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PHARMACEUTICALS IN THE ENVIRONMENT: AN INNOVATIVE PRESCRIPTION

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INTRODUCTION

Pharmaceuticals in the environment, which has caused ecological damage ranging from the widespread feminization of fish to a significant decline in Asian vulture populations, is now being linked to increasing antimicrobial resistance, "one of the most worrying [human] health threats today."[1] According to Erik Solheim, Chief of the U.N.

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1. *Careless Disposal of Antibiotics Could Produce 'Ferocious Superbugs,' UN Environment Experts Warn*, U.N. NEWS (Dec. 5, 2017), https://news.un.org/en/story/

Environment Programme (UNEP), "The warning here is truly frightening: we could be spurring the development of ferocious superbugs through ignorance and carelessness[.]"[2]

The prevalence of pharmaceuticals in the environment is a story of unintended and unexpected consequences. Pharmaceuticals are broadly recognized as contributing to the wellbeing of society, and until twenty years ago, the environmental impact of the pharmaceutical industry, a small industrial sector with a limited environmental footprint and well-controlled manufacturing processes, was not considered of consequence.[3] But the use of these beneficial products (not their manufacture, packaging, or disposal) has resulted in micro-pollution[4] in waters throughout the world, causing significant concerns about negative impacts to human health and the environment.

This Note will provide a background on the current state of pharmaceuticals in the environment ("PIE"), a global public health issue of growing concern. It will explore how existing United States environmental regulations are, in general, not suited to the challenges of PIE. It will then propose how patents and regulatory exclusivity could help incentivize the innovation required to address this highly complex and consequential environmental issue.

I. BACKGROUND

Pharmaceuticals were first identified in drinking water by researchers in the United Kingdom in 1981.[5] PIE then grabbed the attention of the public in the 1990s when vulture populations in India were decimated from feeding on livestock carcasses containing an anti-inflammatory drug, diclofenac, and more recently through widely

2017/12/638352-careless-disposal-antibiotics-could-produce-ferocious-superbugs-un-environment; *see e.g.*, U.N. ENV'T, FRONTIERS 2018/19 EMERGING ISSUES OF ENVIRONMENTAL CONCERN 70 (2019) (outlining pathways for antibiotic resistance).

2. *Careless Disposal of Antibiotics Could Produce 'Ferocious Superbugs,' UN Environment Experts Warn*, *supra* note 1.

3. David Taylor, *The Pharmaceutical Industry and the Future of Drug Development*, *in* 41 ISSUES IN ENVIRONMENTAL SCIENCE AND TECHNOLOGY 7 (R.E. Hester & R.M. Harrison eds., 2016).

4. Micro-pollution is defined as extremely low-level residue from pharmaceuticals, personal care products and other chemicals found in water. *See* M. AHTING ET AL., BACKGROUND: RECOMMENDATIONS FOR REDUCING MICROPOLLUTANTS IN WATERS 9 (M. Helmecke ed., 2018), https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/180709_uba_pos_mikroverunreinigung_en_bf.pdf.

5. N.J. AYSCOUGH ET AL., REVIEW OF HUMAN PHARMACEUTICALS IN THE ENVIRONMENT, RESEARCH AND DEVELOPMENT TECHNICAL REPORT 34 (2000).

published stories of feminized fish and intersex frogs.[6] This Part describes the prevalence of PIE, why PIE is of concern, and how pharmaceuticals enter the environment.

A. Prevalence

To date, over 600 different pharmaceutical compounds (the therapeutic chemical in pharmaceuticals is called the active pharmaceutical ingredient ("API")) have been found globally in various bodies of water.[7] The first comprehensive United States study of micro-chemical pollutants (APIs as well as other chemicals, including personal care products) was conducted between 1999 and 2000.[8] One hundred thirty-nine streams susceptible to contamination in thirty states were sampled and ninety-five chemical compounds were identified including numerous APIs.[9] More recently, a 2011 study measured the concentration of fifty-six APIs in the effluent of dozens of very large waste water treatment facilities in the United States. The resulting data was used to make preliminary PIE risk assessments,[10] evaluating the possible impact of each chemical on humans and the environment.[11]

The concentration of APIs found in the environment is quite low compared to prescribed doses. Therapeutic pharmaceutical doses are typically in the milligram range while the quantities found in the environment are often in the sub-microgram per liter range—a reduction

6. Damian Carrington, *Drugs Flushed into the Environment Could Be Cause of Wildlife Decline*, GUARDIAN (Oct. 12, 2014), https://www.theguardian.com/environment/2014/oct/13/drugs-flushed-into-the-environment-could-be-cause-of-wildlife-decline.

7. Anette Küster & Nicole Adler, *Pharmaceuticals in the Environment: Scientific Evidence of Risks and Its Regulation*, 369 PHILOSOPHICAL TRANSACTIONS ROYAL SOC'Y B 1, 1 (2014).

8. Dana W. Kolpin et al., *Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance*, 36 ENVTL. SCI. & TECH. 1202, 1202 (2002).

9. *Id.* at 1202, 1204–05 (noting that APIs were found in 80% of the samples).

10. Mitchell S. Kostich et al., *Concentrations of Prioritized Pharmaceuticals in Effluents from 50 Large Wastewater Treatment Plants in the US and Implications for Risk Estimation*, 184 ENVTL. POLLUTION 354, 354 (2014) (finding drugs, including hydrochlorothiazide, atenolol, and valsartan, in over 90% of the treated wastewater tested); *see* Küster & Adler, *supra* note 7 (summarizing recent environmental monitoring in Germany which found 156 pharmaceuticals in surface and groundwaters).

11. Risk assessments often focus on persistence, bioaccumulation, and toxicity. T. DeBlonde & P. Hartemann, *Environmental Impact of Medical Prescriptions: Assessing the Risks and Hazards of Persistence, Bioaccumulation and Toxicity of Pharmaceuticals*, 127 PUB. HEALTH 312, 313 (2013); *see also* J. Klaminder et al., *Long-Term Persistence of an Anxiolytic Drug (Oxazepam) in a Large Freshwater Lake*, 49 ENVTL. SCI. & TECH. 10406, 10406 (2015) (holding that oxazepam, an anti-anxiety medication, has persisted in sediments in a Swedish lake since the 1970s).

of a hundred to a thousand-fold or greater.[12] But APIs are designed to be highly biologically active and will interact with chemical receptors in humans and animals, not only with the intended pharmaceutical target. A wide range of effects to aquatic life has been reported including changes to reproductive systems,[13] growth rates,[14] and feeding patterns.[15] Additional negative effects from combinations of APIs are also very likely and, due to the complexity of the mixtures, not well understood.[16]

B. Pharmaceuticals of Concern

Certain classifications of drugs are of particular interest. Antibiotics are of heightened concern because their improper use and overuse have resulted in antibiotic-resistant microorganisms[17] that cause over 23,000 deaths a year in the United States alone.[18] Antibiotic resistance is also exacerbated by the use of antibiotics in lower than therapeutic doses.[19] A December 2017 United Nations report warned antibiotic waste in the environment is an important factor in the evolution of drug-resistant bacteria.[20] The report noted that most consumed antibiotics, up to 80%, are excreted into the environment along with resistant bacteria.[21] A

12. *See* Mitchel Kostich & Reinhard Länge, *Ecotoxicology, Environmental Risk Assessment and Potential Impact on Human Health*, *in* 41 ISSUES IN ENVIRONMENTAL SCIENCE AND TECHNOLOGY 197 (R.E. Hester & R.M. Harrison eds., 2016).

13. *E.g.*, Christopher G. Daughton & Thomas A. Ternes, *Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?*, 107 ENVTL. HEALTH PERSP. 907, 910 (1999) (studying crayfish).

14. *E.g.*, Francesco Pomati et al., *Effects of Erythromycin, Tetracycline and Ibuprofen on the Growth of Synechocystis Sp. and Lemna Minor*, 67 AQUATIC TOXICOLOGY 387, 387 (2004) (studying cyanobacteria and aquatic plants).

15. *E.g.*, Tomas Brodin et al., *Dilute Concentrations of a Psychiatric Drug Alter Behavior of Fish from Natural Populations*, 339 SCI. MAG. 814, 814–15 (2013); *see also* Alistair B. A. Boxall, *The Environmental Side Effects of Medication*, 5 EMBO REP. 1110, 1114 (2004) (listing reported subtle effects of PIE).

16. *See* Boxall, *supra* note 15, at 1113; Lawrence K. Duffy et al., *Bias, Complexity, and Uncertainty in Ecosystem Risk Assessment: Pharmaceuticals, a New Challenge in Scale and Perspective*, 9 ENVTL. RES. LETTERS 1, 1 (2014).

17. *Antibiotic Resistance*, WORLD HEALTH ORG. (Feb. 5, 2018), https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.

18. *Antibiotic/Antimicrobial Resistance, Biggest Threats and Data*, CTRS. FOR DISEASE CONTROL (Sept. 10, 2018), https://www.cdc.gov/drugresistance/biggest_threats.html.

19. *Combating Antibiotic Resistance*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm092810.htm (last updated Sept. 10, 2018).

20. FRONTIERS 2017: EMERGING ISSUES OF ENVIRONMENTAL CONCERN, UNITED NATIONS ENVTL. PROGRAMME 13 (2017), https://wedocs.unep.org/bitstream/handle/20.500.11822/22255/Frontiers_2017_EN.pdf?sequence=1&isAllowed=y.

21. *Antimicrobial Resistance from Environmental Pollution Among Biggest Emerging Health Threats, Says UN Environment*, U.N. ENV'T (Dec. 5, 2017), https://www.unenvironment.org/news-and-stories/press-release/antimicrobial-resistance-environmental-pollution-among-biggest; *see also* Jim O'Neill, *Antimicrobials in Agriculture and the*

number of technical reports have addressed the impact antibiotics can have on specific microbes in the environment, including in wastewater systems, surface water, and sediments.[22]

Exposure to even very low levels of endocrine disrupters is thought by scientists to have a significant biological impact.[23] The ongoing United States Environmental Protection Agency ("EPA") Endocrine Disrupter Screening Program[24] reports a number of endocrine disrupters have their most extreme effect at very low (and very high) doses.[25] While the complexities of the mechanisms and impacts of endocrine disrupters in the environment remain poorly understood, studies show delayed and multigenerational effects in fish populations from these compounds.[26]

Impacts on plants and animals have also been observed outside of these two drug classes. Some of the more widely reported studies have shown the effects of various psychiatric medications, including increased activity and reduced sociability of fish exposed to low levels of the anxiolytic drug oxazepam[27] and antidepressants including fluoxetine and venlafaxine.[28] In another study, metformin, one of the most widely

Environment: *Reducing Unnecessary Use and Waste*, REV. ON ANTIMICROBIAL RESISTANCE (Dec. 2015), https://amr-review.org/sites/default/files/Antimicrobials%20in %20agriculture %20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf.

22. *E.g.*, Klaus Kümmerer, *Antibiotics in the Aquatic Environment—A Review—Part I*, 75 CHEMOSPHERE 417, 429–31 (2009). Wastewater treatment can become a "selection machine for drug-resistant bacteria." Sonia Shaw, *As Pharmaceutical Use Soars, Drugs Taint Water and Wildlife*, YALE ENV'T 360 (Apr. 15, 2010), https://e360.yale.edu/features/as_pharmaceutical_use_soars_drugs_taint_water_and_wildlife.

