 2 It is therefore unsurprising that we are seeing industry-wide efforts unfold at unprecedented scale and pace. Whereas there is always scope for more activity, industry is currently contributing in a variety of ways. Examples include pharmaceutical companies donating existing compounds to assess their utility in the fight against COVID19; screening existing compound libraries in-house or with partners to see if they can be repurposed; accelerating trials for potentially effective medicine or vaccine candidates; and in some cases rapidly accelerating in-house research and development to discover new treatments or vaccine agents and develop diagnostics tests.3,4 Pharmaceutical companies are collaborating with each other in some of these efforts and participating in global R&D partnerships (such as the Innovative Medicines Initiative effort to accelerate the development of potential therapies for COVID-19) and supporting national efforts to expand diagnosis and testing capacity and ensure affordable and ready access to potential solutions.3,5,6 The primary purpose of such innovation is to benefit patients and wider population health. Although there are also reputational benefits from involvement that can be realised across the industry, there are likely to be relatively few companies that are ‘commercial’ winners. Those who might gain substantial revenues will be under pressure not to be seen as profiting from the pandemic. In the United Kingdom for example, GSK has stated that it does not expect to profit from its COVID-19 related activities and that any gains will be invested in supporting research and long-term pandemic preparedness, as well as in developing products that would be affordable in the world’s poorest countries.7 Similarly, in the United States AbbVie has waived intellectual property rights for an existing combination product that is being tested for therapeutic potential against COVID-19, which would support affordability and allow for a supply of generics.8,9 Johnson & Johnson has stated that its potential vaccine – which is expected to begin trials – will be available on a not-for-profit basis during the pandemic.10 Pharma is mobilising substantial efforts to rise to the COVID-19 challenge at hand. However, we need to consider how pharmaceutical innovation for responding to emerging infectious diseases can best be enabled beyond the current crisis. Many public health threats (including those associated with other infectious diseases, bioterrorism agents and antimicrobial resistance) are urgently in need of pharmaceutical innovation, even if their impacts are not as visible to society as COVID-19 is in the immediate term. The pharmaceutical industry has responded to previous public health emergencies associated with infectious disease in recent times – for example those associated with Ebola and Zika outbreaks.11 However, it has done so to a lesser scale than for COVID-19 and with contributions from fewer companies. Similarly, levels of activity in response to the threat of antimicrobial resistance are still low.12 There are important policy questions as to whether – and how – industry could engage with such public health threats to an even greater extent under improved innovation conditions. The COVID-19 pandemic is a game-changer among global public health threats. The risk to human life (both in terms of morbidity and quality of life), the economic risks, the epidemiology of the disease and speed of escalation have led to a crisis-response by many governments around the world. This has in turn influenced the immediate industry efforts. Many other infectious disease threats may not manifest as crises in the short term and in the same way as COVID-19, but they could nevertheless escalate. They are not considered to be crises from a short term perspective because they are contained to specific regions and affect fewer people at present – or are re-emerging (e.g. Ebola) – or their impacts have not yet materialised at a scale that would qualify as an immediate crisis (e.g. growing risks of antimicrobial resistance to some infectious pathogens). However, such diseases and issues are recognised as global threats that could become crises in the future.13 The emerging threats raise important policy questions about how government and the pharmaceutical industry can work together to ensure that pharmaceutical industry innovation is incentivised sustainably and at scale. This is important to help mitigate against current and emerging threats becoming crises further down the line. At present, there are no clear and specific criteria to determine when a disease can trigger the types of healthcare-innovation-related policy actions that have been deployed in response to the COVID-19 crisis. For example, this applies to criteria for securing financial resources for innovation-related activities, reforming regulation to accelerate trials and regulatory approval processes, and securing reimbursement mechanisms that help enable industry engagement and the search for rapid solutions. The WHO guidance on what constitutes a pandemic phase does provide guidance on national policy response options, but not specifically as they relate to healthcare innovation activity.14 There are also questions as to whether such policy initiatives and incentives should only be applied in crisis situations, or also as part of proactive government and industry efforts to innovate in the areas of public health threats in order to prevent future global calamities. A crisis and ‘emergency mode’ response may be inevitable for some diseases, but more can be done to mitigate against the need for such a response – especially in cases where emerging threats and their consequences can be foreseen and are known to be a risk. We need to anticipate and act now in terms of how we plan and incentivise better for the future, and how we distinguish between different types of infectious disease threats and phases in framing incentives and regulation. Innovative financial instruments must be integral to any sustainable and scalable approach to incentivising pharmaceutical innovation for tackling emerging threats to public health from infectious diseases The pharmaceutical industry has a responsibility to both its shareholders and to society at large. Incentivising the pharmaceutical industry to innovate solely on the grounds of being a socially responsible sector is unlikely to lead to a sustainable and scalable approach for innovating in response to emerging infectious disease threats. There are also potential challenges to the types of innovation (i.e. how radical or incremental) a reliance on incentives rooted solely in a social responsibility argument can lead to. Donating existing compounds for testing is important, but it is different to at-scale, industry-wide intensive investment in R&D geared at developing highly innovative diagnostics, medicines and vaccines. Even in the case of COVID-19, there are significant differences in the scale of innovative activity that focuses on repurposing existing products and technologies – for example, through testing existing antiviral compounds for potential therapeutic value – and more radically innovative R&D efforts aimed at developing something that acts on the COVID-19 virus in fundamentally novel ways.

#### Bioterror causes extinction

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How worthwhile is it spending resources to study and mitigate the chance of human extinction from biological risks? The risks of such a catastrophe are presumably low, so a skeptic might argue that addressing such risks would be a waste of scarce resources. In this article, we investigate this position using a cost-effectiveness approach and ultimately conclude that the expected value of reducing these risks is large, especially since such risks jeopardize the existence of all future human lives. Historically, disease events have been responsible for the greatest death tolls on humanity. The 1918 flu was responsible for more than 50 million deaths,1 while smallpox killed perhaps 10 times that many in the 20th century alone.2 The Black Death was responsible for killing over 25% of the European population,3 while other pandemics, such as the plague of Justinian, are thought to have killed 25 million in the 6th century—constituting over 10% of the world's population at the time.4 It is an open question whether a future pandemic could result in outright human extinction or the irreversible collapse of civilization. A skeptic would have many good reasons to think that existential risk from disease is unlikely. Such a disease would need to spread worldwide to remote populations, overcome rare genetic resistances, and evade detection, cures, and countermeasures. Even evolution itself may work in humanity's favor: Virulence and transmission is often a trade-off, and so evolutionary pressures could push against maximally lethal wild-type pathogens.5,6 While these arguments point to a very small risk of human extinction, they do not rule the possibility out entirely. Although rare, there are recorded instances of species going extinct due to disease—primarily in amphibians, but also in 1 mammalian species of rat on Christmas Island.7,8 There are also historical examples of large human populations being almost entirely wiped out by disease, especially when multiple diseases were simultaneously introduced into a population without immunity. The most striking examples of total population collapse include native American tribes exposed to European diseases, such as the Massachusett (86% loss of population), Quiripi-Unquachog (95% loss of population), and the Western Abenaki (which suffered a staggering 98% loss of population).9 In the modern context, no single disease currently exists that combines the worst-case levels of transmissibility, lethality, resistance to countermeasures, and global reach. But many diseases are proof of principle that each worst-case attribute can be realized independently. For example, some diseases exhibit nearly a 100% case fatality ratio in the absence of treatment, such as rabies or septicemic plague. Other diseases have a track record of spreading to virtually every human community worldwide, such as the 1918 flu,10 and seroprevalence studies indicate that other pathogens, such as chickenpox and HSV-1, can successfully reach over 95% of a population.11,12 Under optimal virulence theory, natural evolution would be an unlikely source for pathogens with the highest possible levels of transmissibility, virulence, and global reach. But advances in biotechnology might allow the creation of diseases that combine such traits. Recent controversy has already emerged over a number of scientific experiments that resulted in viruses with enhanced transmissibility, lethality, and/or the ability to overcome therapeutics.13-17 Other experiments demonstrated that mousepox could be modified to have a 100% case fatality rate and render a vaccine ineffective.18 In addition to transmissibility and lethality, studies have shown that other disease traits, such as incubation time, environmental survival, and available vectors, could be modified as well.19-21 Although these experiments had scientific merit and were not conducted with malicious intent, their implications are still worrying. This is especially true given that there is also a long historical track record of state-run bioweapon research applying cutting-edge science and technology to design agents not previously seen in nature. The Soviet bioweapons program developed agents with traits such as enhanced virulence, resistance to therapies, greater environmental resilience, increased difficulty to diagnose or treat, and which caused unexpected disease presentations and outcomes.22 Delivery capabilities have also been subject to the cutting edge of technical development, with Canadian, US, and UK bioweapon efforts playing a critical role in developing the discipline of aerobiology.23,24 While there is no evidence of state-run bioweapons programs directly attempting to develop or deploy bioweapons that would pose an existential risk, the logic of deterrence and mutually assured destruction could create such incentives in more unstable political environments or following a breakdown of the Biological Weapons Convention.25 The possibility of a war between great powers could also increase the pressure to use such weapons—during the World Wars, bioweapons were used across multiple continents, with Germany targeting animals in WWI,26 and Japan using plague to cause an epidemic in China during WWII.27

