that only target bacteria. Phage therapy uses speci c phages to ght infection-causing bacteria.

Historically, many medical advances including antibiotics have originated in the United States and other Western countries. This can be attributed to institutions and

2 Literature Review

during the Progressive Era (Gabriel 2010; Valuck et al. 1992). Wiebe (1967) viewed Progressive Era regulations as an attempt to stabilize society and mitigate change in the face of rapid development. Pharmaceutical regulation during this time often did not adequately address the real public health problems in the pharmaceutical industry (Cassedy 1964; Friedman and Friedman 1980). Viewing the paradigm of pharmaceutical regulation in this light helps explain why it has proven ill-equipped to combat antibiotic resistance, as section 3 shows.

been the thrust of most recent economic research on antibiotic resistance, which has largely ignored institutional incentives and alternative therapies. In discussing the future of phage therapy, Anomaly (2020) notes that the value of phages may be a public good that the market underprovides, just like antibiotics. This is an artifact of the regulatory regime governing this market for pharmaceuticals, so it is to some degree a government failure as well as a market failure. There is little potential for a private solution of the sort articulated by Ostrom (1990) when government failure is the problem.

problems with resistant infections, including tuberculosis, prompting successful e orts to reduce their use (Schoenmakers 2020). Focusing on the United States, Adda (2020) casts doubt on whether agricultural use is a problem, showing that use of antibiotic use in humans is more closely linked to resistant bacterial infections in humans. Alarmingly, he also showed that resistant infections are most sensitive to the newest antibiotic drugs, which are often variations on existing drugs. Regardless of who is right, resistant strains of bacteria are on the rise and antibiotic use more generally is a major contributing factor.

The proximate cause of antimicrobial resistance is antibiotic overuse, but the ultimate cause is the institutional structure governing the pharmaceutical industry. In very broad terms, the critical problem with existing pharmaceutical regulation and the IP regime is that they do not encourage the use or development of antimicrobial therapies that take into account organic evolution. They encourage the use of inorganic antibiotics, the e cacy of which is a nonrenewable resource. Worsening the problem, they have not encouraged development of new antibiotics and discouraged the use of antimicrobial therapies that take organic evolution into account. Wiebe's 1967 view of Progressive Era regulation as a stabilizing, though not necessarily e ciency-enhancing, force is relevant here.

3.2 Pharmaceutical Regulation

Ine ciencies of the drug approval process, and of the FDA in general, have been well documented, so this section provides only a brief overview with relevance for phage therapy. Obtaining FDA approval to market a new drug is a time-consuming and expensive process. Costs are easily in the millions of dollars and can exceed one billion.

nal marketing approval from the FDA exhausts most of the patent term. A set of FDA regulations grants market exclusivity to the developing term beyond the patent length (Feldman 2016). The function of a patent is mostly to preserve exclusivity during the development phase, after which FDA exclusivity regulations are what matter.

High costs of development and regulatory approval make IPRs and FDA exclusivity regulations necessary for drug development. However, the size of the pro t stream is highly dependent on the type of drug produced. Chronic conditions like cancer and heart disease that require ongoing treatments have received much attention. Vaccines and antibiotics have received far less. This could be due to the threat of compulsory licensing in foreign countries that lack strong IPRs. Alternatively, it could simply result from the high costs of drug development that discourage production of something that only needs to be taken once or occasionally. The most recent high pro le vaccines, those that prevent COVID-19 infection, are protected by IPRs as of the time this paper was written, but they were developed with large government subsidies and purchase commitments. Many countries pleaded for IPRs to be waived.

3.5 Why Can't We Easily End State Involvement?

Governments in developed countries are involved in the production, regulation, and marketing of new drugs. The desirability of this may be questioned, however ending it is a political non-starter. Setting aside arguments about the history of unsafe medicines before government regulation, which may or may not be well-founded, existing institutional structures will impede the development of new, safe, and e ective drugs. This section discusses these issues, reaching the conclusion that state involvement in drug regulation cannot easily be ended.

3.5.1 Perfect Information

Elementary models of e cient free markets assume that buyers and sellers both have perfect information. Lack of perfect information is a source of market failure. In the absence of drug patents and FDA regulation, both of which require disclosure of information, consumers will not have perfect information. If there were no IP or FDA disclosures, the only logical way to maintain pro tability is through trade secrets.

Trade secrets are widely used in other sectors, but their use in pharmaceuticals is mostly limited to production processes, not the nature of active ingredients.

Trade secrets were widely used in the pharmaceutical industry before regulation, and many dangerous substances were marketed during this time. This was a major impetus for regulation and for the medical community to embrace drug patents, which it had previously derided as contrary to medical ethics (Gabriel 2014). A return to trade secrets instead of patents and regulation could mean a return to these days. It is already unreasonable to expect ordinary consumers to know enough biological science to judge whether a substance should be taken. Doctors are expected to know these things but if they do not know what a medicine contains, they cannot make these judgments.