23. *Endocrine Disrupters*, NAT'L INST. ENVTL. HEALTH SCI. (May 2010), https://www.niehs.nih.gov/health/materials/endocrine_disruptors_508.pdf.

24. *Three Final EDSP Tier 2 Test Guidelines Are Released*, EPA, https://www.epa.gov/endocrine-disruption (last updated June 24, 2019).

25. *See* Alexis Abboud, *US Endocrine Disruptor Screening Program*, EMBRYO PROJECT ENCYCLOPEDIA (Feb. 2, 2017), https://embryo.asu.edu/pages/us-endocrine-disruptor-screening-program (discussing a U-shaped activity curve for some endocrine disruptors).

26. Joanne L. Parrott et al., *Uncertainties in Biological Responses that Influence Hazard and Risk Approaches to the Regulation of Endocrine Active Substances*, 13 INTEGRATED ENVTL. ASSESSMENT & MGMT. 293, 294–95 (2016). The cost to society of endocrine disruptors in the environment (including many non-pharmaceutical compounds) has been estimated at $165 billion to $256 billion annually in Europe alone. Ernie Hood, *Researchers Tally Substantial Economic Impact of EDC Exposures* 32–33, NAT'L INST. ENVTL. HEALTH SCI.: ENVTL. FACTOR (Apr. 2015), https://factor.niehs.nih.gov/2015/4/science-edceconomics/index.htm.

27. Brodin et al., *supra* note 15.

28. Brian Bienkowski, *Fish on Prozac Prove Anxious, Antisocial, Aggressive*, SCI. AM.: ENVTL. HEALTH NEWS (June 12, 2013), https://www.scientificamerican.com/article/fish-on-prozac-prove-anxious-anti-social-agressive/; *see also* Matt Harvey, *Your Tap Water Is Probably Laced with Antidepressants*, SALON (Mar. 15, 2013), https://www.salon.com/2013/03/14/your_tap_water_is_probably_laced_with_anti_depressants_partner/ (explaining antidepressants are often found in drinking water in urban areas).

prescribed diabetes drugs in the world,[29] acted as an endocrine disrupter (although the drug is not typically considered in that class)[30] causing minnows to develop intersex organs.[31]

C. Pathways to the Environment

Pharmaceuticals can enter the environment through three primary paths (veterinary medicine excluded).[32] A small percentage of the total, estimated at 2%, comes from waste streams generated in the manufacture of the pharmaceutical product.[33] These waste streams, solid and liquid, are typically well controlled and minimized because of the value of the API.[34] Localized high concentrations have been measured, however.[35]

Discarded pharmaceuticals (i.e. drugs that are unused in homes or hospitals), estimated at less than 10% of the total,[36] also enter the environment through solid waste disposal and in wastewater streams.[37]

29. Daniel J. DeNoon, *The 10 Most Prescribed Drugs*, WEBMD (Apr. 20, 2011), http://www.webmd.com/news/20110420/the-10-most-prescribed-drugs.

30. Ronald David MacLaren et al., *Environmental Concentrations of Metformin Exposure Affect Aggressive Behavior in the Siamese Fighting Fish, Betta Splendens*, PLOS ONE (May 15, 2018), https://doi.org/10.1371/journal.pone.0197259.

31. Nicholas J. Niemuth & Rebecca D. Klaper, *Emerging Wastewater Contaminant Metformin Causes Intersex and Reduced Fecundity in Fish*, 135 CHEMOSPHERE 38, 38–39 (2015).

32. However, veterinary medicines, especially antibiotics, are a significant source of PIE. Fabio Kaczala & Shlomo E. Blum, *The Occurrence of Veterinary Pharmaceuticals in the Environment: A Review*, 12 CURRENT ANALYTICAL CHEMISTRY 169, 169 (2016).

33. *See* Daniel J. Caldwell, *Sources of Pharmaceutical Residue in the Environment and Their Control*, *in* 41 ISSUES IN ENVIRONMENTAL SCIENCE AND TECHNOLOGY 99 (R.E. Hester & R.M. Harrison eds., 2016).

34. *Id.*

35. *Factories Dumping Drugs into Sewage*, NBC NEWS (Apr. 19, 2009, 12:18 PM), http://www.nbcnews.com/id/30267705/ns/health-health_care/t/factories-dumping-drugs-sewage/#.XCpdPvZFxPY (reporting high concentrations of pharmaceuticals in water downstream from manufacturing plants in Michigan and India).

36. Caldwell, *supra* note 33, at 100.

37. *See How to Dispose of Medicines Properly*, EPA (Apr. 2011), https://www.epa.gov/sites/production/files/2015-06/documents/how-to-dispose-medicines.pdf (recommending discard in the trash unless a take back program is available); *Medicine Disposal: Questions and Answers*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/ensuringsafeuseofmedicine/safedisposalofmedicines/ucm186188.htm#2 (last updated Sept. 27, 2018) (recommending disposal of some pharmaceuticals in the toilet). Drug take back programs are not common in the U.S. and those that exist typically focus on the potential for abuse of controlled substances. *National Prescription Drug Take Back Day*, U.S. DEP'T JUST.: DIVERSION CONTROL DIV., https://www.deadiversion.usdoj.gov/drug_disposal/takeback/ (last visited Jan. 11, 2019); *see also* Naomi Lubick, *Drugs in the Environment: Do Pharmaceutical Take-Back Programs Make a Difference?*, 118 ENVTL. HEALTH PERSP. A210, A214 (May 2010) (commenting that there is no evidence take back programs have an impact on PIE).

But the vast majority of APIs in the environment, around 90%, are the unmetabolized (and partially metabolized) drugs consumed and excreted by humans (and animals) into domestic and other wastewater streams.[38] These APIs often survive the wastewater treatment process and are reintroduced into the aquatic environment in the exiting treated wastewater.[39]

Regardless of the source, solids typically end up in landfills. Ideally, landfills completely contain their contents, but older facilities without leachate containment ultimately allow contents into the surrounding groundwater.[40] Liquid wastes (again, irrespective of the source) are more likely to pass untreated into the environment.[41] In the United States, over 75% of wastewater from homes and other sources is treated in a publicly owned treatment works ("POTWs") and about 25% in septic systems.[42] POTWs are not required to remove low level pharmaceutical wastes nor are they designed to,[43] and 30% to 90% of APIs are estimated to pass through sewerage treatment plants untreated.[44] The efficacy of septic tanks in removing low level pharmaceuticals is not known, but it is unlikely better than current POTWs.[45] Both approaches to wastewater treatment are also subject to bypass, septic systems through poor

38. Elizabeth Grossman, *Downstream Drugs: Big Pharma's Big Water Woes*, GREENBIZ (Aug. 15, 2015, 1:30 AM), https://www.greenbiz.com/article/downstream-drugs-big-pharmas-big-water-woes.

39. Karl Fent et al., *Ecotoxicology of Human Pharmaceuticals*, 38 AQUATIC TOXICOLOGY 122, 125 (June 15, 2006).

40. *See* Lubick, *supra* note 37, at A212–13.

41. *E.g.*, *National Pollutant Discharge Elimination System (NPDES), Combined Sewer Overflows*, EPA, https://www.epa.gov/npdes/combined-sewer-overflows-csos (last updated Aug. 30, 2018).

42. U.S. ENVTL. PROT. AGENCY, PRIMER FOR MUNICIPAL WASTE WATER TREATMENT FACILITIES 4 (Sept. 2004), https://www3.epa.gov/npdes/pubs/primer.pdf.

43. Pharmaceutical degradation in conventional wastewater treatment is incomplete, varying significantly by compound. Reports include beta blocker (cardiac medication) degradation of less than 60%, morphine degradation over 80%, carbamazepine (anticonvulsant) degradation of less than 30%, and ibuprofen (anti-inflammatory) degradation of over 60%. Caldwell, *supra* note 33, at 105, 114. Additionally, antibiotics have the potential to affect the efficacy of biological waste treatment operations. *See* Kümmerer, *supra* note 22, at 429–30.

44. *See* GWYNN LYONS, PHARMACEUTICALS IN THE ENVIRONMENT: A GROWING THREAT TO OUR TAP WATER AND WILDLIFE 5 (2014), http://www.chemtrust.org.uk/wp-content/uploads/CHEM-Trust-Pharma-Dec14.pdf. There would be significant technical issues in any effort to upgrade the myriad of POTWs to have any measurable impact on PIE. *See* Alex Scott, *Cleaning up Drugs in Wastewater*, 93 CHEMICAL & ENGINEERING NEWS 24, 24 (Aug. 3, 2015).

45. *See* Lubick, *supra* note 37, at A212.

maintenance and lax local regulation,[46] and POTWs from structural combined flow system overflows.[47]

In summary, APIs at extremely low levels exist in waterways, groundwater, and sediment around the world. At present, the direct risk to humans as modeled through drinking water consumption is considered low[48] although this risk could be exacerbated by the increased need to use recycled wastewater as potable water.[49] Typical lifetime human exposure to pharmaceuticals in the environment through current drinking water use patterns is estimated at less than a single lifetime dose of most drug products.[50] But, the level of risk to aquatic life and the ecosystem is likely much more significant. Data is limited for plants and animals that spend their entire existence in water, and, while studies to date show that most pharmaceutical exposures are likely not problematic,[51] aquatic risks remain a significant concern for some pharmaceuticals (e.g. endocrine disrupters).[52] The effect of peak environmental concentrations (e.g. downstream of POTWs) may also adversely impact aquatic and other populations.[53] But the most significant risk is probably from antibiotics through increased antimicrobial resistance, which has a direct, and potentially devastating, impact on humans.[54]

II. UNITED STATES ENVIRONMENTAL REGULATIONS

This lack of clarity on the level of risk makes it very difficult to decide what, if anything, should be done about PIE. This Part discusses why regulation of PIE would be difficult under the current United States environmental structure.

46. Rayman Mohamed, *Why Households in the United States Do Not Maintain Their Septic Systems and Why State-Led Regulations Are Necessary: Explanations from Public Goods Theory*, 4 INT'L J. SUSTAINABLE DEV. & PLAN. 143, 149–50 (2009).

47. *National Pollutant Discharge Elimination System (NPDES)*, *supra* note 41; *see also* Mary Ann Evans, *Flushing the Toilet Has Never Been Riskier, Some of Today's Sewers Were Built Before Bathrooms as We Know Them Existed. It's Time to Upgrade*, ATLANTIC (Sept. 17, 2015), https://www.theatlantic.com/technology/archive/2015/09/americas-sewage-crisis-public-health/405541/ (explaining combined sewer overflow and its health impact).

48. Kostich & Länge, *supra* note 12.

49. *See* Jean-François Debroux et al., *Human Health Risk Assessment of Nonregulated Xenobiotics in Recycled Water: A Review*, 18 HUM. & ECOLOGICAL RISK ASSESSMENT 517, 539–40 (2012).

50. Kostich & Länge, *supra* note 12.

51. *Id.* at 206.

52. Kostich et al., *supra* note 10, at 358.

53. Kostich & Länge, *supra* note 12, at 209–10.

54. *Id.* at 208–09.