#### **Disease alone causes extinction.**

Ord ‘20 [Toby; reporter for the Guardian; 3-6-2020; "Why we need worst-case thinking to prevent pandemics"; Guardian; https://www.theguardian.com/science/2020/mar/06/worst-case-thinking-prevent-pandemics-coronavirus-existential-risk]

The world is in the early stages of what may be the **most deadly pandemic** of the **past 100 years**. In China, thousands of people have already died; large outbreaks have begun in South Korea, Iran and Italy; and the rest of the world is bracing for impact. We do not yet know whether the final toll will be measured in thousands or hundreds of thousands. For all our advances in medicine, humanity remains much **more vulnerable** to pandemics than we would like to believe. To understand our vulnerability, and to determine what steps must be taken to end it, it is useful to ask about the very worst-case scenarios. Just how bad could a pandemic be? In science fiction, we sometimes encounter the idea of a pandemic so severe that it could cause **the end of civilisation,** or even of **humanity itself.** Such a risk to humanity’s entire future is known as an **existential risk.** We can say with certainty that the novel coronavirus, named Covid-19, does not pose such a risk. **But could the next pandemic?** To find out, and to put the current outbreak into greater context, let us turn to the past. In 1347, death came to Europe. It entered through the Crimean town of Caffa, brought by the besieging Mongol army. Fleeing merchants unwittingly carried it back to Italy. From there, it spread to France, Spain and England. Then up as far as Norway and across the rest of Europe – all the way to Moscow. Within six years, the Black Death had taken the continent. Tens of millions fell gravely ill, their bodies succumbing to the disease in different ways. Some bore swollen buboes on their necks, armpits and thighs; some had their flesh turn black from haemorrhaging beneath the skin; some coughed blood from the necrotic inflammation of their throats and lungs. All forms involved fever, exhaustion and an intolerable stench from the material that exuded from the body. There were so many dead that mass graves needed to be dug and, even then, cemeteries ran out of room for the bodies. The Black Death **devastated Europe.** In those six years, between a **quarter and half of all Europeans were killed**. The Middle East was ravaged, too, with the plague killing about **one in three Egyptians and Syrians**. And it may have also laid waste to parts of central Asia, India and China. Due to the scant records of the 14th century, we will never know the true toll, but our best estimates are that somewhere between **5% and 14% of all the world’s people were killed**, in what may have been the **greatest catastrophe** humanity has seen. The Black Death was not the only biological disaster to scar human history. It was not even the only great bubonic plague. In AD541 the plague of Justinian struck the Byzantine empire. Over three years, it **took the lives** of roughly **3% of the world’s people.** When Europeans reached the Americas in 1492, the two populations exposed each other to completely novel diseases. Over thousands of years, each population had built up resistance to their own set of diseases, but were extremely susceptible to the others. The American peoples got by far the worse end of the exchange, through diseases such as measles, influenza and, especially, smallpox. During the next 100 years, a combination of invasion and disease took an immense toll – one whose scale may never be known, due to great uncertainty about the size of the pre-existing population. We can’t rule out the loss of more than 90% of the population of the Americas during that century, though the number could also be much lower. And it is very difficult to tease out how much of this should be attributed to war and occupation, rather than disease. At a rough estimate, as many as 10% of the world’s people may have been killed. Centuries later, the world had become so interconnected that a truly global pandemic was possible. Towards the end of the first world war, a devastating strain of influenza, known as the 1918 flu or Spanish flu, spread to six continents, and even remote Pacific islands. About a third of the world’s population were infected and between 3% and 6% were killed. This death toll outstripped that of the first world war. Yet even events like these fall short of being a threat to humanity’s long-term potential. In the great bubonic plagues we saw civilisation in the affected areas falter, but recover. The regional 25%-50% death rate was not enough to precipitate a continent-wide collapse. It changed the relative fortunes of empires, and may have substantially altered the course of history, but if anything, it gives us reason to believe that human civilisation is likely to make it through future events with similar death rates, even if they were global in scale. The Spanish flu pandemic was remarkable in having very little apparent effect on the world’s development, despite its global reach. It looks as if it was lost in the wake of the first world war, which, despite a smaller death toll, seems to have had a much larger effect on the course of history. The full history of humanity covers at least 200,000 years. While we have scarce records for most of these 2,000 centuries, there is a key lesson we can draw from the sheer length of our past. The chance of human extinction from natural catastrophes of any kind must have been very low for most of this time – or we would not have made it so far. But could these risks have changed? Might the past provide false comfort? Our population now is a **thousand times greater** than it was for most of human history, so there are vastly **more opportunities** for new **human diseases to originate.** And our farming practices have created **vast numbers of animals** living in **unhealthy conditions** within **close proximity to humans**. This increases the risk, as many major diseases originate in animals before crossing over to humans. Examples include HIV (chimpanzees), Ebola (bats), Sars (probably civets or bats) and influenza (usually pigs or birds). We do not yet know where Covid-19 came from, though it is very similar to coronaviruses found in bats and pangolins. Evidence suggests that diseases are crossing over into human populations from animals at an increasing rate. **Modern civilisation** may also make it much easier for a **pandemic to spread**. The higher density of people living together in cities **increases the number of people** each of us may infect. Rapid **long-distance transport** greatly increases the **distance pathogens can spread**, reducing the **degrees of separation** between any two people. Moreover, we are no longer divided into isolated populations as we were for most of the past 10,000 years. Together these effects suggest that we might expect **more new pandemics**, for them to **spread more quickly**, and to reach a **higher percentage** of the **world’s people**. But we have also changed the world in ways that offer protection. We have a healthier population; improved sanitation and hygiene; preventative and curative medicine; and a scientific understanding of disease. Perhaps most importantly, we have public health bodies to facilitate global communication and coordination in the face of new outbreaks. We have seen the benefits of this protection through the dramatic decline of endemic infectious disease over the past century (though we can’t be sure pandemics will obey the same trend). Finally, we have spread to a range of locations and environments unprecedented for any mammalian species. This offers special protection from extinction events, because it requires the pathogen to be able to flourish in a vast range of environments and to reach exceptionally isolated populations such as uncontacted tribes, Antarctic researchers and nuclear submarine crews. It is hard to know whether these combined effects have increased or decreased the existential risk from pandemics. This uncertainty is ultimately bad news: we were previously sitting on a powerful argument that the **risk was tiny**; now **we are not.** We have seen the indirect ways that our actions aid and abet the origination and spread of pandemics. But what about cases where we have a much more direct hand in the process – where we deliberately use, improve or create the pathogens? Our understanding and control of pathogens is very recent. Just 200 years ago, we didn’t even understand the basic cause of pandemics – a leading theory in the west claimed that disease was produced by a kind of gas. In just two centuries, we discovered it was caused by a diverse variety of microscopic agents and we worked out how to grow them in the lab, to breed them for different traits, to sequence their genomes, to implant new genes and to create entire functional viruses from their written code. This progress is continuing at a rapid pace. The past 10 years have seen major qualitative breakthroughs, such as the use of the gene editing tool Crispr to efficiently insert new genetic sequences into a genome, and the use of gene drives to efficiently replace populations of natural organisms in the wild with genetically modified versions. This progress in biotechnology seems unlikely to fizzle out anytime soon: there are no insurmountable challenges looming; no fundamental laws blocking further developments. But it would be optimistic to assume that this uncharted new terrain holds only familiar dangers. To start with, let’s set aside the risks from malicious intent, and consider only the risks that can arise from well-intentioned research. Most **scientific and medical research** poses a negligible risk of harms at the scale we are considering. But there is a small fraction that uses **live pathogens** of kinds that are known to **threaten global harm**. These include the agents that cause the **Spanish flu, smallpox, Sars and H5N1 or avian flu**. And a small part of this research involves **making strains** of these pathogens that pose **even more danger** than the natural types, increasing their **transmissibility**, lethality or resistance to vaccination or treatment. In 2012, a Dutch virologist, Ron Fouchier, published details of an experiment on the recent H5N1 strain of bird flu. This strain was extremely deadly, killing an estimated **60% of humans it infected** – far beyond even the Spanish flu. Yet its inability to pass from human to human had so far **prevented a pandemic**. Fouchier wanted to find out whether (and how) H5N1 could naturally develop this ability. He passed the disease through a series of 10 ferrets, which are commonly used as a model for how influenza affects humans. By the time it passed to the final ferret, his strain of H5N1 had become directly transmissible between mammals. The work caused fierce controversy. Much of this was focused on the information contained in his work. The US National Science Advisory Board for Biosecurity ruled that his paper had to be stripped of some of its technical details before publication, to limit the ability of bad actors to cause a pandemic. And the Dutch government claimed that the research broke EU law on exporting information useful for bioweapons. But it is not the possibility of misuse that concerns me here. Fouchier’s research provides a clear example of well-intentioned scientists enhancing the destructive capabilities of pathogens known to threaten global catastrophe. Of course, such experiments are done in secure labs, with stringent safety standards. It is highly unlikely that in any particular case the enhanced pathogens would escape into the wild. But just how unlikely? Unfortunately, we don’t have good data, due to a lack of transparency about incident and escape rates. This prevents society from making well-informed decisions balancing the risks and benefits of this research, and it limits the ability of labs to learn from each other’s incidents. Security for highly dangerous pathogens has been **deeply flawed**, and remains insufficient. In 2001, Britain was struck by a devastating outbreak of foot-and-mouth disease in livestock. Six million animals were killed in an attempt to halt its spread, and the economic damages totalled £8bn. Then, in 2007, there was another outbreak, which was traced to a lab working on the disease. Foot-and-mouth was considered a **highest-category pathogen**, and required the highest level of biosecurity. Yet the virus escaped from a **badly maintained pipe**, leaking into the **groundwater at the facility**. After an investigation, the **lab’s licence was renewed** – only for **another leak to occur two weeks later.** In my view, this track record of escapes shows that even the **highest biosafety level** (BSL-4) is **insufficient for working on pathogens** that pose a risk of global pandemics on the scale of the Spanish flu or worse. Thirteen years since the last publicly acknowledged outbreak from a **BSL-4 facility** is not good enough. It doesn’t matter whether this is from insufficient standards, inspections, operations or penalties. What matters is the poor track record in the field, made worse by a lack of transparency and accountability. With current BSL-4 labs, an **escape of a pandemic pathogen** is only a **matter of time.**