3.5.2 The Role of Tort Law

Friedman's argument that the FDA is unnecessary because drug makers know it is not pro table to poison consumers is intuitive, yet countered by historical examples of unsafe drugs (Gabriel 2014). His argument that it sti es the development of new drugs had considerable merit. However, it need not follow that abolishing the FDA would necessarily stimulate rapid new drug development or lead to the rapid adoption of phage therapy. Other incentives can prevent the development and marketing of potentially useful drugs.

Tort law is a major part of the incentive not to do harmful things { not only will a business lose customers, it could face substantial penalties for negligence or overtly harmful products. Tort claims in medicine, along with malpractice insurance premiums, can be exorbitant (Viscusi and Born 2005). Without FDA approval, and especially without full disclosure of substances, malpractice claims and insurance premiums would likely increase markedly. There is a real possibility that the threat of judgment could deter investment in drugs in the absence of FDA regulation. Moreover, FDA approval does not always grant a drug manufacturer immunity from tort claims (Field 2009). If private organizations took over the role of vetting drugs, the threat of tort liability still exists and, if anything, is magni ed. The FDA has sovereign immunity from judgment, which these private organizations will lack. Drug certi cation organizations will join drug makers and doctors as yet another entity subject to judgment,

further increasing the deterrent e ect of tort liability.

Nothing in this section should be taken as a rejection of arguments against the FDA and pharmaceutical IP; both have contributed to the crisis of antibiotic resistance. I present tort law and information issues simply to show that abolishing the FDA and drug patents may not lead to the desired circumstances that both the FDA and drug patents proximately prevent.

4 Bacteriophage Therapy

Phages are viruses that infect and kill bacteria, but not other organisms. There are estimated to be 10^{31} phages on earth, making them more abundant than any other type of organism, including bacteria (Comeau et al. 2008). Phages are highly speci c, meaning that each phage kills only a very small range of bacteria, although any type of bacteria may be susceptible to a vast number of phages. Antibiotics, in contrast, are broad-spectrum and a ect all bacteria that are not resistant, including bene cial bacteria in the human gut microbiome. Phages exist that target infectious but not bene cial bacteria (Loc-Carrillo and Abedon 2011; Principi et al. 2019). Antibiotics can be thought of as a macroeconomic policy like altering interest rates, and phages in contrast being analogous to nely targeted micro interventions.

Phages were discovered by English researcher Frederick Twort in 1915 and French microbiologist Felix d'Herelle in 1917. D'Herelle experimented with phages for treating infections. Like many new treatments, phage therapy was controversial, although it was used in France and d'Herelle came to the United States for more research. Antibiotics were developed shortly thereafter and, because they were broad spectrum, they attracted far more attention than highly speci c phages. In 1934, d'Herelle co-founded the Eliava Institute in Tbilisi with Georgian colleage George Eliava. This was in part due to the lack of enthusiasm in the West for phage therapy and the need for infections to be treated in the Soviet Union, which had limited access to Western pharmaceuticals. After the Second World War, the tensions of the Cold War dampened any interest in phage therapy in the West (Summers 2012).

As living organisms, phages evolve alongside bacteria, unlike antibiotics. Phages found in nature can be isolated, cultured, and administered to a patient to cure bac-

terial infections. This is the practice of phage therapy (Lin et al. 2017). Bacteria can evolve resistance to phages, but the vast availability of evolving phages means that untreatable infections are unlikely to develop. Continual reformulation of treatments, however, is necessary to provide the most up-to-date treatments. Producing phage therapeutic treatments is straightforward and low-cost. Importantly, because resistance mechanisms di er, resistance to phages or antibiotics never implies resistance to the other (Loc-Carrillo and Abedon 2011).

Phage therapy requires ongoing research. Some phages can have muted e ects or possibly reprogram bacteria to have antibiotic resistance, thus being counterproductive. These phages have a lysogenic cycle. In contrast, phages with a lytic life cycle rapidly kill target bacteria, but there is still a risk of horizontal gene transfer that could lead to antibiotic resistance (Anomaly 2020).

5 Model

This section describes a regulatory model that will support phage therapy. It rst describe the needed attributes of a system, and then presents speci c details about intellectual property, reporting and practices, and pharmaceutical regulation.

5.1 Needed Attributes

To promote the use of phage therapy, a regulatory system must be exible enough to permit the updating of therapeutics as phages and bacteria evolve. Related to this, it must encourage optimal use, which the current antibiotic-based approach does not. Lastly, the interaction between regulation and IP must not prevent the use of phages.

5.1.1 Evolutionary Stability

Phages are not a silver bullet to instantly and permanently cure bacterial infections. Bacteria can develop resistance to phages as well as antibiotics. Developing resistance to phages can have tness costs to the bacteria, possibly bene ting the host by making antibiotics more e ective (Oechslin 2018). Discovery e orts to nd new phages must be ongoing, but this should be possible because phages mutate and evolve. Only

with continual development that respects the evolutionary tendencies of bacteria and

ing safety, especially because cocktails must be regularly updated and reformulated. One example of how such a standard could work is a requirement for in vitro tests of new cocktails, which could then permit limited in vivo trials (with patient informed consent), after which safe harbor for general use would be established. Rules for establishing safe harbor should focus on safety, not efficacy because new strains of bacteria could be discovered and a seemingly useless but safe phage could eventually find use. To establish safe harbor, physicians and cocktail manufacturing firms have a strong incentive to record all relevant data and report it to a repository. To promote competition among repository organizations, a rule requiring doctors to report to at least two or three independent repositories could be beneficial.