A. Lack of PIE Regulation

In practice, there are essentially two approaches to regulating complex, emerging environmental issues—wait for near-scientific certainty to determine the appropriate regulatory path forward or regulate anticipated risks even when there is scientific uncertainty (commonly referred to as the precautionary principle).[55] In the early administration of United States environmental laws, including the Clean Air Act ("CAA"), regulators relied on precautionary intent.[56] In *Lead Industries Ass'n v. EPA*, the Court of Appeals for the D.C. Circuit supported the EPA's position that in the CAA "Congress directed the Administrator to err on the side of caution" and made it clear that economic and technical feasibility considerations were subordinate to public health in setting limits.[57] However, seven years later, in *National Resources Defense Council v. EPA*, the D.C. Circuit concluded "'safe' does not mean 'risk free'" and "something is 'unsafe' only when it threatens humans with 'a significant risk of harm.'"[58] The court said the EPA was directed by Congress to prevent only significant risks, adding that cost could be considered in determining standards.[59] Use of strong precautionary intent in United States environmental regulations is not common today.[60] At present, the United States does not have any environmental legislation or regulation focused directly on PIE. In the uncertain risk environment, regulators are apparently taking a wait-

55. The precautionary principle focuses on responsibility towards future generations and encourages taking actions in advance of and to prevent environmental damage. While it encompasses scientific research, the principle also encourages action when "conclusively ascertained understanding by science is not yet available" and "develop[ing] . . . processes that significantly reduce environmental burdens, especially those brought about by the introduction of harmful substances." World Comm'n on the Ethics of Sci. Knowledge & Tech., The Precautionary Principle, U.N. Doc. SHS-2005/WS/21, at 1, 10 (2005), https://unesdoc.unesco.org/ark:/48223/pf0000139578. The precautionary principle has also been considered in terms of environmental surprise—taking a proactive approach when complex issues may have unpredictable consequences. Christian G. Daughton, *Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health. I. Rationale for and Avenues Toward a Green Pharmacy*, 111 ENVTL. HEALTH PERSP. 757, 762 (May 2003).

56. Janine Maney, *Carbon Dioxide Emissions, Climate Change, and the Clean Air Act: An Analysis of Whether Carbon Dioxide Should Be Listed as a Criteria Pollutant*, 13 N.Y.U. ENVTL. L.J. 298, 347–48 (2005).

57. 647 F.2d 1130, 1153, 1155 (D.C. Cir. 1980).

58. 824 F.2d 1146, 1153 (D.C. Cir. 1987) (quoting Indus. Union Dep't, AFL–CIO v. Am. Petroleum Inst., 448 U.S. 607, 642 (1980)).

59. 824 F.2d 1146, 1153, 1163 (D.C. Cir. 1987).

60. *See* John S. Applegate, *The Precautionary Preference: An American Perspective on the Precautionary Principle*, 6 HUM. & ECOLOGICAL RISK ASSESSMENT 413, 430–31 (2000).

and-see approach,[61] although there is ongoing research sponsored by United States regulatory agencies into water quality, endocrine disrupters, and other PIE-related issues.[62] Interested commentators, however, have considered various legal and regulatory modifications, a few of which are briefly considered here.[63]

Frequently mentioned is the Clean Water Act ("CWA"), originally passed in 1972 with the ten-year goal of making all waters in the United States fishable and swimmable,[64] a target that has not yet been met.[65] Under the CWA, states develop water quality guidelines and issue water effluent permits[66] based on national guidance developed by the EPA.[67] While water effluent standards could arguably be modified to include maximum levels of potentially dangerous pharmaceuticals in wastewater permits, there is no regulatory imperative to do so. The structure of the CWA focuses on point source pollution (e.g. factories)[68] and on a limited number of known and dangerous chemical pollutants.[69]

PIE, on the other hand, is generally nonpoint source pollutions (i.e. millions of homes), the risk is not clearly defined, and the technologies to remove significant quantities of PIE from water do not exist. Even if the technology was available, the costs would likely be extraordinary.[70]

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61. *See* Allie Newrat, *Pharma and the Environment: Pollution Continues Despite Public Pressure*, PHARMACEUTICAL TECH. (Oct. 2, 2018), https://www.pharmaceutical-technology.com/features/pharma-and-the-environment-pollution-trend/.

62. *E.g.*, *Three Final EDSP Tier 2 Test Guidelines Are Released, supra* note 24.

63. *E.g.*, Gabriel Eckstein, *Drugs on Tap: Managing Pharmaceuticals in Our Nation's Waters*, 23 N.Y.U. ENVTL. L.J. 37, 52–70 (2015).

64. 33 U.S.C. § 1251(a)(2) (2012).

65. *See* CLAUDIA COPELAND, CONG. RESEARCH SERV., RL30030, CLEAN WATER ACT: A SUMMARY OF THE LAW 2 (2016).

66. 33 U.S.C. § 1342 (2012).

67. *Id.* § 1314; *see also National Recommended Water Quality Criteria*, EPA, https://www.epa.gov/wqc/national-recommended-water-quality-criteria (last updated Dec. 20, 2018).

68. PIE is largely nonpoint source pollution. Matieu Nsenga Kumwimba et al., *Removal of Non-point Source Pollutants from Domestic Sewage and Agricultural Runoff by Vegetated Drainage Ditches (VDDs): Design, Mechanism, Management Strategies, and Future Directions*, 639 SCI. TOTAL ENV'T 742, 743–44 (2018). The CWA requires states to develop nonpoint source management plans but only to get nonpoint source funding. *Introduction to the Clean Water Act*, EPA, https://cfpub.epa.gov/watertrain/moduleFrame.cfm?parent_object_id=2788 (last updated Feb. 27, 2017).

69. Ryan James Albrecht, *Pharmaceuticals in the Environment: Looking to Green Governance for a Remedy*, 3 GEO. WASH. J. ENERGY & ENVTL. L. 182, 189–90 (2012).

70. *See* Anthony King, *Environmentally Benign by Design*, CHEMISTRY WORLD (Aug. 15, 2017), https://www.chemistryworld.com/earth/environmentally-benign-by-design/3007842.article. The cost just to correct combined overflows in the United States was estimated at $88.8 billion in 2004. Evans, *supra* note 47. The cost of removing some pharmaceuticals, where technically feasible, would be higher. At 355 billion gallons of water use per day, the cost of even one unproven technology at a few cents per cubic meter of water would be over

Judicial review has been proposed as a mechanism to compel federal agency action on PIE under existing law.[71] Judicial review was unsuccessful in driving change, however, in a 2015 challenge to the EPA's interpretation of the CWA in *Gulf Restoration Network v. McCarthy*.[72] In *Gulf Restoration Network*, the Fifth Circuit confirmed the appropriateness of judicial review in CWA actions.[73] But the court held, in an opinion highly deferential to the EPA, that the agency could refuse to act (in regulating nonpoint source nitrogen and phosphorous pollution causing dead zones in the Gulf of Mexico)[74] if there was a reasonable explanation grounded in the CWA.[75] Judicial review does not seem a likely path to force federal regulatory action when the EPA is reluctant to act on an evolving nonpoint source issue.

Another environmental law, the Resource Conservation and Recovery Act ("RCRA"), also intersects with PIE. RCRA regulates solid wastes if they are made up of hazardous materials.[76] Only about thirty pharmaceutical/medicinal products are listed under RCRA.[77] Healthcare facilities are required to dispose of these regulated wastes in a manner that is environmentally sound.[78] But specifically excluded from RCRA

$10 billion per year. MOLLY A. MAUPIN ET AL., U.S. GEOLOGICAL SURVEY, CIRCULAR 1405, ESTIMATED USE OF WATER IN THE UNITED STATES IN 2010 1 (2014), https://pubs.usgs.gov/circ/1405/pdf/circ1405.pdf; *see, e.g.*, Scott, *supra* note 44, at 25. There are at least 9000 different drugs (molecular entities) approved for human and animal use worldwide not including potential metabolites, and unidentified pharmaceuticals may actually create the major biological stress. *See* Christian G. Daughton, *Pharmaceuticals in the Environment: Sources and Their Management, in* 62 COMPREHENSIVE ANALYTICAL CHEMISTRY 37, 45, 56–57 (Mira Petrovic et al. eds., 2013).

71. Christopher T. Nidel, *Regulating the Fate of Pharmaceutical Drugs: A New Prescription for the Environment*, 58 FOOD & DRUG L.J. 81, 95–100 (2003).

72. 783 F.3d 227, 244 (5th Cir. 2015).

73. *Id.* at 242.

74. *Gulf of Mexico Dead Zone*, NATURE CONSERVANCY, https://www.nature.org/en-us/about-us/where-we-work/priority-landscapes/gulf-of-mexico/stories-in-the-gulf-of-mexico/gulf-of-mexico-dead-zone/?gclid=EAIaIQobChMI2tLGj5Lc3wIViR6GCh0Fngk-EAAYASAAEgLyOvD_BwE (last visited Jan. 22, 2019).

75. *Gulf Restoration Network*, 783 F.3d at 243–44; *see also, e.g.*, William C. Mumby, Gulf Restoration Network v. McCarthy*: The Necessity of the Clean Water Act's Necessity Determination Mechanism to Ensure Government Accountability*, 43 ECOLOGY L.Q. 495, 499–501 (2016) (providing one perspective on this decision).

76. *Resource Conservation and Recovery Act (RCRA) Laws and Regulations*, EPA, https://www.epa.gov/rcra (last updated Feb. 12, 2019).

77. Albrecht, *supra* note 69.

78. 40 C.F.R. § 262.10 (2012). Compliance can be challenging, however, due to the numerous and complicated rules; *see, e.g., Veterans Affairs Hospitals Will Pay Nearly $534K to Settle Hazardous Waste Allegations*, HCPRO: HOSP. SAFETY INSIDER (Aug. 26, 2009), http://www.hcpro.com/SAF-238025-874/Veterans-Affairs-hospitals-will-pay-nearly-534K-to-settle-hazardous-waste-allegations.html. RCRA rules for hospitals are being updated to reduce complexity and improve compliance. A.J. Plunkett, *EPA Announces Final Rule to Set New Standards on Hazardous Waste Pharmaceuticals*, HCPRO: HOSP. SAFETY INSIDER

are effluent from wastewater facilities and home-generated pharmaceutical wastes, resulting in RCRA regulation of a very small percentage of waste streams containing pharmaceuticals.[79]

A third federal law, the National Environmental Policy Act of 1969, requires the Food and Drug Administration ("FDA") to solicit environmental risk assessments.[80] Environmental Assessments ("EA") are part of new drug applications ("NDAs") and other FDA drug approval applications, unless there is a categorical exclusion.[81] Failure to submit either an EA or a claim of categorical exclusion is sufficient grounds for the FDA to refuse to file or approve an application.[82]

EA testing covers the acute effects of the API on fish, daphnids, algae, and other aquatic life and the results are publicly available.[83] But the real-world value of the data is questionable because the tests are of short duration, focus on mortality (not on subacute factors like growth, fertility, or behavior), do not consider pharmaceuticals in sediments, and do not recognize higher concentrations that may occur in the environment.[84] The testing also does not take into account the cumulative impacts of the drugs, especially where drugs with a similar mode of action accumulate together.[85] Nor does the testing contemplate microbial resistance.[86] Additionally, there are categorical exclusions from the EA requirement for drugs that will enter the environment at less than one part per billion or when the material exists naturally in the environment,[87] exclusions which may be inappropriate given the micro-pollutant nature of PIE. But in recent years, in recognition of potential adverse environmental effect, additional guidance has been provided for

(Dec. 20, 2018), http://www.hcpro.com/SAF-332183-874/EPA-announces-final-rule-to-set-new-standards-on-hazardous-waste-pharmaceuticals.html.