#### Simulations, empirics, and surging connectivity prove

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\*figures omitted for readability\*

Several epidemics, such as the Black Death and the Spanish flu, have threatened human life throughout history; however, it is unclear if humans will remain safe from the sudden and fast spread of epidemic diseases. Moreover, the transmission characteristics of epidemics remain undiscovered. In this study, we present the results of an epidemic simulation experiment revealing the relationship between epidemic parameters and pandemic risk. To analyze the time-dependent risk and impact of epidemics, we considered two parameters for infectious diseases: the recovery time from infection and the transmission rate of the disease. Based on the epidemic simulation, we identified two important aspects of human safety with regard to the threat of a pandemic. First, humans should be safe if the fatality rate is below 100%. Second, even when the fatality rate is 100%, humans would be safe if the average degree of human social networks is below a threshold value. Nevertheless, certain diseases can potentially infect all nodes in the human social networks, and these diseases cause a pandemic when the average degree is larger than the threshold value. These results indicated that certain infectious diseases lead to human extinction and can be prevented by minimizing human contact.

1. Introduction

The emergence of a pandemic is one of the various scenarios frequently discussed as a human extinction event, and it is listed as one of the global catastrophic risks in studies regarding the future [1,2,3]. In particular, several pandemics, such as the Black Death [4,5], Spanish flu [6], and those caused by smallpox [7], severe acute respiratory syndrome (SARS) [8], and Ebola [9], have affected a large population throughout history. The risk of pandemics increases with an increase in population mobility between cities, nations, and continents, thereby threatening humankind [10,11,12]. It is essential to analyze the epidemic spread in society to minimize the damage from epidemic disasters; however, extinctive epidemic spreading experiments have limitations in real-world situations, as they predict stochastic effects on the spread without considering the structure of human society. Network-based approaches have been proposed to overcome these limitations and perform epidemic spreading simulations by considering the network structure of numerous real-world connections [13,14,15]. These methods use various models of epidemic spreading, such as the susceptible–infectious–susceptible (SIS) [16,17,18], susceptible–infectious–recovered (SIR) [19,20,21], and Watts threshold models [22]. While these methods are mathematically convenient, they are epidemiologically unrealistic for various infections because they require exponentially distributed incubation and infectious periods [23,24,25]. Moreover, previous epidemic studies did not perform quantitative assessment of the pandemic risk depending on the network connectivity in individuals and fatality rate of various diseases [26].

In the present study, we applied an SIR epidemic model to a scale-free network with Monte Carlo simulation to identify the quantitative relationship between infectious diseases and human existence. Our fundamental hypothesis states that when the epidemic spreads to all nodes of the network and the fatality rate is 100%, it can increase the pandemic risk. To address this, we initially constructed a scale-free network to simulate a society. Moreover, for the epidemic spreading simulation, an SIR model was applied to the network to describe the immune state of an individual after infection. From the simulation study, we found that the mean degree of a scale-free network was an essential factor in determining whether epidemics threaten humans. This approach provides important insights into epidemic spreading analysis by investigating the relationship between epidemic and scale-free network parameters. Furthermore, it highlights the necessity of determining information flow during an epidemic.

2. Materials and Methods

We designed an epidemic simulation process to identify the relationship between pandemic risk and network parameters. This study was performed in four steps (Figure 1): (i) generating a scale-free network model to reflect real-world conditions; (ii) applying an SIR model to the scale-free network for epidemic spreading simulations; (iii) adapting the Monte Carlo method to reflect the stochastic process in the node status of the SIR model; and (iv) iteratively performing simulation for every parameter set and analyzing the results. We have provided the source code and sample results of epidemic simulation in Supplementary Materials.

Figure 1. Overview of epidemic simulation process based on the Monte Carlo method. (A) We generated scale-free networks for a fixed population (N = 1,000,000) and various node degrees (k = 2, 5, 7, and 10). (B) Epidemic spreading was simulated by applying a susceptible–infectious–recovered (SIR) model to the scale-free network. We set the epidemic parameters, β and γd. β represents the spreading rate of epidemics, and γd is the reciprocal of γ and reflects the time interval between infection and recovery. Randomly, 0.05% of nodes were initially infected. (C) We adapted the Monte Carlo method to determine the status of the transition from the infection node to immunization node. Repeated simulations were performed until a steady state was achieved. (D) For every parameter set, 10,000 simulations were performed.

2.1. Network Generation Based on a Scale-Free Model

We constructed a network model for the epidemic spreading simulation (Figure 1). The nodes and edges of the network represent people in the society and their physical contacts, respectively. We used a scale-free network model, which follows the preferential attachment property observed in numerous real-world networks, such as social networks, physical systems, and economic networks [27,28,29]. In the scale-free network, when a node is added to the network, its likelihood of connecting to existing nodes increases with an increase in the node’s degree. Hub nodes, which lead to fast and vast spreading of epidemics, exist. Two characteristic parameters, including N and k, affect the form of scale-free networks. The parameter N denotes all nodes in the network. In the real world, N indicates the whole population size. The parameter k is the average degree of the network, which determines the degree of the newly attached node for each step during network generation. Following the characteristics of the network model, we generated scale-free networks representing human contacts for epidemic spread. The scale-free network was generated by the Barabasi–Albert graph distribution, in which the network is constructed from a cycle graph with three vertices, followed by the addition of k edges at each construction step [30]. The k edges are randomly attached to the vertex based on the degree distribution of the vertex. After network generation, we investigated the degree distribution properties of the network (Figure 2). The results indicate that the degree distributions have similar tendency for networks with varying number of nodes and edges. This study constructed scale-free networks with the largest number of nodes considering computational complexity (N = 1,000,000).

Figure 2. Degree distribution of the scale-free network. We analyzed the degree distribution of the network based on the number of nodes (N) and mean degree (k).

2.2. Epidemic Spreading Based on the SIR Model

For the epidemic spreading simulations, we applied an SIR model to the generated scale-free network. The classical SIR model can be expressed by the following nonlinear differential equations [21]:

where S, I, and R represent susceptible, infected, and recovered compartments, respectively, in the whole population. S represents people who have not been infected yet but can be infected in future. I represents infected people who can spread the epidemic to susceptible people through physical contact. R denotes people who have recovered or died from the epidemic and who no longer participate in the epidemic spreading process. The sum of the S, I, and R values represents the whole population size N. Epidemics have two parameters in the SIR model, transmission rate (β) and recovery rate (γ), which arise from the basic reproduction number R0 (Figure 1B). The basic reproduction number is the number of infections caused by one infective node [31,32,33]. If the R0 is more than 1, the infection can spread in a population, whereas if R0 is less than 1, the infection cannot spread. We express the basic reproduction number as R0 = β/γ, where β represents the spreading rate of epidemics between infective nodes and adjacent susceptible nodes and γ represents the probability of recovery from infection [34]. We mainly used γd, which is the reciprocal of γ and reflects the time interval between infection and recovery.

2.3. Investigation of Epidemic Status Based on the Monte Carlo Method

The epidemic simulation was performed for a time series event by constructing epidemic status matrix (z) to represent the status of the nth node at time step t. For each node, the value of epidemic status matrix at time step t can be 0, 1, or 2, indicating that a node is susceptible, infective, or recovered, respectively. We initially (t = 0) set every value of epidemic status matrix to 0 because all nodes are susceptible before the epidemic spreads. At the initial infection stage, randomly selected 0.05% of nodes were infected. At every time period, we performed immunization and observed the infection stages (Figure 3).