79. *See* 40 C.F.R. § 262.10 (2012).

80. National Environmental Policy Act of 1969, Pub. L. No. 91-190, § 102, 83 Stat. 852, 853–54 (1970).

81. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY ENVTL. ASSESSMENT OF HUM. DRUG AND BIOLOGICS APPLICATIONS 1 (1998), https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf.

82. *Id.*

83. Boxall, *supra* note 15, at 1112. Some pharmaceutical companies publish environmental risk information in an accessible format. *E.g.*, *AstraZeneca's Environmental Risk Summaries*, ASTRAZENECA, https://www.astrazeneca.com/content/dam/az/PDF/2017/Environmental_risk_data_relating_to_our_medicines.pdf (last visited Nov. 13, 2019).

84. Boxall, *supra* note 15, at 1112.

85. Daughton & Ternes, *supra* note 13, at 935.

86. CTR. FOR DRUG EVALUATION & RES., U.S. FOOD & DRUG ADMIN., ENVTL. ASSESSMENTS AND CLAIMS OF CATEGORICAL EXCLUSIONS 6–7 (2017), https://www.fda.gov/media/72537/download.

87. *Id.*

drug applications of potential endocrine disrupters.[88] However, a properly completed EA has never resulted in a non-approval from FDA for any new pharmaceutical.[89]

B. Lifecycle Approach

Layered on the wait-and-see approach of Congress and regulators is the overall structure of United States environmental law. Early commentators pointed out that EPA regulations relied too much on "control" of existing pollution and too little on "prevention" of pollution.[90] While there remains little legal emphasis on preventing pollution, the Pollution Prevention Act[91] exempted, administrative programs that focus on the life cycle of wastes include the concept of prevention (e.g. "Reduce, Reuse, Recycle").[92] A more holistic approach to the lifecycle of pharmaceuticals, sometimes called "Green Pharmacy," has similarly been developed.[93] Christian Daughton, retired EPA expert on emerging contaminants, has described it as an "optimized system of healthcare . . . that would not generate any leftover medications and also result in minimal excretion of [drug] residues."[94]

Organized collection of unused drugs was an early example of the lifecycle approach to PIE, but it focuses on a very small part of the problem and addresses the issue after the fact.[95] Today, the green pharmacy concept recognizes that the use and excretion of drugs is the major source of PIE.[96] Researchers have begun to focus on causation (e.g.

88. *See* Alexander Gaffney, *FDA Guidance Aimed at Helping to Protect Fish from Certain Drug Products*, RAPS (Apr. 28, 2015), https://www.raps.org/regulatory-focus™/news-articles/2015/4/fda-guidance-aimed-at-helping-to-protect-fish-from-certain-drug-products.

89. Nidel, *supra* note 71, at 94.

90. BARRY COMMONER, MAKING PEACE WITH THE PLANET 41–44 (1990) (arguing control is self-defeating and results in little or no improvement because the control device always allows some pollution); *see also* OECD, DIFFUSE POLLUTION, DEGRADED WATERS: EMERGING POLICY SOLUTIONS 12 (2017), https://www.oecd.org/environment/resources/Diffuse-Pollution-Degraded-Waters-Policy-Highlights.pdf (confirming prevention is generally more effective and less expensive than remediation).

91. 42 U.S.C. § 13101 (1990). "Opportunities for source reduction are often not realized because of existing regulations, and the industrial resources required for compliance, focus on treatment and disposal." *Summary of the Pollution Prevention Act*, EPA, https://www.epa.gov/laws-regulations/summary-pollution-prevention-act (last updated Aug. 15, 2019).

92. *Reduce, Reuse, Recycle*, EPA, https://www.epa.gov/recycle (last updated Oct. 3, 2019).

93. Daughton, *supra* note 70, at 60.

94. *Id.* at 63.

95. *See id.* at 59, 63.

96. *See* King, *supra* note 70.

"benign by design")[97] and use of pharmaceutical products. Ideas for prevention of PIE include reducing the prescribing dose of pharmaceuticals where appropriate,[98] alternative and more efficient drug delivery,[99] selecting medications based on more favorable excretion profiles,[100] and developing highly biodegradable drugs.[101]

Of these, the "Holy Grail" is the creation of pharmaceuticals in targeted areas of concern that are clinically effective but degrade completely when exposed to the environment[102] or are no longer pharmacologically active. However, reaching the ultimate—100% use or degradation—is probably not necessary. Other results that might be more feasible include achieving high levels of oral absorption or environmental degradation, metabolization to inert substances, and increased receptor specificity.[103] Today a few forward-thinking researchers are looking into these ideas.[104]

Overall, current environmental laws focus on cleanup.[105] They were not designed to deal with micro-pollutants that make up PIE and are highly unlikely to be effective in dealing with the myriad of issues and current level of scientific uncertainty surrounding PIE.[106] The concepts encompassed in the life cycle approach of green pharmacy and the focus on preventing certain pharmaceuticals[107] from ever reaching the environment (at least in potentially unsafe levels) will ultimately be the fastest and least expensive way to address the problem.

Given the long-term risks associated with PIE, a proactive approach to the problem is required. Despite some favorable changes in the pharmaceutical industry, levels of PIE are only going to increase as the

97. *See id*.

98. *See* Christian G. Daughton & Ilene S. Ruhoy, *Environmental Footprint of Pharmaceuticals: The Significance of Factors Beyond Direct Excretion to Sewers*, 28 ENVTL. TOXICOLOGY & CHEMISTRY 2495, 2496–97 (2009).

99. *See* Daughton, *supra* note 55, at 765–67.

100. Christian G. Daughton, *Eco-Directed Sustainable Prescribing: Feasibility for Reducing Water Contamination by Drugs*, 493 SCI. TOTAL ENV'T 392, 394 (2014).

101. King, *supra* note 70.

102. *Benign by Design: The Long Road to Biodegradable Drugs*, PHARM. TECH. (July 6, 2016), https://www.pharmaceutical-technology.com/uncategorised/featurebenign-by-design-the-long-road-to-biodegradable-drugs-4913115/.

103. *See* Taylor, *supra* note 3, at 26.

104. *See, e.g.*, *Developing a Biodegradable Antibiotic*, DEUTSCHE BUNDESSTIFTUNG UMWELT, https://www.dbu.de/123artikel36417_2548.html (last visited Nov. 14, 2019); Brigitte Osterath, *Benign by Design: How Chemists Aim to End Pharmaceutical Pollution of the Environment*, DEUTSCHE WELLE (Apr. 7, 2016), https://www.dw.com/en/benign-by-design-how-chemists-aim-to-end-pharmaceutical-pollution-of-the-environment/a-19170547.

105. COMMONER, s*upra* note 90.

106. *See* Eckstein, *supra* note 63.

107. *See* Küster & Adler, *supra* note 7, at 2.

population ages and consumes more medications.[108] While efforts to reduce PIE through better prescribing and waste handling practices are ongoing and continue to be introduced,[109] these efforts only impact a small percentage of PIE sources.[110] What is needed to significantly reduce PIE is to address the underlying issue, that some pharmaceuticals as currently formulated and used are environmentally unsustainable.[111] To do this, many more people who have the knowledge to design environmentally sustainable pharmaceuticals need to be incentivized to work on PIE. And most of these people work in the pharmaceutical industry.

III. POTENTIAL SOLUTION—INCENTIVES

The previous Part demonstrated the difficulty in regulating PIE and outlined how a life cycle approach to PIE could eliminate or reduce the negative impacts of PIE. This Part presents the concept of incentivizing the pharmaceutical industry to actively address and pursue a reduction in the sources of PIE, through research into more environmentally friendly compounds or the modification of existing compounds.[112] Both new drugs and generic drugs are discussed.

A. Drug Development

To better understand this proposal for supporting the elimination of environmental risks at the source requires a step back to briefly explain the drug approval process and the intersection of drug marketing exclusivity and patents. The process for developing pharmaceuticals and getting FDA approval is a lengthy and expensive one. It can take ten to

108. *See* Brian Owens, *Pharmaceuticals in the Environment: A Growing Problem*, PHARMACEUTICAL J. (Feb. 19, 2015), https://www.pharmaceutical-journal.com/news-and-analysis/features/pharmaceuticals-in-the-environment-a-growing-problem/20067898.article?firstPass=false.

109. Adela Maghear, *The Safer Pharma Campaign to Eliminate Pharmaceuticals in the Environment*, HEALTH EUROPA (July 27, 2018), https://www.healtheuropa.eu/safer-pharma-campaign-pharmaceuticals-in-the-environment/87448/.

110. Grossman, *supra* note 38.

111. Sustainability is a complex concept that has many definitions. Perhaps the most frequently used is "[s]ustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs." REPORT OF THE WORLD COMMISSION ON ENVIRONMENT AND DEVELOPMENT: OUR COMMON FUTURE (1987), https://sustainabledevelopment.un.org/content/documents/5987our-common-future.pdf. Here, an environmentally sustainable pharmaceutical is one that can be used and excreted without the resulting pharmaceutical waste causing societal problems (e.g. antibiotic resistance) that negatively impact future generations. Environmentally unsustainable drug products create these problems.

112. King, *supra* note 70.

fifteen years[113] at an average cost of $2.6 billion[114] to get a drug to market in the United States.[115]

The initial step in the development of a new drug or new chemical entity ("NCE") involves basic research to identify possible API candidates and preclinical testing to predict their efficacy and safety in humans.[116] During this period of three to six years, the number of compounds potentially effective against the disease is whittled down from several thousand to perhaps five (for each ultimately successful compound).[117] Costs for this early discovery and development of new drugs has been estimated at over $300 million.[118]

The next step in drug development is clinical testing designed to prove the safety and efficacy of an NCE in humans.[119] Phase I clinical trials test the most promising compounds in twenty to eighty people to determine safety and side effects of the drug.[120] Phase II trials are used to determine appropriate dosing and are generally conducted in several hundred people.[121] Phase III trials, the final preapproval clinical testing, are designed to support the ultimate FDA filing by showing the efficacy of the drug and determining its indication and the target population.[122] This series of clinical trials is typically conducted over a period of six to seven years, involving thousands of volunteers[123] at a median cost over $1.2 billion.[124] A drug can fail at any point along the path—most do.[125] If

113. PHRMA, DRUG DISCOVERY AND DEVELOPMENT: UNDERSTANDING THE R&D PROCESS 1 (2007), http://www.astp4kt.eu/downloads/BPL/Drug_Discovery_and_Development.pdf.

114. *See* Ed Silverman, *What Does It Cost to Develop a New Drug? Latest Study Says $2.6 Billion*, WALL STREET J. (Nov. 20, 2014, 7:19 PM), https://www.wsj.com/articles/what-does-it-cost-to-develop-a-new-drug-latest-study-says-2-6-billion-1416529149.

115. *See generally* JORGE MESTRE-FERRANDIZ ET AL., THE R&D COST OF A NEW MEDICINE (2012) (showing a range of costs from $1.031 billion to $1.867 billion in 2011 dollars).

116. *See* PHRMA, *supra* note 113.

117. *Id.*

118. *See* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 25 (2016).

119. *NIH Clinical Research Trials and You, The Basics*, NAT'L INSTS. HEALTH, https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics (last updated Oct. 20, 2017).

120. *Id.*

121. *Id.*

122. *Id.*

123. *See* PHRMA, *supra* note 113.

124. Rick Mullin, *Tufts Study Finds Big Rise in Cost of Drug Development*, CHEMICAL & ENGINEERING NEWS (Nov. 20, 2014), https://cen.acs.org/articles/92/web/2014/ 11/Tufts-Study-Finds-Big-Rise.html.

125. *See* Chris Lo, *Counting the Cost of Failure in Drug Development*, PHARMACEUTICAL TECH. (June 19, 2017), https://www.pharmaceutical-technology.com/features/feature counting-the-cost-of-failure-in-drug-development-5813046/.

the clinical trials are successful in showing efficacy and safety, the drug is submitted to the FDA for review and approval as part of a New Drug Application ("NDA"). FDA approval signifies that the drug has been shown "to provide benefits that outweigh its known and potential risks for the intended population."[126] FDA approval also means the product can be marketed and sold in the United States.[127] And, for an NCE, approval grants a five-year marketing exclusivity period.[128] Pharmaceutical companies rely on both patents and FDA-granted marketing exclusivity to protect their inventions.[129]

B. Patents

Patents are essentially a mechanism designed to incentivize creativity for the public good.[130] The United States Constitution states that Congress is empowered to "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[131] Under United States law, inventors who successfully obtain a patent have an exclusive right to their invention for twenty years and the opportunity to recoup their costs and some profit during that time period.[132] The pharmaceutical industry has flourished under this system, patenting almost 500 NCEs from 1970 to 2010[133] and becoming the largest single funder of business research and development ("R&D") in the country.[134]

126. *Development & Approval Process: Drugs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/developmentapprovalprocess/default.htm (last updated Oct. 28, 2019).

127. *See Step 4: FDA Drug Review*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405570.htm (last updated Jan. 4, 2018).

128. *See* Aaron S. Kesselheim, *Determinants of Market Exclusivity for Prescription Drugs in the United States*, COMMONWEALTH FUND (Sept. 13, 2017), https://www.commonwealthfund.org/publications/journal-article/2017/sep/determinants-market-exclusivity-prescription-drugs-united.

129. *See* Zachery Brennan, *Patents vs. Market Exclusivity: Why Does It Take So Long to Bring Generics to Market?*, RAPS (Aug. 17, 2016), https://www.raps.org/regulatory-focus™/news-articles/2016/8/patents-vs-market-exclusivity-why-does-it-take-so-long-to-bring-generics-to-market.

130. *See* 1 PETER S. MENELL ET AL., INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE: 2018, at 167 (2018).

131. U.S. CONST. art. I, § 8, cl. 8.

132. MENELL ET AL., *supra* note 130, at 37. But a patent is not a license to market a pharmaceutical. *See* 21 C.F.R. § 314.108.

133. *See* ROSS C. DEVOL ET AL., THE GLOBAL BIOMEDICAL INDUSTRY: PRESERVING U.S. LEADERSHIP 5 (2011), http://assets1c.milkeninstitute.org/assets/Publication/ResearchReport/PDF/CASMIFullReport.pdf (showing the percentage of global NCE patents to United States firms has gone from 31% in the 1970s to 57% in the 2000s).

134. PHRMA, BIOPHARMACEUTICALS IN PERSPECTIVE 25, 35 (2019), http://phrma-docs.phrma.org/files/dmfile/PhRMA_2019_ChartPack_Final.pdf (noting over $97 billion was invested in drug research in 2017).

To receive a United States patent the invention must meet five basic requirements. First, patentable subject matter is defined as a process, machine, manufacture or composition of matter.[135] NCEs are patented as composition of matter, although pharmaceutical companies also patent delivery systems (e.g. transdermal patch), manufacturing processes, etc.[136] Second, patent utility generally means that the invention has a practical use, although this requirement is viewed more critically for pharmaceuticals.[137] Third, patents must be nonobvious, embodying a significant enough technical advance over the prior art to warrant patent protection.[138] Fourth, the invention must be novel or new by showing that it was not previously published or sold (or otherwise in the prior art).[139] And fifth, to ensure the public good part of the patent bargain, there must be disclosure or enablement so that others can replicate the invention at the expiry of the patent term.[140]

Pharmaceutical companies typically patent an NCE very early in the development process, despite the reduction in useful patent life after FDA approval.[141] This ensures that the NCE does not become part of the prior art. Early patenting also helps in obtaining broad claims because the patent of the particular NCE may predate attempts by other inventors to patent similar drug compounds.[142] Early disclosure through patenting is also important to researchers, allowing the continuation of research in the field (while protecting the NCE).[143]

However, in order to file for a patent, the invention must meet the five requirements of patentability, which can push the timing of the patent application to later in the development process. Sufficient research must have occurred to ensure enablement. Additionally, proving utility might delay the application. The patent utility requirement that

135. 35 U.S.C. § 101 (2012).

136. Jan Berger et al., *How Drug Life-Cycle Management Patent Strategies May Impact Formulary Management*, AJMC (Jan. 20, 2017), https://www.ajmc.com/journals/supplement/2016/how-drug-life-cycle-management-patent-strategies-may-impact-formulary-management/a636-article.

137. 35 U.S.C. § 101 (2018).

138. 35 U.S.C. § 103 (2012).

139. *Id.* § 102.

140. *Id.*

141. Rebecca S. Eisenberg, *Patents and Regulatory Exclusivity*, *in* THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 167, 170 (Patricia M. Danzon & Sean Nicholson eds., 2012).

142. *Id.*

143. *See generally* Bernard H. Munos & William W. Chin, *A Call for Sharing: Adapting Pharmaceutical Research to New Realities*, 1 SCI. TRANSLATIONAL MED. 1, 1 (Dec. 2, 2009), http://stm.sciencemag.org/content/1/9/9cm8 (arguing for sharing information in pharmaceutical R&D).

the invention have specific and substantial utility[144] is applied strictly for pharmaceuticals.[145] And an NCE must meet the non-obvious requirement. The non-obviousness test for chemical compounds, including NCEs, includes an assumption that small changes in chemical structure are "prima facie obvious" unless there are surprising or advantageous properties.[146] Additional testing for compounds similar to those already patented might also delay patent filing.[147]

C. Marketing Exclusivity

A patent on an NCE does not permit the sale of the drug because only the FDA can authorize sale.[148] While much of the twenty-year patent life may be used up during R&D and the FDA approval period,[149] the remaining time (or patent exclusivity from other patents on the same drug) often extends beyond the five years of exclusivity awarded by the FDA. If not, the inventor can rely on exclusivity. The information on pharmaceutical exclusivity and patents is maintained by the FDA in a document commonly called the Orange Book.[150]

144. Specific utility means the invention is specific to the subject matter claimed and "provide[s] a well-defined and particular benefit to the public." *In re* Fisher, 421 F.3d 1365, 1371 (Fed. Cir. 2005). Substantial utility requires that the invention has "a significant and presently available benefit to the public." *Id.*

145. *See* Eisenberg, *supra* note 141, at 170–71; *2017 Guidelines for Examination of Applications for Compliance with the Utility Requirement [R-11.2013]*, U.S. PATENT & TRADEMARK OFFICE, https://www.uspto.gov/web/offices/pac/mpep/s2107.html (last updated Jan. 24, 2018). In most cases, proof of usefulness in humans is not necessary, but some level of animal testing is. *In re Brana* held *in vivo* testing in mice was sufficient, putting a stake in the ground after Phase I clinical trials by stating that "requir[ing] Phase II testing in order to prove utility" would result in costs that "would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." 51 F.3d 1560, 1568 (Fed. Cir. 1995).

146. *See* Eisenberg, *supra* note 141, at 171–72.

147. *Id.*

148. *Unapproved Drugs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs (last updated Oct. 17, 2019).

149. *See* PHRMA, *supra* note 113. However, the Hatch Waxman Act allows restoration of part of the time lost awaiting premarket regulatory approval to the term of some drug patents. *See* 35 U.S.C. § 156 (2012).

150. *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/informationondrugs/ucm129662.htm (last updated Oct. 18, 2019); Kesselheim, *supra* note 128 (reporting an average exclusivity period of twelve years for most NCEs). As a simple example of drug patent strategy, the NCE in Advair, an asthma medication developed and sold by GlaxoSmithKline, was approved for marketing by the FDA in 2000. The United States patent on the NCE expired in 2010, but the patent on the delivery device, critical to the successful dosing of the product, lasted until 2016. John Bottrell, *Generic Advair Inhalers:*

Marketing exclusivity may be granted by the FDA not only for the approval of an NCE (five years) but also for the development of pediatric drugs, orphan drugs, and antibiotics, among others.[151] In addition, the agency grants other forms of incentive for invention, including priority review vouchers, for the development of drugs to treat tropical diseases and certain rare conditions.[152] These various mechanisms have been broadly referred to as regulatory exclusivity.[153]

Regulatory exclusivity is a relatively new phenomenon that has grown through congressional and agency action outside of the traditional intellectual property scheme.[154] In 2015, over 40% of new pharmaceuticals received some form of exclusivity.[155] Regulatory exclusivity rights are considered by some to be stronger than patents because the FDA cannot approve a generic during this period[156] and the right to exclude is enforced by the federal government, not the holder of the patent.[157]

An example of marketing exclusivity[158] for pharmaceuticals is the Orphan Drug Act, which grants a seven-year exclusivity period that runs from the time of the NDA approval.[159] The Act was originally designed to spur research into and treatments for rare diseases when no "reasonable expectation that the cost of developing . . . will be recovered from sales in

3 Reasons Why It's Taking So Long?, ASTHMA.NET (Aug. 21, 2017), https://asthma.net/living/generic-advair-inhalers-3-reasons-whys-taking-long/.

151. *See Frequently Asked Questions on Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/developmentapprovalprocess/ucm079031.htm#howlongpatentterm (last updated May 2, 2018).

152. David Ridley, *Priority Review Vouchers*, PRIORITY REV. VOUCHER, https://priorityreviewvoucher.org/ (last visited Nov. 16, 2019).

153. *See* Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM. J.L. & ARTS 53, 54–56 (2016).

154. *Id.* Regulatory exclusivity is considered by some to be a new property right with characteristics of patents and trade secrets and the challenges of accidental property, while others see exclusivity as filling innovation gaps where patent incentives have not worked. Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299, 300 (2015).

155. *Novel Drugs Summary*, U.S. FOOD & DRUG ADMIN, https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drugs-summary-2015 (last updated Jan. 12, 2016).

156. E-mail from Michael Carrier, Distinguished Professor of Law, Rutgers Law Sch., to author (Apr. 26, 2019, 10:01 EST) (on file with author).

157. *See* Feldman, *supra* note 153, at 60.

158. Renu Lal, *Patents and Exclusivity*, CDER SMALL BUS. & INDUS. ASSISTANCE (May 19, 2015), https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf (outlining exclusivity periods beyond that for NCEs).