At the immunization stage, we identified infective nodes and determined whether these nodes would be recovered in the next time step. To calculate the transition probability of infected and recovered phenomena, the Monte Carlo method was applied [35,36]. When infection and recovery parameters are provided, it is possible to investigate whether a node transitions from an epidemic state to another state. To accomplish this, we compared the method revealing the change in each population in every compartment over time (Figure 4).

The final steady state of the epidemic spreading simulation model indicates the total number of casualties of the epidemic who either are dead or have recovered from the disease. Infective nodes at time t (zn [t] = 1) are transformed to recovered nodes at time t + 1 (zn [t + 1] = 2) when 1/γd is larger than a random real number between 0 and 1. We determined whether the neighbor nodes of the infection node would be infected by identifying susceptible nodes adjacent to the infective nodes at time t (zn [t] = 0, with the adjacent infective node) (Figure 5). When β is larger than a random real number between 0 and 1, a susceptible node becomes an infective node at time t + 1 (zn [t + 1] = 1); this scenario represents epidemic spread. For each time step, we recorded the number of susceptible, infective, and recovered nodes during epidemic spread.

2.4. Simulation Parameters

We carried out simulation trials for various mean degrees of networks (k = 2, 5, 7, and 10). Each network considered the following epidemic parameters: β ranges from 0.05 to 0.95 and γd ranges from 1 to 10. The Monte Carlo model was repeatedly simulated to observe saturation of the recovery process. Considering that the simulation pipeline contains random processes such as initial infection and Monte Carlo trials, we performed the simulation iteratively until the status of nodes remained unchanged. After simulation, time series data from every simulation were interpolated in the time domain.

The fatality rate determines the ratio of deceased and recovered individuals in the final population [37,38,39]. If the fatality rate is below 100%, the recovered population contains both dead and recovered individuals. Such a situation does not always cause a pandemic. In this simulation, we assumed a 100% fatality rate. To accomplish this, we enumerated the recovered nodes as dead for considering the pandemic risk.

3. Results

Through our method, we obtained epidemic spreading data with various network and epidemic parameter sets. In the present study, we focused on the case where the epidemic infects all nodes and defined this phenomenon as “extinctive spread”. Diseases causing extinctive spread are potential candidates of high pandemic risk. In the real world, extinctive spreading indicates that the disease will infect every person in the society. From the simulation data, we calculated the extinctive spread score by dividing the total number of simulation trials by the number of extinctive spread cases. Thereafter, we identified that the number of extinctive spread cases is mainly influenced by spreading speed, which is determined by β, γd, and k (Figure 6).

The extinctive spread region (brown area in Figure 6) is expanded as the value of mean degree of network (k) is increased, thereby indicating that the area of extinctive spread becomes noticeably wider in a dense network than in a sparse network. Thus, the more contact between people, the higher the risk of epidemics. Moreover, high γd and high β cause extinctive spread across a large region, indicating that the high spreading rate and short time interval between infection and recovery are risk factors of epidemic diseases. In contrast, the infective nodes recover before they transmit the disease to their neighbors in low β and low γd scenarios, thus disconnecting the network and preventing extinctive spread. This occurs because the infective nodes need more time to transmit the disease in low β and high γd scenarios. Therefore, the disease begins to subside due to a lack of new infective nodes.

Furthermore, we investigated the range of β and γd for existing epidemics of the common cold [40,41] and fatal diseases, namely, cholera [42,43], Marburg [44,45], Ebola (Congo and Uganda) [46,47,48,49], SARS [50], and MERS [51] (Table 1). We selected diseases with relatively well-known epidemic parameters, such as average duration of infection and basic number of reproductions from previous studies. Transmission rates were calculated using the mean duration of infectious periods and basic reproduction numbers of the epidemics. Different studies reveal multiple values of infectious period and transmission rate for some of these diseases; we considered these values separately [40,41,42,43,46,47,48,49]. For example, the infectious period of a common cold is from 3 to 7 days and that of Ebola is 6.5 days. Next, we placed the possible regions of these epidemics as a disease band for various k values (colored lines in Figure 6). When k > 5, fatal diseases have an opportunity to cause a pandemic. Even when k = 5, diseases such as cholera and Ebola (Congo) can be threatening in regions of low γd and high, thus demonstrating that the knowledge of network parameters of the society and the characteristics of epidemic diseases can aid in quantifying the risk of epidemics.

4. Discussion

Many previous studies have made stochastic SIR models to analyze the dynamics or stability of epidemic diseases. They investigated the distribution of susceptible, infected, and removed populations for specific epidemic disease spreading, such as cholera, SARS, Marburg, and MERS, based on mathematical modelling [52,53,54,55]. However, they did not conduct a quantitative assessment of pandemic risk taking into account physical contact between people. To solve this limitation, we performed epidemic spreading simulations by applying an SIR model to scale-free networks with Monte Carlo simulation. In the simulation, we consider various connectivity and disease characteristics on scale-free networks. For each network and epidemic parameter set, the probability of extinctive spread was calculated. The results revealed that certain infectious diseases can lead to extinction. Moreover, even if the disease band extends over the extinctive spread regions, it does not indicate that human extinction results from the disease, as the fatality rate is below 100%; however, in the case of 100% fatality, the disease can cause a human extinction event. The risk of infectious disease is influenced by the network structure. A dense network has a higher risk of spreading infectious disease than a sparse network, as we observed in the extinctive spreading maps. According to our results, when the average degree of human social networks is below the risk threshold, i.e., less than 4 in this study, human society is safe from an extinctive outbreak based on our knowledge regarding the epidemic parameters of the infectious disease. Nevertheless, in other cases, human extinction is possible. For example, if the population is 1,000,000 and there are 4 or more instances of physical contact between people, human extinction events may occur, depending on the fatality rate of the epidemics. Hence, physical contact between people is closely related to an extinction event of infectious diseases. Eventually, from a public health perspective, lowering the average contact level of society is an appropriate way to increase the robustness of strategies against the occurrence of extinction. In the real world, reducing network density can be accomplished by epidemic prevention activity, such as isolation and quarantine treatment. This action prevents epidemic risk to the society, thereby avoiding human extinction.

Additional considerations may improve our analysis. First, large population size and various proportions of initial infective nodes were not considered in the experiments. We have confirmed that the result was consistent when the proportion of initial infective nodes was 0.05% of the total population; however, this can vary depending on the distinct proportion of initial infective nodes in a different population. To achieve robust results, we need to perform additional experiments for various parameters; however, we could not address this issue due to computational complexity. Second, we did not consider numerous known epidemic diseases. We calculated the transmission rates of epidemic diseases using the known infectious periods and reproduction numbers of the epidemics from evidence in the literature. In the present study, we only considered five epidemic diseases, since the information on infectious periods and reproduction numbers of diseases was mostly unavailable for other epidemic diseases. Third, this study only considers the SIR model on scale-free networks in epidemic simulation. Since the dynamics of epidemic diseases can be varied in different models or networks, it is important to experiment in various simulation environments to confirm the robustness of the results. Nevertheless, these limitations can be considered in future experiments or using improved computational methods. With these further improvements, our approach can be used as a computational tool to analyze the risk of epidemic diseases.

5. Conclusions

In this study, we analyzed the risk of epidemic diseases by creating an epidemic simulation on a scale-free network. Based on the simulation results for various epidemic parameters, we confirmed that certain infectious diseases can lead to extinction and can be prevented by minimizing human contact. We believe that identifying potential candidate diseases that may lead to human extinction is crucial in addressing epidemic prevention activities such as quarantine.

#### Small-molecule antibiotics guarantee ABR AND induce microbiome breakdowns through off-target effects. Biologics are key to solve

Cynthia A. Challener 18, PhD, is a contributing editor to BioPharm International, “Fighting Bacterial Resistance with Biologics,” Pharmaceutical Technology, Vol. 42, No. 12, December 2018, pp 36–37

Antibody-based drugs offer new mechanisms of action and greater specificity.

The rise of antibiotic-resistant bacteria is recognized as a significant threat to the future practice of medicine. Continually rising resistance rates have resulted in infections with bacteria resistant to all existing antibiotic treatment options. There is concern that if the current treatment system remains unchanged, the resistance epidemic could push the world into a post-antibiotic era.

Alternatives are therefore needed to replace current small-molecule antibiotics. Given that the development of resistance is a natural form of evolution for bacteria, the challenge is to find new drugs that kill bacteria in a way that dramatically slows down their ability to counteract them. Biologic drug substances-monoclonal antibodies (mAbs) in particular-may be a key component of the solution.

Resistance is multifaceted

Regardless of the antibiotic, resistance will develop, according to MedImmune’s director of microbial sciences Bret Sellman. “Most available antibiotics are related to natural products for which resistance already exists in nature,” he explains. Bacteria also divide rapidly, which increases the likelihood for antibiotic-resistant mutants to evolve.

In addition, over the past four decades there have been few truly novel antibiotics, according to James Levin, director of preclinical development at Cidara Therapeutics. “We have been targeting the same limited subset of essential proteins, and therefore, bacteria have ample opportunity to evolve and become resistant to entire antibiotic classes over time,” he observes.

Sellman argues that development of antibiotic resistance has less to do with the structure or chemistry of antibiotics than it does their method of attacking a pathogen and their widespread use in modern medicine and farming. “By killing bacteria directly, antibiotics select for the outgrowth of resistant mutants. In addition, the misuse of antibiotics to treat viral diseases (e.g., the common cold) unnecessarily exposes patients and their bacteria to antibiotics and fails to treat the actual disease being experienced. This ease of access only increases exposure and subsequently the risk of resistance,” he asserts.

Resistance can arise from chemical modification of the antibiotic by bacterial enzymes or mutations to the antibiotic target, adds Levin. He also notes that bacteria are able to swap genes that impart antibiotic resistance with other bacteria, allowing resistance to spread rapidly.

Adding to these escape mechanism issues, Levin points out that gram-negative bacteria are intrinsically resistant to many antibiotics because they possess an outer membrane that is impermeable to most drugs-and they can mutate to reduce permeability further when under selective pressure.

The problem with broad-spectrum antibiotics

There is an additional problem associated with the use of broad-spectrum antibiotics: they kill not only harmful pathogens, but “good” bacteria that make up the microbiome within humans. Doing so results in the development of resistance in the target pathogen as well as the members of healthy microbiome, which can then transfer resistance to pathogens they encounter, further spreading the problem, according to Sellman.

Damage to the healthy microbiome can have significant consequences as well. “Killing of the healthy microbiome has been linked not only to the development of Clostridium difficile diarrhea but also diabetes, obesity, immune defects, and antibiotic resistance spread through gene transfer,” he says.

Pathogen-specific strategies

While antibiotics will always play an important role in saving and preserving life, the growing antibiotic resistance epidemic and increasing understanding of the adverse effects of broad-spectrum antibiotics on the healthy microbiome necessitate the development of alternatives such as pathogen-specific strategies to prevent or treat bacterial infections, according to Sellman. “We firmly believe that moving away from traditional small molecules is the path forward in anti-infectives research,” Levin agrees.

Most efforts are focused on new drugs based on mAbs because of their specificity. “Such targeted antibacterials should have reduced toxicity, cause less harm to patients’ beneficial microbiomes, and not promote resistance in bacteria not targeted,” Sellman comments.

Antibacterial mAbs also directly neutralize bacterial virulence mechanisms and engage the patient’s immune system, according to Sellman. “By boosting the immune system to kill the pathogen rather than killing the bacteria directly, the emergence of resistance might be reduced,” he explains.

Cidara Therapeutics is developing antimicrobial antibody-drug conjugates (ADCs). “These bispecific molecules capitalize on the potency of antibiotics coupled with the beneficial aspects of an effective and robust immune response and can be designed with a prolonged half-life,” says Levin. He believes that any antimicrobial, including small molecules, that binds to a surface or cell-wall component of the bacterium is a viable candidate for conjugation to an antibody fragment crystallizable (Fc) region.

In addition to antibody-based drug candidates, Sellman notes that researchers across industry and academia are also exploring phage lysins and viral phage approaches as alternatives to small-molecule antimicrobials.

Antibacterial biologics require new thinking

Development of mAb antimicrobial drugs does not come without challenges, but those difficulties are not solely in the scientific arena. “In order to realize the promise of biologics in infectious disease, we need to evolve the way we plan to manufacture and diagnose for these medicines,” Sellman states. Because antibacterial mAbs would likely be most effective in the earlier stages of infections, a move to integrate mAbs into the mainstream infectious disease protocol would require a commitment to more rapid diagnostic methods.

In addition, he notes that because pathogen-specific mAb treatments must account for bacterial strain diversity and the expression of multiple virulence determinants by the infecting pathogen, mAb combinations may be required for optimal efficacy.

The higher cost of biologic antibiotic drug substances compared to their small-molecule counterparts could also be an issue, according to Levin. His hope is, though, that the significantly longer half-life that should be achievable for biologic antibiotics, including ADCs, will enable less frequent dosing and thus offset the higher cost.

An ADC approach

Cidara Therapeutics set out to develop ADC antibiotics that exert a direct killing effect on the pathogen; engage the immune system, bringing a second mechanism of killing into play; potentiate standard-of-care antibiotics by attacking the bacterial cell wall and allowing them to penetrate the cell more effectively; and have superior (antibody-like) pharmacokinetic and distribution properties.

The company conjugates surface-acting antimicrobials (targeting moieties [TMs]) to Fc regions of human antibodies using non-cleavable linkers. The bispecific Cloudbreak ADCs exert direct killing activity on bacteria while targeting the cell for destruction by the immune system, according to Levin. “We believe that by developing drugs with a dual killing mechanism we will reduce the opportunity for the target pathogen to develop resistance. In addition, since our TMs do not have to reach the inside of the cell to kill the bacterium, we avoid the daunting problem of having to breach the bacterial membrane in gram-negative bacteria,” he says. In addition, because antibodies can remain at effective concentrations in plasma for a month or longer, Cidara believes its ADCs can ultimately be engineered to achieve a similar half-life.

The company recently demonstrated proof of concept with an ADC comprising a peptidic antimicrobial conjugated to a human Fc. “Although not our final drug candidate, this ADC was efficacious in murine Acinetobacter and Pseudomonas pneumonia models. It also demonstrated a much longer half-life than the polypeptide alone,” Levin notes. In-house characterization by Cidara’s immunology team further demonstrated the ability of this conjugate to successfully engage the immune system to enhance bacterial killing. Some of this work was performed in collaboration with Professor Ashraf Ibrahim at UCLA and has yielded important insights into the mechanism of action of ADCs.

The Cloudbreak ADCs are in preclinical development, but Levin expects a clinical candidate to be nominated in 2019. Current efforts are focused on evaluation of lead candidates in preclinical toxicology studies and exploration of Fc modifications to further extend in-vivo half-life. The company received a National Institutes of Health grant in 2018 in conjunction with Professor David Perlin at Rutgers that should accelerate the pace of its ADC program, according to Levin. Cidara is also applying its Cloudbreak technology to the development of antivirals.

Two mAb assets in development

Within MedImmune, the global biologics research and development arm of AstraZeneca, two Phase II mAb assets are in clinical testing. MEDI4893 (suvratoxumab) is under investigation for the prevention of Staphylococcus aureus pneumonia in intensive care unit patients, while MEDI3902 is being developed for the prevention of Pseudomonas aeruginosa pneumonia in intensive care unit patients.

“As we continue to explore this field, we are constantly learning about the critical role of the commensal microbiome in maintaining overall health, and even the role it can play in possibly treating certain diseases. With this understanding comes a commitment to exploring new therapeutic options that avoid damaging these beneficial bacteria. The targeting specificity of biologics offers tremendous promise in making this goal a reality,” Sellman concludes.

#### Case by case *Actavis* analysis is woefully inadequate at combatting pay for delay monopolization efforts in the status quo, only broad overhaul solves

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The strategic behaviors in the Hatch-Waxman arena are troubling from the perspective of the theoretical underpinnings of both patent and antitrust law. The patent concern traces back to the constitutional provision that frames all of patent law. From the activities that should be free to all and reserved to none, the patent system chooses to dedicate to some, for a limited period of time, the exclusive use of an innovation based on the theory that this exclusion will redound to the benefit of society.315 The bargain, however, is not unlimited. When the patent expires, everyone should be free to engage in those activities, returning to a competitive environment. HatchWaxman is intended to ensure the prompt return to a competitive environment at the end of the patent term, as well as to create incentives to weed out weak patent claims that are improperly keeping competitors out of the particular innovative space. Pharmaceutical company behavior that extends the period in which the company can hold off competition runs contrary to the patent bargain.

The behaviors described in this article also raise antitrust concerns, although those concerns are framed at a slightly different angle.316 As a general matter in antitrust doctrine, big is not bad; it is what you do with your size that matters.317 Thus, brand-name companies that have earned a monopoly in the market with their blockbuster drugs are targets of antitrust concern only when they attempt to extend their monopoly improperly by colluding with competitors or inappropriately suppressing competition. As scholarly works by this author and others have noted, agreements not to compete and activities that abuse the regulatory process to block competitors raise antitrust concerns.318 Thus, when pharmaceutical company behavior improperly delays or impedes the entry of generic competition, that behavior runs contrary to the open, competitive market environment for which antitrust law yearns.