159. Erin Smith et al., *Repeal of the Orphan Drug Tax Credit: A Step Backwards, for Rare Disease Research*, RARE DISEASE REV. (May 28, 2018), https://www.rarediseasereview.org/publications/2018/5/28/repeal-of-the-orphan-drug-tax-credit-a-step-backwards-for-rare-disease-research (noting the elimination of tax incentives).

the United States."[160] The FDA is barred from approving other applications for the same disease during the entire seven-year exclusivity period.[161]

Marketing exclusivity that works as an extension to patent and other exclusivity rights can be exemplified by the pediatric exclusivity provision, first addressed in the Food and Drug Administration Modernization Act of 1997[162] and later modified in the Best Pharmaceuticals for Children Act ("BPCA").[163] The BCPA provides an additional six months of market protection at the end of the last of the patents and/or marketing exclusivity listed in the Orange Book.[164] Similar to the Orphan Drug Act, the purpose of the legislation is to incentivize pharmaceutical companies, in this case to conduct (but not necessarily successfully conclude)[165] expensive pediatric clinical testing on existing drugs to confirm their safety and efficacy in children (children are often prescribed drugs off label that have only been tested in adults).[166]

Priority review vouchers are provided for the development of medication for a neglected tropical disease or a rare pediatric disease.[167]

160. The Act was later amended to include all diseases affecting fewer than 200,000 people. 21 U.S.C. § 360bb(a)(2) (2018).

161. 21 C.F.R. § 316.31 (2019).

162. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 111, 111 Stat. 2296, 2305–09 (codified as amended in scattered sections of 21 U.S.C.).

163. Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107–109, 115 Stat. 1408 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

164. *Id.*

165. U.S. FOOD & DRUG ADMIN, QUALIFYING FOR PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT: FREQUENTLY ASKED QUESTIONS ON PEDIATRIC EXCLUSIVITY, https://www.fda.gov/drugs/developmentapproval process/developmentresources/ucm077915.htm (last updated Oct. 13, 2016).

166. *See* Lal, *supra* note 158. A total of 192 drugs were granted pediatric exclusivity between 1997 and mid-2012. *See* NATE AUMOCK ET AL., DO INCENTIVES DRIVE PEDIATRIC RESEARCH? 4 (2013), https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/public%20sector/regulatory%20excellence/do_incentives_drive_pediatric_research.ashx. The level of off-label pediatric prescribing has dropped as the result of this exclusivity. Katelyn Yackey et al., *Off-label Medication Prescribing Patterns in Pediatrics: An Update*, 9 HOSP. PEDIATRICS 186, 192 (2019). The cost of pediatric testing on an already approved drug is less than for a new drug since preclinical and Phase I testing is already completed. *See* Ann M. Thayer, *Drug Repurposing*, 90 CHEMICAL & ENGINEERING NEWS 15, 15 (Oct. 1, 2012), https://cen.acs.org/articles/90/i40/Drug-Repurposing.html.

167. *See* 21 U.S.C. § 360n (2018) (covering tropical diseases); 21 U.S.C. § 360ff (2018) (covering rare pediatric diseases). Vouchers were first proposed in David B. Ridley et al., *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313, 313 (Mar.–Apr. 2006). FDA grants priority review (vs. standard review) if a potential new drug represents a significant improvement to current treatment. *Priority Review*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm (last updated Jan. 4, 2018). Although priority review grants a quicker decision timeline by the agency, it does not guarantee approval—but a speedier decision facilitates earlier sales if the drug is

This approach has been used when extension of the exclusivity period would still not provide a marketing incentive for development, for instance when the market is too small or the patients too poor. The vouchers, which can be traded or sold, entitle the bearer to a priority review on an NCE.[168] Vouchers are generally sold, with prices sometimes exceeding $100 million.[169]

D. Incentives

APIs exist in the environment as micro-pollution. Some of these APIs are not environmentally sustainable because they negatively impact the environment and human health. To date pharmaceutical companies have only addressed the problem indirectly.[170] In reality, there is currently little incentive for pharmaceutical companies to tackle PIE risks beyond testing their products according to regulatory protocols and maintaining their reputations through heightened transparency and supply chain rigor, while there is huge risk (and limited reward) to embarking on a trip to find the "Holy Grail" of PIE.[171] Few people would argue, given the uncertainty in the science around PIE, that the value of a significant new drug is not greater than the possible risk of that drug being present in the environment as micro-pollution.[172]

For this reason, particular environmentally unsustainable pharmaceuticals cannot simply be outlawed as some chemical pollutants have been in the past. When a phaseout of sale or manufacture of such chemicals has been effectively mandated, there were proven technical equivalents available as alternatives to the banned substance.[173] Here, a different approach is required to get more of the people most likely to be able to solve the problem engaged. This can be accomplished through incentivizing the pharmaceutical industry to address PIE.

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approved. Peter Loftus, *Drug Makers Buy Pricey Vouchers to Speed Products to Market*, WALL STREET J. (Nov. 1, 2015), https://www.wsj.com/articles/drug-firms-buy-pricey-vouchers-to-speed-products-to-market-1445333403.

168. *Id.*

169. *See* Alexander Gaffney et al., *Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers*, RAPS (Nov. 6, 2018), https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers.

170. *See* Ignacio Aliagas et al., *Sustainable Practices in Medicinal Chemistry Part 2: Green by Design*, 60 J. MEDICINAL CHEMISTRY 5955, 5964 (2017).

171. According to Max Hempel of the German Federal Environmental Foundation, "There is currently no benefit to industry in developing an environmentally benign drug. . . . We need some incentives." King, *supra* note 70.

172. *Id.*

173. *E.g.*, Michael Weisskopf, *U.S. to End CFC Production 4 Years Earlier Than Planned*, WASH. POST, Feb. 12, 1992, at A2.

The first challenge in an incentivization scheme is to determine what exactly needs to be incentivized (beyond, say, an outcome that is better for the environment). Open questions with PIE include which drugs or drug characteristics cause significant harm (and what is significant harm), what level of biodegradability is acceptable in a particular drug, and so on. This Note will make no attempt to address this myriad of technical questions, assuming instead environmentally sustainable and unsustainable drug characteristics and products can be determined. The Note also assumes the environmental profile of some pharmaceuticals can be improved (while maintaining drug safety and efficacy), and a relatively small percentage of current and future drugs are environmentally unsustainable.[174]

There are structural changes occurring in the pharmaceutical industry that will reduce some PIE risks without any additional action. The most significant is likely the ongoing shift to biological pharmaceutical products. Biological products are generally very large molecular entities made up of or developed from living organisms, while most current drugs (i.e. APIs) are synthetically developed chemical compounds, often referred to as small molecules.[175] Biological products, in general, degrade quickly and are not persistent in the environment.[176] Seven of the top eight selling drugs in the United States in 2013 were biologics with sales totaling $58 billion.[177] Twenty percent of the pharmaceuticals approved between 2011 and 2015 were biologics[178] and these drugs make up a growing proportion of pharmaceutical research efforts.[179] However, countering this trend from an environmental perspective is that almost 90% of all drug prescriptions in the United States are for generics.[180] Generics are almost exclusively made up of sm-

174. *See* Küster & Adler, *supra* note 7, at 1, 3.

175. *Small and Large Molecules*, BAYER, pharma.bayer.com/en/innovation-partnering/technologies-and-trends/small-and-large-molecules/ (last visited Nov. 29, 2019).

176. Taylor, *supra* note 3, at 27–28 (noting, however, some proteins are stable in the environment).

177. Rob Wright, *Can Big Pharma Survive in a Big Biotech World?*, LIFE SCI. LEADER: BLOG (May 15, 2014), http://www.lifescienceleader.com/doc/can-big-pharma-survive-in-a-big-biotech-world-0001.

178. Asher Mullard, *2015 FDA Drug Approvals*, 15 NATURE REVIEWS DRUG DISCOVERY 73, 73 (2016).

179. IAN LLOYD, PHARMA R&D ANNUAL REVIEW 2017, at 14–15 (2017), https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/files/pdfs/whitepapers/rd-review-2017.pdf.

180. Erica Klinger, *2017 Generic Drug Access and Savings in the U.S. Report*, ASS'N ACCESSIBLE MEDS., https://accessiblemeds.org/resources/blog/2017-generic-drug-access-and-savings-us-report (last visited Nov. 29, 2019).

all molecules and will continue to be for some time.[181]

Another industry trend that will positively impact PIE is the increased use of personalized medicine. In personalized medicine, therapies selected will be the most effective for a particular individual, which should, among other things, reduce drug waste through more exact dosing and drug delivery.[182] While this approach will reduce the use of certain drugs, it may have no impact on the properties (including environmentally important characteristics) of the drugs being used, and it may result in drugs with more bioactivity.[183] Therefore, it can be assumed that many of the current environmentally unsustainable pharmaceuticals will remain in use for the foreseeable future[184] and new drugs with similar environmental profiles will continue to be developed, although as a lower percentage of the whole.[185]

1. NCEs

NCEs require different incentives than generic drugs. Developing incentives for NCEs is the most straightforward opportunity, comparable with the marketing incentives granted to orphan or pediatric drugs. Improving the environmental sustainability of a particular drug is unlikely to provide any reasonable expectation of recovery through additional product sale.[186]

181. *See* Andrii Buvailo, *Will Biologics Surpass Small Molecules in the Pharma Race?*, BIOPHARMATREND (July 11, 2018), https://www.biopharmatrend.com/post/67-will-small-molecules-sustain-pharmaceutical-race-with-biologics/. Biosimilars (generic biologics) are fairly new and harder to manufacture than small molecule generics, in part because biologics are often protected by broad patents and trade secrets. Erwin A. Blackstone & Joseph P. Ruhr, *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS 469, 471–72 (Sept./Oct. 2013); W. Nicholson Price & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1028, 1046, 1050–51 (2016). Lack of incentives for the first to market biosimilars may also delay competition. Benjamin P. Falit et al., *Biosimilar Competition in the United States: Statutory Incentives, Payers, and Pharmacy Benefit Managers*, 34 HEALTH AFF. 294, 294–95 (Feb. 2015).

182. *See Personalized Medicine*, MAYO CLINIC, http://mayoresearch.mayo.edu/center-for-individualized-medicine/personalized-medicine.asp (last visited Feb. 4, 2019).

183. *Cf.* Mullard, *supra* note 178 (noting, for example, high percentage of oncology products).

184. *See* DeNoon, *supra* note 29. Small molecule pharmaceuticals were targeted at diseases affecting many people. Kevin Outterson et al., *Repairing the Broken Market for Antibiotic Innovation*, 34 HEALTH AFF. 277, 278 (Feb. 2015).

185. LLOYD, *supra* note 179.

186. Of course, when considering the environmental impact of NCEs, there is also the option of just mandating an improved environmental profile for new drugs. A problem with this approach is the likelihood that some, perhaps many, NCEs—even with the most assiduous research efforts—cannot be made environmentally sustainable. *See, e.g.*, Osterath, *supra* note 104. Also, such a mandate would probably shift pharmaceutical research efforts to easier targets. Both outcomes would result in unmet medical needs. The

Development of a pharmaceutical that significantly or completely biodegrades or has some sort of degradation trigger is a more expensive project (in time and money) than developing an NCE without these constraints, barring serendipity.[187] Arguably, two approaches could be taken to finding more environmentally sustainable NCEs. First would be focusing early discovery efforts on making the NCE inherently environmentally sustainable[188] or choosing to develop a lead candidate that is environmentally sustainable.[189] Second would be to discover an NCE, then modify it—chemically, through delivery method or otherwise—to have an improved environmental profile, while remaining safe and effective.[190] In either scenario, steps are added upfront in the R&D process, specifically in discovery.[191]

The additional variable research costs would likely total tens of millions of dollars,[192] but the more significant issue would be time. The chemical structure of a drug, including quantities of tiny impurities inherent in the synthesis of the compound, is set very early in the R&D process, prior to large clinical trials.[193] Any changes (to enhance biodegradability, for example) later in the timeline would typically mean looping back to the start of clinical trials or conducting additional trials to prove equivalency.[194] The longer discovery process would delay patentability,[195] subjecting the NCE to the possibility of additional prior

cost of drugs is an important policy debate, but improving the environmental profile of drugs is unlikely to shed much light on the subject. There will be costs with any efforts to reduce PIE, whether it is making drugs more environmentally friendly or cleaning them out of the nation's waters. The challenge is to find the sweet spot.