The theoretical concerns translate into tangible damage to society as well. With patents, the legal system chooses to tolerate certain societal losses for the innovation effects that may result. When brand-name companies extend their monopoly power beyond the expiration of the patent, however, there are unanticipated deadweight losses to society in the form of higher prices. Whether Congress has chosen the optimal parameters for the patent system is a separate question. Once those parameters are set, behaviors that cause additional deadweight losses for society are contrary to the system’s incentive structure, and the damage to society should not be tolerated. The Hatch-Waxman manipulations also are damaging to society in the form of activities that are wasteful for companies and institutions alike. Hide-and-seek games that the courts, the FDA, the FTC, and the Patent and Trademark Office are forced to play are wasteful to all. The games are particularly burdensome on the court system, with pharmaceutical litigation over generic competition now joining patent troll litigation as a major component of new patent lawsuit filings.319 Sadly, given the amount of money at stake, the behaviors are likely to continue unless the legal system finds a way to change the incentives or to create sufficient disincentives. This is not to suggest that progress has been negligible. The shift from simple pay-fordelay agreements to side deals and then to micro-obstructions reflects the progress that regulatory agencies have begun to achieve in the courts. In addition, although micro-obstructions can create a valuable delay in competition, they are more difficult to achieve and often less lengthy than pay-fordelay.

Nevertheless, although the form of the behavior may have shifted, the behavior remains. And although changes such as the Supreme Court decision in Actavis and various congressional amendments have been important, by the time the changes are implemented, the market has moved beyond. The question is, what should come next.

The following discussion explores new directions for the legal system in its continuing efforts to alleviate the gamesmanship that the Hatch-Waxman system has wrought. The discussion is not intended to provide a blueprint for legislation or a description of specific doctrinal provisions. Rather, it is an attempt to suggest the contours of how new approaches could be structured, and to generate discussion of a shift in approach.

B. Systems, Simplification, Sunshine, and Standards-Based Doctrines

In addition to the approaches that have been undertaken so far, managing the evolution of the Hatch-Waxman games will require a systems approach. One could use an analogy from the medical field itself.320 Under the old approach to cancer treatment, physicians would attack a tumor by trying to reduce its size or deny substances that seemed to be feeding it. Modern medical research has suggested, however, that cancer treatment can be far more effective when using a systems approach. Specifically, tumors seem to operate in a networked or systems fashion. Cutting off one approach may simply lead the tumor to develop work-around approaches, and the new approaches may be even more dangerous and damaging than the original pathway. Thus, attacking the problem by trying to mitigate it when it emerges may be as outdated an approach for the patenting and approval of medicines as it is for treatments in which those medicines will be involved.321

Taking a systems approach may allow us to move away from what one of the authors has called death by tinkering—a problem endemic throughout the patent system.322 In this problematic approach, legal actors address difficult questions by adjusting the doctrines a little here and a little there without developing a comprehensive logic for the full breadth of the legal area. Eventually, the entire doctrinal base threatens to collapse under its own weight.

One can see a classic example of death by tinkering in the Federal Circuit’s failed attempts to create a workable rule for determining what types of inventions should qualify as patentable subject matter. For years, the court clung to its “machine-or-transformation” test, making ever finer distinctions to try to avoid uncomfortable results. In the end, the test required considerable hand waving, and one had to suspend a certain amount of disbelief to overlook the logical discrepancies.323 After a series of three cases gently encouraging the Federal Circuit to develop a workable test, the Supreme Court eventually gave up and supplied its own test.324

A similar phenomenon plagues the various doctrines related to whether the definition of an invention reaches beyond the state of the art at the time of the invention. Doctrines developed for mechanical inventions, in which one generally understands all aspects of the technology, have led to uncomfortable results for biologic inventions, in which many unknown factors may be at play. For example, when an invention is a doorknob, one generally understands the various parts and their operation. There are no unexplained pieces and no hints that the door frame may be integrating with the door in ways no one has dreamed.325 Such is not the case with biotechnology inventions, however, and in that realm, society grants rights in the face of significant unknowns.

Doctrinal rules that fit comfortably with mechanical inventions can lead to uncomfortable results in life science cases. Struggling with the problem, different Federal Circuit panels have created doctrinal rules that contradict each other and point in different theoretical directions.326 The rules reach what seem to be good results in each case, but at the expense of doctrinal coherence and the ability to predict the boundaries of patents going forward. The entire area now threatens to collapse. Doctrines related to defining an invention for purposes of comparing it to later inventions are clashing against doctrines related to defining the invention for purposes of comparing it to earlier inventions. Unless one is happy holding up a piece of fruit and declaring that looking in one direction, it is an apple, and looking in another direction, it is an orange, the doctrines are untenable.327

Therefore, the first step in a systems approach would involve focusing on the extent to which different systems interact in the process. These include not only the patent approval system, but also the patent litigation system,328 FDA approval systems—including the Orange Book, REMS, citizens petitions, and other FDA processes—and antitrust doctrines as they may apply to this arena. Effective progress will require working with all of these systems at the same time, lest adjustments to one area lead to counteraction in another. With thirty years of Hatch-Waxman experience, it is time to consider a comprehensive overhaul of the system for generic approval, one that looks more broadly at the interaction of all of the systems.

The second step is to ruthlessly simplify. For those who value complexity, the Hatch-Waxman system is a garden of delights. Complexity breeds opportunity, however, and, in the case of Hatch-Waxman, the Act’s complexity has spawned opportunities for manipulation. An overhaul of the Hatch-Waxman system that resulted in equivalent or even greater complexity would serve little purpose, other than as a full employment act for lawyers. In contrast, a simplified, slimmed-down system would provide fewer opportunities for clever gamesmanship.

From this perspective, the 2009 Biologics Price Competition and Innovation Act (“BPCIA,” also commonly known as the “Biologics Act”) is not encouraging. The legislation was intended to provide a pathway for swift approval of biosimilars, or what could be called generic biologic drugs, in the same way that Hatch-Waxman provided a speedier pathway for ordinary generic drugs. Biologics are complex cell-derived drugs that include antibodies that fight autoimmune diseases and proteins that boost white blood cell counts during chemotherapy. The Biologics Act, however, is even more complex and convoluted than Hatch-Waxman and seems designed on entirely the wrong template.329 It took until September 2015—six years after the act’s passage—for the first biosimilar to reach the market.330 Simplification is not the instinct of lawyers in general nor of patent lawyers in particular. Lawyers are trained to see the nuances in any circumstance and may wish to keep options open for whatever their clients need. Moreover, the patent bar has never been accused of an attraction to exorbitant simplicity. Overcoming these instincts, which are deeply imbedded in the habits of patent stakeholders, will be an essential component of designing a more effective system.

The third step is to let the sun shine in. Both markets and regulators work best when information is fully available—information that invites competition where competition is needed and exposes behavior that regulators can challenge. Moreover, in a world of instant communication, information plays a powerful role in disciplining behavior. Information in pharmaceutical deals and pricing is increasingly segmented, however, and hidden from key players in the industry—whether those players are competitors, regulators, or consumers.

In particular, pharmaceutical pricing is not necessarily drug-specific anymore. Rather, pharmaceutical benefit managers, known as “PBMs,” negotiate the prices for the vast majority of commercially insured drug purchases.331 In other words, PBMs are third-party intermediaries that negotiate drug prices between payers and others. This frequently results in bundled drug pricing, tucked into which may be pricing that reaps supracompetitive rewards or blocks generic competition. For example, a drug company could offer attractive discounts on one drug in exchange for pricing or listing practices that block competition where prices are elevated or competition would be a greater threat.

None of this information is available, either to the market or to regulators. The pharmaceutical ecosystem would benefit tremendously from sunshine rules that require disclosure of PBM pricing deals and rebates. This is not to suggest regulation of pricing, but rather to provide the information that markets and regulators need for efficient functioning.

A fourth step would be to move away from the Supreme Court’s rule of reason analysis for pharmaceutical deals that involve generics. Despite the opening that the Supreme Court created in Actavis, the lower courts largely have been unable or unwilling to walk through it. The burden remains too great for anyone to bear. Rather, with deals involving generic entry, Congress should place the burden on those making the deals to show that they are proper.332 The taint of anticompetitive behavior is too strong throughout these arrangements, and the extent to which these deals undermine HatchWaxman’s intent to introduce generics early and often is too great. One who creates complexity, and the resultant capacity to hide behind that complexity, should have the burden to demonstrate that the effects are justifiable. The most important step, however, is to make more liberal use of standards-based legal doctrines. The Hatch-Waxman system and its various amendments have tended to focus on precise and particularized legal rules. Brand-name drug companies are forbidden from receiving more than one thirty-month stay; the FDA must take final action on a citizen petition in 150 days.

Some fixes have leaned toward the standards approach. For example, the FDA’s ability to deny a citizen petition at any time if it believes a petition was “submitted with the primary purpose of delaying the approval of an application” is an excellent standards-based approach. The amendment granting that power, however, goes on to require that the “petition does not on its face raise valid scientific or regulatory issues,”333 a provision that moves back toward the realm of rule-based approaches. A classic standards-based approach can be found in the tax code’s step transaction doctrine. The doctrine allows tax authorities to collapse all the steps of a transaction together if the authority deems that they are part of an overall plan by the taxpayer.334 The doctrine is aimed at ensuring that taxpayers may not avoid legal restrictions by taking individual steps or a circuitous route.335 A more liberal use of this type of standards-based approach could give courts and regulators the latitude to shut down strategic behavior, as opposed to playing cat and mouse across the regulatory provisions.