187. *E.g.*, Osterath, *supra* note 104.

188. *See* Aliagas et al., *supra* note 170, at 5964.

189. King, *supra* note 70.

190. *See* Tushar Rastogi et al., *Re-Designing of Existing Pharmaceuticals for Environmental Biodegradability: A Tiered Approach with β-Blocker Propranolol as an Example*, 49 ENVTL. SCI. & TECH. 11756, 11756–57 (2015).

191. Discovery through Phase I clinical trials are typically 15% of overall R&D costs but still very expensive. *See* John LaMattina, *Should Pharma Companies Give Up Discovery Research?*, FORBES (Sept. 10, 2013), http://www.forbes.com/sites/johnlamattina/2013/09/10/should-pharma-companies-give-up-discovery-research. Investment in an environmentally sustainable pharmaceutical would probably not result in a higher priced drug (incentivizing sustainable product research) since drug pricing in the United States is generally set by market forces and that drug's clinical value. *See* Sarah Kliff, *The True Story of America's Sky-High Prescription Drug Prices*, VOX (May 10, 2018), https://www.vox.com/science-and-health/2016/11/30/12945756/prescription-drug-prices-explained.

192. *See* LaMattina, *supra* note 191.

193. *In re* Brana, 51 F.3d 1560, 1565 (Fed. Cir. 1995).

194. *Id.* at 1567.

195. *Id.* at 1568.

art competition and potentially more restrictive claims.[196] It would ultimately delay FDA approval and the subsequent launch of the product.

Expediting launch is a priority in the pharmaceutical industry.[197] Even if one company has the exclusive rights to a particular NCE, there are generally similar drugs in development at other companies, and the first to market advantage is often considered the key factor in gaining a higher market share.[198] While there has been some challenge to the critical nature of this factor, the first to market drug in a particular class, on average, has a higher percentage of the market than other factors would dictate.[199] It is doubtful that a pharmaceutical company would embark on a voluntary research effort delaying product launch without a sufficient reward.

An add-on market exclusivity period, triggered by the successful development and approval of a sustainable drug,[200] is probably the most appropriate incentive in the case of an NCE. An NCE has Orange Book patent(s) and/or market exclusivity to extend. Like pediatric exclusivity, the intent would be to incentivize research in an area that has little financial benefit to the pharmaceutical company but would provide public good. However, the incentive would need to focus on compensating for potential loss of market share, not just the direct costs of the additional research, although both should be considered. The most appropriate length for said exclusivity would require a rigorous financial analysis that includes many more factors than discussed here.

But existing market exclusivity programs can provide some guidance. Pediatric exclusivity is widely considered a successful program,[201] and there are public policy parallels with an exclusivity program to drive creation of more sustainable drugs. Pediatric exclusivity was designed to "hold out an extremely attractive carrot for research that would not otherwise be done."[202] And it has been argued that opportunities to better understand use of a drug in children should

196. Eisenberg, *supra* note 141, at 171–72.

197. *See* Myoung Cha & Flora Yu, *Pharma's First to Market Advantage*, MCKINSEY & COMPANY (Sept. 2014), https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharmas-first-to-market-advantage.

198. *Id.*

199. *Id.*

200. Whereas for pediatric drug exclusivity, only completion of clinical trials is required.

201. Arron S. Kesselheim et al., *Six-Month Market Exclusivity Extensions to Promote Research Offer Substantial Returns for Many Drug Makers*, 36 HEALTH AFF. 362, 362 (2017).

202. Sarah Karlin-Smith, *How Trump's HHS Nominee's Drug Company 'Gamed' a Patent*, POLITICO (Jan. 8, 2017, 5:00 AM), https://www.politico.com/story/2018/01/08/trump-azar-patent-drug-company-268942 (quoting University of Missouri law professor, Erika Lietzan).

not be overlooked simply because the underlying drug already has high sales.[203] However, pediatric exclusivity incentives can be inefficient with drug companies focusing their efforts on high revenue drugs over drugs important to children and older drugs with less remaining patent protection over newer drugs.[204] With incentives for sustainable drug development, the FDA would need to avoid these pitfalls and ensure incentives are only provided where the environmental benefit justifies the cost to the consuming public and initial development of sustainable NCEs is prioritized over modifying existing drugs.[205]

The Orphan Drug Act can provide insight into how the length of exclusivity might be determined. As would be expected, small molecule orphan drugs have significantly less generic competition than other small molecule drugs, in part because of seven-year exclusivity.[206] A 2017 study of a limited number of small molecule orphan drugs showed that an additional six months of exclusivity would have resulted in a median net benefit to cost ratio of 1.6 to 1.0.[207] At the same time, the overall return on investment in the pharmaceutical industry has dropped from 10.1% in 2010 to a projected 3.2% in 2017.[208] While these two calculations cannot be compared directly, they do suggest that six additional months of orphan drug protection would be very generous to the pharmaceutical industry.[209] Similar analyses would be possible for development of sustainable drugs allowing a balancing of additional profits with public policy interests. A thoughtful program of market exclusivity that provides a positive but not excessive return to pharmaceutical companies is likely a bargain compared to an attempt to take residue of the environmentally unsustainable drugs out of the environment.[210]

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203. Erika Lietzan, *Pediatric Exclusivity 101*, OBJECTIVE INTENT (Mar. 3, 2018), https://objectiveintent.blog/2018/03/03/pediatric-exclusivity-101/.

204. Mary K. Olsen & Nina Yin, *Examining Firm Responses to R&D Policy: An Analysis of Pediatric Exclusivity*, 4 AM. J. HEALTH ECON. 321, 321 (2018).

205. *See id.* at 324. Modification of existing drugs with patent protection or other exclusivity would, however, have to be a priority at the beginning of the program.

206. Nicholas Bagley et al., *It's Time to Reform the Orphan Drug Act*, NEJM CATALYST (Dec. 19, 2018), https://catalyst.nejm.org/time-reform-orphan-drug-act/.

207. Kesselheim et al., *supra* note 201, at 366. Biological products (Cetuximab, Adalimumab, Bevacizumab, Rituximab, and Trastuzumab) were removed from the calculations by the author.

208. Nuala Moran, *ROI Continues to Decline for Top Pharma Firms: Deloitte*, BIOWORLD, http://www.bioworld.com/content/roi-continues-decline-top-pharma-firms-deloitte (last visited Nov. 10, 2019).

209. *Cf.* Kesselheim et al., *supra* note 201, at 369 (noting a similar finding for rare diseases).

210. *Cf.* Scott, *supra* note 44, at 24–25 (noting market exclusivity would likely be less expensive).

Incentives for environmental sustainability bring a number of additional issues that would have to be considered as part of any regulatory scheme to encourage more such drugs. For example, the FDA would not be able to approve potential future drugs relying on the same underlying API when an environmentally sustainable version has been approved since it would negate at least part of the environmental advantage. There would also have to be an enhanced approach to the pharmaceutical EA, including assessment of longer-term environmental impacts and more rigorous sustainability requirements. One might even imagine a labeling scheme for all drugs to show which are environmentally sustainable (a black box type warning, or, in a more positive vein, a green box that shows the environmental sustainability of the drug).[211]

2. Generics

Any effective program to improve the sustainability of pharmaceuticals would have to include generics. While incentivizing environmentally sustainable NCEs would be an excellent start, the vast majority, almost 90%, of prescription drugs are generic.[212] Some of the most prescribed pharmaceuticals have been in use for decades because of their overall safety and efficacy.[213] Use of generics is expected to continue to be high.[214]

In addition to the expected long-term use of many generic products, there are other more subtle forces potentially driving the use of environmentally unsustainable generics. Take antibiotics as an example. Despite decades of warnings about overuse causing resistance,[215] antibiotics (the vast majority of which are generic) continue to be

211. There is already such a program in Sweden. STOCKHOLMS IÄNS IANDSTING, ENVIRONMENTALLY CLASSIFIED PHARMACEUTICALS 1–6 (2014).

212. Klinger, *supra* note 180.

213. For example, the antidepressant fluoxetine was introduced in 1987, and the generic was approved in 2001. Cynthia A. Mascarenas & Lisa M. Mican, *Is Prozac More Effective than Generic Fluoxetine?*, 1 CURRENT PSYCHIATRY 50, 50 (2002). There were almost twenty-four million prescriptions written in the United States for fluoxetine in 2016. *See Fluoxetine Hydrochloride Drug Usage Statistics, United States, 2006-2016*, CLINCALC.COM, https://clincalc.com/DrugStats/Drugs/FluoxetineHydrochloride (last visited Nov. 10, 2019).

214. *See* Norman E. Sharpless, *Statement on Continued Progress Enhancing Patient Access to High-Quality, Low-Cost Generic Drugs*, U.S. FOOD & DRUG ADMIN. (Oct. 16, 2019), https://www.fda.gov/news-events/press-announcements/statement-continued-progress-enhancing-patient-access-high-quality-low-cost-generic-drugs.

215. C. Lee Ventola, *The Antibiotic Resistance Crisis*, 40 PHARMACY & THERAPEUTICS 277, 278 (2015).

prescribed at high rates in the United States.[216] And the increased use of biologics (which generally have sustainable environmental profiles) may also result in increases in antibiotic use because biologics often suppress the immune system, causing increased risk of infection.[217]

While incentivizing improvements to existing non-sustainable generic drugs would be critical to a successful program to reduce harmful PIE, it would also be very challenging. Generics, by design, have no patent or marketing exclusivity (except for a relatively short period of time)[218] and the cost structure of the generics industry does not support significant research.[219] FDA defines a generic as a drug that is marketed after patent and exclusivity protection ends, or the patent owner waives its rights, and FDA requirements are met.[220] The FDA requires that a generic drug have the same API(s), as well as the same route of administration, dosage form, strength, conditions of use, and inactive ingredients already approved in the original NDA.[221] The generic must also be equivalent to the branded product by other measures.[222]

The generics market is quite different from the innovative pharmaceutical market, even though innovator and generic products (containing the same API) are almost identical. Generic drugs are significantly less expensive than branded pharmaceuticals.[223] When

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216. *Trends in U.S. Antibiotic Use, 2018*, PEW (Aug. 1, 2018), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2018/08/trends-in-us-antibiotic-use-2018.