#### Rejection of reform fails – the plan’s incremental step towards affordable access to drugs is crucial for broader revolution. Alternatives doom the working class to die at the hands of disease while the ruling classes survive in swanky hospitals

Williams, 13

(Steve, Fellow @the Rosa Luxemburg Stiftung, co-founder and executive director of People Organized to Win Employment Rights, a San Francisco community-based organization of low-income and working class people dedicated to transformative organizing, “DEMAND EVERYTHING: Lessons of the Transformative Organizing Model”, Rosa Luxembourg Siftung, March 2013, <https://community-wealth.org/content/demand-everything-lessons-transformative-organizing-model)\\JM>

3. Revolutionary Edge of Reform In San Francisco, the unemployment rate among African Americans and Latinos is roughly 25%—more than double the national average. The incarceration rate is skyrocketing, and the housing crisis has stolen more than 40% of the African American community’s pre-2008 wealth. Funding for public education, public transit, and public heath systems—which overwhelmingly serve African American, Latino, Asian American, and Pacific Islander communities—has been slashed dramatically over the past ten years. Meanwhile, corporations like Twitter, GenenTech, and large developers receive tens of millions of dollars in public subsidies. San Francisco is in no way unique in this respect. Communities all over the globe are experiencing similar levels of cutbacks and crackdowns while the one percent are living the gated lives of robber barons. In this context, there’s no shortage of meaningful campaigns that an organization might take up. Certainly, resistance is critical. It is important to fight back against bad policies and practices; in an era of never-ending neoliberal assault, any and all resistance is noble. While resistance is necessary, it is not sufficient if we aim to achieve true liberation and the elimination of overlapping systems of exploitation and oppression. Our resistance must move us towards achieving our larger objectives, and some campaigns are simply more strategic to helping us reach our goals than others. The task of the transformative organization is to seek out those campaigns and activities that have the greatest potential to improve the lives of the constituency and of the working class and also to unleash new opportunities to engage and win future fights that move us towards our long-term vision. The transformative organization must not fall into the trap of reformism, but at the same time it must not cling to extreme demands that offer no opportunity for social struggle. The question is how to find the revolutionary edge of reform fights. In attempting to balance these concerns, transformative organizing is guided by the ideas of hegemony and counter-hegemony developed by the Italian Marxist Antonio Gramsci. The ruling class, Gramsci observed, has not only the coercive power of the state apparatus but is also able to exert moral and intellectual leadership. This moral and intellectual leadership allows the ruling class to win the consent of dominated classes to their continued domination by convincing those classes that the interests of the ruling class are the interests of all. Gramsci poses that the task for revolutionaries in these contexts is not vainly calling for the most radical demands; rather, he advocates political struggle in which the popular and exploited classes struggle for hegemony. Those classes do that by engaging in campaigns and advancing demands that bring various sectors of society together in fights which begin to shift the terrain of struggle, thereby making struggles for more radical demands possible. This orientation, of course, requires clarity around vision, assessment of forces, and strategy. The process of identifying new campaigns for POWER always begins by surveying members and constituents. That information is combined with a revised assessment of the organization’s vision. All this is then placed in the particular context of San Francisco’s economic, social, and political conditions. Using the power analysis tools developed by Anthony Thigpen, POWER attempts to assess which constituencies and organizations might be aligned with our objectives and which we might be able to win over. This information begins to give shape to the organization’s campaign work. To assist us in finding the revolutionary edge of reform struggles, POWER members and staff assess the degree to which a campaign provides opportunities to: ⇒ Improve the living and working conditions for POWER’s membership and constituency and for the broader working class. ⇒ Establish building blocks of the organization’s long-term vision. ⇒ Build the power of and deepen the solidarity among various sectors of the working class, of low-income people, and of people of color. ⇒ Undermine the power of the ruling class and its institutions. ⇒ Shift public discourse to make larger victories possible by undermining the logic oppression (i.e., capitalism, imperialism, white supremacy, patriarchy, etc.). ⇒ Develop the leadership of the organization’s members and staff. ⇒ Expand and deepen strategic and tactical alliances with key forces. ⇒ Grow the membership and strengthen the organization. Perhaps the greatest danger to the transformative organization attempting to find the revolutionary edge of reform fights is dressing a reformist fight in revolutionary rhetoric. These criteria, along with regular reflection and evaluation of the organization’s work, help our assessment be as sober and grounded as possible. While the criteria are not a mathematical formula, they do provide a set of parameters for the transformative organization to evaluate potential campaign work. A campaign may not score well on all the criteria, but we can use these factors to evaluate which campaigns offer the most potential. They also help determine how the organization shapes the campaign strategy. Transformative organizing, at its best, seeks the revolutionary potential of campaign struggles and then wages those campaigns with tenacity and finesse.

#### Pay-for-delay guarantees inequality – the burden is specifically on lower-income groups

Feldman, 5/12

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The skyrocketing price of prescription medication continues to plague the pharmaceutical industry. For example, an analysis of one million Medicare patients between 2010 and 2017 found that the average dosage-unit price of brand-name drugs increased by 313 percent even after accounting for rebates.2 Similarly, one in four Americans have difficulty affording their medications, and three in ten say costs have prohibited them from taking their medications as prescribed.3 With rising out-of-pocket costs and patients dangerously rationing medication, these prices are causing real pain for American patients. Diabetic patients, for example, paid nearly $6000 a year out of pocket for insulin in 2016, and patients with arthritis saw the price of Humira rise to $1552 a month in 2019.4 As difficult as the burdens are for any patient, the burden of paying high prices lands particularly hard on lower-income groups, threatening access to life-saving treatments and creating further gaps in equity across society. Since the passage of legislation in the early 1980s, the nation has pinned its hopes on the disciplining effects of generic drugs. Generics are expected to enter the market rapidly when a drug’s patent protection expires, driving prices down to competitive levels.5 Something, however, is seriously amiss. Although generics continue to enter the market in record numbers, drug prices, out-of-of pocket costs, and real spending on drugs continue to soar unabated. The pharmaceutical industry is a complex and convoluted market, with significant distortions and inefficiencies.6 Among these problems, however, one cannot expect generic competitors to create a disciplining effect on prices, if brand companies are able to collude with their generic competitors. In a landmark decision nearly a decade ago, the Supreme Court opened the door for antitrust suits against brand and generic pharmaceutical companies who engage in collusive settlements to delay the time for the generic to come to market. With these “pay-for-delay” agreements, brand-name companies offer prospective generic competitors cash in exchange for the generic’s promise not to enter the market until an agreed-upon date. Laying the groundwork for the lawsuit that would eventually lead to the Actavis decision, the Federal Trade Commission (FTC) published a study estimating that pay-for-delay agreements cost American consumers $3.5 billion annually, a figure that has been cited repeatedly by scholars and policy-makers alike.7 Similar concerns led Congress, in 2003, to require that brand and generic manufacturers file settlement agreements concerning the manufacture, marketing, or sale of generic drugs with the FTC and tasked the FTC with publishing an annual report on the state of pay-for-delay. 8 As this article will demonstrate, the $3.5 billion figure vastly understates the landscape.

#### Competing rights claims collapse- only ethical option is to minimize unnecessary deaths

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What turn-of-the-millennium science is telling us is that human moral judgment is not a pristine rational enterprise, that our moral judgments are driven by a hodgepodge of emotional dispositions, which themselves were shaped by a hodgepodge of evolutionary forces, both biological and cultural. Because of this, it is exceedingly unlikely that there is any rationally coherent normative moral theory that can accommodate our moral intuitions. Moreover, anyone who claims to have such a theory, or even part of one, almost certainly doesn't. Instead, what that person probably has is a moral rationalization. It seems then, that we have somehow crossed the infamous "is"-"ought" divide. How did this happen? Didn't Hume (Hume, 1978) and Moore (Moore, 1966) warn us against trying to derive an "ought" from and "is?" How did we go from descriptive scientific theories concerning moral psychology to skepticism about a whole class of normative moral theories? The answer is that we did not, as Hume and Moore anticipated, attempt to derive an "ought" from and "is." That is, our method has been inductive rather than deductive. We have inferred on the basis of the available evidence that the phenomenon of rationalist deontological philosophy is best explained as a rationalization of evolved emotional intuition (Harman, 1977). Missing the Deontological Point I suspect that rationalist deontologists will remain unmoved by the arguments presented here. Instead, I suspect, they will insist that I have simply misunderstood what Kant and like-minded deontologists are all about. Deontology, they will say, isn't about this intuition or that intuition. It's not defined by its normative differences with consequentialism. Rather, deontology is about taking humanity seriously. Above all else, it's about respect for persons. It's about treating others as fellow rational creatures rather than as mere objects, about acting for reasons rational beings can share. And so on (Korsgaard, 1996a; Korsgaard, 1996b). This is, no doubt, how many deontologists see deontology. But this insider's view, as I've suggested, may be misleading. The problem, more specifically, is that it defines deontology in terms of values that are not distinctively deontological, though they may appear to be from the inside. Consider the following analogy with religion. When one asks a religious person to explain the essence of his religion, one often gets an answer like this: "It's about love, really. It's about looking out for other people, looking beyond oneself. It's about community, being part of something larger than oneself." This sort of answer accurately captures the phenomenology of many people's religion, but it's nevertheless inadequate for distinguishing religion from other things. This is because many, if not most, non-religious people aspire to love deeply, look out for other people, avoid self-absorption, have a sense of a community, and be connected to things larger than themselves. In other words, secular humanists and atheists can assent to most of what many religious people think religion is all about. From a secular humanist's point of view, in contrast, what's distinctive about religion is its commitment to the existence of supernatural entities as well as formal religious institutions and doctrines. And they're right. These things really do distinguish religious from non-religious practices, though they may appear to be secondary to many people operating from within a religious point of view. In the same way, I believe that most of the standard deontological/Kantian self-characterizatons fail to distinguish deontology from other approaches to ethics. (See also Kagan (Kagan, 1997, pp. 70-78.) on the difficulty of defining deontology.) It seems to me that consequentialists, as much as anyone else, have respect for persons, are against treating people as mere objects, wish to act for reasons that rational creatures can share, etc. A consequentialist respects other persons, and refrains from treating them as mere objects, by counting every person's well-being in the decision-making process. Likewise, a consequentialist attempts to act according to reasons that rational creatures can share by acting according to principles that give equal weight to everyone's interests, i.e. that are impartial. This is not to say that consequentialists and deontologists don't differ. They do. It's just that the real differences may not be what deontologists often take them to be. What, then, distinguishes deontology from other kinds of moral thought? A good strategy for answering this question is to start with concrete disagreements between deontologists and others (such as consequentialists) and then work backward in search of deeper principles. This is what I've attempted to do with the trolley and footbridge cases, and other instances in which deontologists and consequentialists disagree. If you ask a deontologically-minded person why it's wrong to push someone in front of speeding trolley in order to save five others, you will get characteristically deontological answers. Some will be tautological: "Because it's murder!" Others will be more sophisticated: "The ends don't justify the means." "You have to respect people's rights." But, as we know, these answers don't really explain anything, because if you give the same people (on different occasions) the trolley case or the loop case (See above), they'll make the opposite judgment, even though their initial explanation concerning the footbridge case applies equally well to one or both of these cases. Talk about rights, respect for persons, and reasons we can share are natural attempts to explain, in "cognitive" terms, what we feel when we find ourselves having emotionally driven intuitions that are odds with the cold calculus of consequentialism. Although these explanations are inevitably incomplete, there seems to be "something deeply right" about them because they give voice to powerful moral emotions. But, as with many religious people's accounts of what's essential to religion, they don't really explain what's distinctive about the philosophy in question.

#### Extinction outweighs – any risk is a reason to err aff.

Seth D. Baum and Anthony M. Barrett 18. Global Catastrophic Risk Institute. 2018. “Global Catastrophes: The Most Extreme Risks.” Risk in Extreme Environments: Preparing, Avoiding, Mitigating, and Managing, edited by Vicki Bier, Routledge, pp. 174–184.

\*GCR = global catastrophic risk

2. What Is GCR And Why Is It Important? Taken literally, a global catastrophe can be any event that is in some way catastrophic across the globe. This suggests a rather low threshold for what counts as a global catastrophe. An event causing just one death on each continent (say, from a jet-setting assassin) could rate as a global catastrophe, because surely these deaths would be catastrophic for the deceased and their loved ones. However, in common usage, a global catastrophe would be catastrophic for a significant portion of the globe. Minimum thresholds have variously been set around ten thousand to ten million deaths or $10 billion to $10 trillion in damages (Bostrom and Ćirković 2008), or death of one quarter of the human population (Atkinson 1999; Hempsell 2004). Others have emphasized catastrophes that cause long-term declines in the trajectory of human civilization (Beckstead 2013), that human civilization does not recover from (Maher and Baum 2013), that drastically reduce humanity’s potential for future achievements (Bostrom 2002, using the term “existential risk”), or that result in human extinction (Matheny 2007; Posner 2004). A common theme across all these treatments of GCR is that some catastrophes are vastly more important than others. Carl Sagan was perhaps the first to recognize this, in his commentary on nuclear winter (Sagan 1983). Without nuclear winter, a global nuclear war might kill several hundred million people. This is obviously a major catastrophe, but humanity would presumably carry on. However, with nuclear winter, per Sagan, humanity could go extinct. The loss would be not just an additional four billion or so deaths, but the loss of all future generations. To paraphrase Sagan, the loss would be billions and billions of lives, or even more. Sagan estimated 500 trillion lives, assuming humanity would continue for ten million more years, which he cited as typical for a successful species. Sagan’s 500 trillion number may even be an underestimate. The analysis here takes an adventurous turn, hinging on the evolution of the human species and the long-term fate of the universe. On these long time scales, the descendants of contemporary humans may no longer be recognizably “human”. The issue then is whether the descendants are still worth caring about, whatever they are. If they are, then it begs the question of how many of them there will be. Barring major global catastrophe, Earth will remain habitable for about one billion more years 2 until the Sun gets too warm and large. The rest of the Solar System, Milky Way galaxy, universe, and (if it exists) the multiverse will remain habitable for a lot longer than that (Adams and Laughlin 1997), should our descendants gain the capacity to migrate there. An open question in astronomy is whether it is possible for the descendants of humanity to continue living for an infinite length of time or instead merely an astronomically large but finite length of time (see e.g. Ćirković 2002; Kaku 2005). Either way, the stakes with global catastrophes could be much larger than the loss of 500 trillion lives. Debates about the infinite vs. the merely astronomical are of theoretical interest (Ng 1991; Bossert et al. 2007), but they have limited practical significance. This can be seen when evaluating GCRs from a standard risk-equals-probability-times-magnitude framework. Using Sagan’s 500 trillion lives estimate, it follows that reducing the probability of global catastrophe by a mere one-in-500-trillion chance is of the same significance as saving one human life. Phrased differently, society should try 500 trillion times harder to prevent a global catastrophe than it should to save a person’s life. Or, preventing one million deaths is equivalent to a one-in500-million reduction in the probability of global catastrophe. This suggests society should make extremely large investment in GCR reduction, at the expense of virtually all other objectives. Judge and legal scholar Richard Posner made a similar point in monetary terms (Posner 2004). Posner used $50,000 as the value of a statistical human life (VSL) and 12 billion humans as the total loss of life (double the 2004 world population); he describes both figures as significant underestimates. Multiplying them gives $600 trillion as an underestimate of the value of preventing global catastrophe. For comparison, the United States government typically uses a VSL of around one to ten million dollars (Robinson 2007). Multiplying a $10 million VSL with 500 trillion lives gives $5x1021 as the value of preventing global catastrophe. But even using “just" $600 trillion, society should be willing to spend at least that much to prevent a global catastrophe, which converts to being willing to spend at least $1 million for a one-in-500-million reduction in the probability of global catastrophe. Thus while reasonable disagreement exists on how large of a VSL to use and how much to count future generations, even low-end positions suggest vast resource allocations should be redirected to reducing GCR. This conclusion is only strengthened when considering the astronomical size of the stakes, but the same point holds either way. The bottom line is that, as long as something along the lines of the standard riskequals-probability-times-magnitude framework is being used, then even tiny GCR reductions merit significant effort. This point holds especially strongly for risks of catastrophes that would cause permanent harm to global human civilization. The discussion thus far has assumed that all human lives are valued equally. This assumption is not universally held. People often value some people more than others, favoring themselves, their family and friends, their compatriots, their generation, or others whom they identify with. Great debates rage on across moral philosophy, economics, and other fields about how much people should value others who are distant in space, time, or social relation, as well as the unborn members of future generations. This debate is crucial for all valuations of risk, including GCR. Indeed, if each of us only cares about our immediate selves, then global catastrophes may not be especially important, and we probably have better things to do with our time than worry about them. While everyone has the right to their own views and feelings, we find that the strongest arguments are for the widely held position that all human lives should be valued equally. This position is succinctly stated in the United States Declaration of Independence, updated in the 1848 Declaration of Sentiments: “We hold these truths to be self-evident: that all men and 3 women are created equal”. Philosophers speak of an agent-neutral, objective “view from nowhere” (Nagel 1986) or a “veil of ignorance” (Rawls 1971) in which each person considers what is best for society irrespective of which member of society they happen to be. Such a perspective suggests valuing everyone equally, regardless of who they are or where or when they live. This in turn suggests a very high value for reducing GCR, or a high degree of priority for GCR reduction efforts.