217. *See* Susan Berger, *Biologics Are Revolutionizing Care for Some Diseases but They Are Very Costly*, WASH. POST (Mar. 16, 2015), https://www.washingtonpost.com/national/health-science/biologics-are-revolutionizing-care-for-some-diseases-but-they-are-very-costly/2015/03/16/1ffe46b6-b6ed-11e4-9423f3d0a1ec335c_story.html?utm_term=.52286b78cc5c. *See generally* Nick Voulvoulis et al., *Pharmaceutical Residue in Sewage Treatment Works and Their Fate in the Receiving Environment*, *in* 41 PHARMACEUTICALS IN THE ENVIRONMENT 120, 151, 153 (R.E. Hester & R.M. Harrison eds. 2016) (explaining that some APIs are stable in typical environmental conditions (e.g. the antibiotic ciprofloxacin) and, things being equal, will likely stay in the environment for long periods of time). Other APIs degrade but are replaced quickly enough in the environment that their presence remains constant or is increasing (e.g. the anti-inflammatory ibuprofen). And still others are not found in appreciable quantities in the environment (e.g. many biologics). *Id.*

218. The Hatch Waxman Act provides a financial incentive—180 days with protection from other generic competition—for companies that challenge weak drug patents. 21 U.S.C. § 355(j)(5)(B)(iv) (2018).

219. *See Generic Drug Facts*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm167991.htm (last updated June 1, 2018).

220. *Id.*

221. *Id.*

222. *Id.*

223. Ranit Mishori, *Why Are Generic Drugs Cheaper than Brand-Name Ones?*, WASH. POST (July 11, 2011), https://www.washingtonpost.com/national/health-science/why-are-generic-drugs-cheaper-than-brand-name-ones/2011/07/05/gIQAwZdL9H_story.html?utm_term=.614f29d9653d.

patents expire on branded pharmaceuticals, generic manufacturers of that same product can enter the market. The prices of generics are lower, since there is no innovation cost to recoup, resulting in savings estimated at $1.8 trillion dollars in the United States over the past ten years.[224] Additionally, generic company profit margins have been estimated to be 10% lower than those of research-driven pharmaceutical companies.[225] In other words, generics are 89% of prescription drug sales but only 27% of drug costs.[226]

Development of an environmentally sustainable generic drug creates little opportunity for incentivization. Additional research, and the associated funding, would be required (similar to an NCE). But there would be no likelihood of new marketing claims unless consumers became very environmentally conscious and willing to pay a premium for a green generic product, an unlikely prospect. This challenge is exacerbated by a general lack of innovative research in the generic industry since the typical business model is one of using another company's innovation to drive high volume sales at a significantly lower unit price.[227]

There would also be questions as to whether a modified generic drug product would be patentable or have any rights to marketing exclusivity. Questions might be based on obviousness[228] or the prodrug patent strategy of the original filer,[229] among others. Of course, a novel delivery method or biodegradation trigger would likely receive a patent which could be licensed. But in most instances these issues are not on point since there is no market in which to recoup the research investment, even

224. *See* William B. Schultz & Margaret M. Dotzel, *Don't Enact a Law that Diminishes the Incentive for Generic Companies to Challenge Patents*, THE HILL (Mar. 20, 2019), https://thehill.com/blogs/congress-blog/healthcare/434896-dont-enact-a-law-that-diminishes-the-incentive-for-generic.

225. Neeraj Sood, *Follow the Money: The Flow of Funds in the Pharmaceutical Distribution System*, USC SCHAEFFER CTR. 18, https://www.brookings.edu/wp-content/uploads/2017/05/paper-1-sood-brand-rx-transparency.pdf (last visited Feb. 5, 2019).

226. Eric Sagonowsky, *The Top 15 Generic Drugmakers by 2016 Revenue*, FIERCEPHARMA (May 16, 2017), https://www.fiercepharma.com/special-report/top-15-generic-drugmakers-2016.

227. *See* Mishori, *supra* note 223. The firms developing a more sustainable generic drug or the technology to create one would not, of course, have to be generic manufacturers.

228. For example, would a biodegradable version of a drug be surprising or advantageous?

229. A prodrug is a compound that metabolizes into a drug in the body. "[U]nder a broad reading of *Schering [Corporation v. Geneva Pharmaceuticals, Inc.]*, a company seeking to invalidate a competitor's patent on some compound will only need to show that the compound is produced or is capable of being produced via the metabolic breakdown of some other prior art compound." Randy P. Boyer, Schering Corporation v. Geneva Pharmaceuticals, Inc.*: Requiem for the Recognition Requirement in the Law of Inherent Anticipation*, 14 FED. CIR. B.J. 677, 693 n.123, 695 (2004/2005).

if a patent and/or exclusivity was acquired. The generic market is premised on using another's innovation to achieve a low sales price. Additionally, of course, there would be risk. Many millions of dollars would be spent on unsuccessful efforts and any new clinical trial on an existing product brings significant concerns of unexpected safety outcomes.[230]

A priority review voucher ("PRV") incentive appears to be a good fit.[231] But while PRVs might provide an incentive for developing a sustainable version of a generic drug,[232] they would have to be accompanied by a mechanism to ensure that the remaining non-sustainable versions of the product were removed from sale. Otherwise, the cost of the incentive would not be justified. Unlike an NCE with patent or marketing protection (and only one manufacturer), a generic API is often made by many companies.[233]

But removing all of the competition would defeat the purpose of generic drugs. To prevent this, a sharing mechanism (e.g. compulsory licensing[234] or FRAND-like agreements)[235] would almost certainly be required in exchange for the PRV. This would allow access to the new product (or process) by all of the approved manufacturers at a reasonable price, ensuring continued competition while achieving the desired environmental results.

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230. *See* Thayer, *supra* note 166, at 16–17.

231. The PRV would be an alternative to increased sales or a longer exclusivity period, as it is for developing a drug for a neglected tropical disease or a rare pediatric disease.

232. The value of vouchers has been declining in the market and may continue to decline as they become more common. *See* Ned Pagliarulo, *Latest PRV Sale Further Evidence of Sliding Value*, BIOPHARMADIVE (Aug. 2, 2018), https://www.biopharmadive.com/news/ultragenyx-prv-sale-value-regulation-fast-pass/529221/. However, $100 million or so could still fund a lot of research with some profit left over.

233. For example, there are at least twenty-three FDA-approved manufacturers of metformin and fourteen FDA-approved manufacturers of fluoxetine. *Generic Glucophage Availability*, DRUGS.COM, https://www.drugs.com/availability/generic-glucophage.html (last visited Nov. 11 2019); *Generic Prozac Availability*, DRUGS.COM, https://www.drugs.com/availability/generic-prozac.html (Nov. 11, 2019).

234. Compulsory licensing, which allows governments to make an exception to the exclusivity of intellectual property when there is an overriding public interest, might be an option if any patent protection (or, if not, perhaps regulatory exclusivity) attaches to the more sustainable pharmaceutical. Jon Matthews, *Renewing Health Competition: Compulsory Licenses and Why Abuses of the TRIPS Articles 31 Standards Are Most Damaging to the United States*, 4 J. BUS. ENTREPRENEURSHIP & L. 119, 124 (2010).

235. FRAND are fair, reasonable, and non-discriminatory license terms. The concept was developed by standards-setting organizations to ensure, through by-laws or agreement, that any intellectual property embedded in a standard would be shared under FRAND terms to the organization's members. Jeffrey I.D. Lewis, *What Is FRAND All About? The Licensing of Patents Essential to an Accepted Standard*, CARDOZO L., 1–3 (2016), https://cardozo.yu.edu/sites/default/files/Lewis.WhatIsFrandAllAbout.pdf.

Compulsory licenses authorize a third party to make, use or sell a patent without the consent of the patent holder.[236] Although the use of compulsory licenses is controversial,[237] United States law allows it in a variety of situations.[238] Under international law, the issuance of compulsory licenses is allowed as long as there is "adequate remuneration."[239] Although the general view is that compulsory licensing hurts innovation, this is not always the case.[240] It seems likely when the incentive (here the PRV) is not affected by the forced license, companies would still be motivated to develop environmentally sustainable generics.

While a compulsory license is forced by the state in the public good, a FRAND license is a voluntary commitment by the license holder to negotiate fair, reasonable, and non-discriminatory terms.[241] FRAND agreements are frequently associated with information technology where access to multiple patents held by others is often required to achieve interoperability of products.[242] This need for interoperability has led to creation of industry standards, where the technology selected for the standard, as a condition of that selection, must make the technology available to others through FRAND licenses.[243] Similarly, the technology required to make a sustainable pharmaceutical might be considered a standard (of environmental acceptability), and as such, a requirement to provide a FRAND license to other generic manufacturers of the same API could be a condition of getting FDA approval for the product.

236. Colleen Chen, *Cheap Drugs at What Price to Innovation: Does the Compulsory Licensing of Pharmaceuticals Hurt Innovation?*, 18 BERKELEY TECH. L.J. 853, 855 (2003).

237. *Id.* at 858.

238. Under 28 U.S.C. § 1498 (2012), the United States government or those authorized by the government can use or manufacture without a license as long as the patent holder is compensated. The Bayh-Dole Act, the CAA, and other laws allow the government to compel a license when federal funds are used for underlying research. *See* 35 U.S.C. § 200 (2012); 42 U.S.C. § 7608 (2012); *see also* Mark W. Lauroesch, *General Compulsory Patent Licensing in the United States: Good in Theory, but Not Necessary in Practice*, 6 SANTA CLARA HIGH TECH. L.J. 41, 46, 54–55 (1990) (providing examples of compulsory licensing).

239. Agreement on Trade-Related Aspects of Intellectual Property Rights art. 31, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299.

240. *See, e.g.*, U.S. INT'L TRADE COMM'N, TRADE, INVESTMENT AND INDUSTRIAL POLICIES IN INDIA: EFFECTS OF THE US ECONOMY 151 (2014), http://www.usitc.gov/publications/332/pub4501_2.pdf.

241. Srividhya Ragavan et al., *FRAND v. Compulsory Licensing: The Lesser of the Two Evils*, 14 DUKE L. & TECH. REV. 83, 84 (2015).

242. *Id.* at 85–86.

243. *Id.* at 86–87.

CONCLUSION

PIE is a growing concern, especially as it relates to the urgent human health problem of antibiotic resistance. It is also a highly complex issue with many causes and uncertain outcomes.

This complexity is driving inaction, although scientists continue to explore PIE's causes and outcomes and attempt to quantify the risk to humans and ecological receptors. United States environmental regulations are unsuited to dealing with emerging environmental issues of significant complexity (e.g. global warming). Environmental laws are reactive and generally require a high level of certainty about harm before any corrective action is taken.

While scientists around the world are looking into the causes and outcomes of PIE, and some are researching answers, additional resources are needed to find solutions. Many, if not most, of people who have the knowledge to innovative solutions to the problems created by PIE work in the pharmaceutical industry itself. It just makes sense to get them involved.

In the United States, the driver of innovation for the public good has been the incentives created by the intellectual property system. Assuming technical solutions are possible, which they likely are, sustainable NCEs can certainly be incentivized through patents and regulatory exclusivity. Sustainable generics might also be incentivized with PRVs but widespread implementation would be complicated and require more than the invention of the sustainable product.

While making more pharmaceuticals sustainable will not alone solve the environmental and human health issues caused by PIE, sustainable pharmaceuticals are likely achievable and providing incentives for their creation is within the power of Congress and regulatory agencies. The ideas in this Note, and the ideas of others, should be investigated and, if feasible, implemented to stem the PIE tide.