5.4 Antibiotic Regulation

Insofar as excessive use of antibiotics is a proximate cause of antimicrobial resistance, this overuse must be curtailed to prevent potentially deadly consequences. As promising as phage therapy is, one cannot rule out the possibility of a biological disaster that could necessitate the use of broad spectrum antibiotics. Curtailing overuse of antibiotics means limiting their use in humans and sharply curtailing prophylactic use in agriculture and aquaculture.

For humans, phage therapy should be treated as a first-use option, not a last resort. One approach would be to prohibit the use of antibiotics if cocktails of known phages prove ineffective. Doctors would ultimately have discretion, but their use of phage therapy and antibiotics would be reported to information repositories.

Prophylactic use of antibiotics maintains the health of livestock. Not using cheap antibiotics will raise the cost of meat, milk, and eggs because livestock conditions will have to be improved so bacteria will breed less. The cost of maintaining the health of livestock will fall on the consumer in monetary terms. Continuing the prophylactic use of antibiotics also imposes a cost. This cost is to more people than just the consumer, and it is borne in the form of antimicrobial resistance which can threaten populations of humans and animals with disease. Whether prophylactic use of antibiotics is permitted or proscribed, a cost is imposed. To the extent that antimicrobial resistance is viewed as a serious threat, this prophylactic use should be prohibited or sharply curtailed.

Conly, J. and B. Johnston (2005). Where are all the new antibiotics? The new antibiotic paradox. *Canadian Journal of Infectious Diseases and Medical Microbiology 16*(3), 159{160.

DiMasi, J. A., H. G. Grabowski, and R. W. Hansen (2020, 5). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics 47*, 20{33.

DiMasi, J. A., R. W. Hansen, and H. G. Grabowski (2003, 3). The price of innovation: New estimates of drug development costs. *Journal of Health Economics 22*(2), 151{185.

Eswaran, M. and N. Gallini (2019, 3). Can competition and patent policies avert the antibiotic crisis? *Canadian Public Policy 45*(1), 74{92.

Feldman, R. (2016). Regulatory property: The new IP. *Columbia Journal of Law and the Arts 40*(1), 53{104.

Field, R. I. (2009). When can patients sue drug companies? *Pharmacy and Therapeutics 34*(5), 243{244.

Food and D. Administration (2020, 9). FDA's critical role in ensuring supply of in uenza vaccine. https://www.fda.gov/consumers/consumer-updates/fdas-critical-role-ensuring-supply-in uenza-vaccine, accessed 27 May 2021.

Friedman, M. and R. Friedman (1980). *Free to Choose: A Personal Statement*. New York: Harcourt.

Furfaro, L. L., M. S. Payne, and B. J. Chang (2018, 10). Bacteriophage therapy: Clinical trials and regulatory hurdles. *Frontiers in Cellular and Infection Microbiology 8*(376), 376.

Gabriel, J. M. (2010). Restricting the sale of `deadly poisons': Pharmacists, drug regulation, and narratives of su ering in the Gilded Age. *Journal of the Gilded Age and Progressive Era 9*(3), 313{336.

Gabriel, J. M. (2014). *Medical Monopoly: Intellectual Property Rights and the Origins of the Modern Pharmaceutical Industry*. Chicago: University of Chicago Press.

Gallini, N. M. (2017). Do patents work? Thickets, trolls, and antibiotic resistance. *Canadian Journal of Economics 50* (4), 893{926.

Geiringer, D. H. and S. Peltzman (1973). The bene ts and costs of new drug regulation. In R. L. Landau (Ed.), *Regulating New Drugs*, pp. 114{211. Chicago: University of Chicago Press.

Grose, J. H. and S. R. Casjens (2014, 11). Understanding the enormous diversity of bacteriophages: The tailed phages that infect the bacterial family *enterobacteriaceae*. *Virology 468{470*, 421{443.

Kowalska, J. D., J. Kazimierczak, P. Sowinska, E. A. Wojcik, A. K. Siwicki, and J. Dastych (2020). Growing trend of ghting infections in aquaculture environment { opportunities and challenges of phage therapy. *Antibiotics 9* (6), 301{317.

Kutateladze, M. (2015, 2). Experience of the Eliava Institute in bacteriophage therapy. *Virology Sinica 30* (1), 80{81.

Kutter, E., D. De Vos, G. Gvsalia, Z. Alivadze, L. Gogokhia, S. Kuhl, and S. T. Abedon (2010). Phage therapy in clinical practice. *Current Pharmaceutical Biotechnology 11* (1), 69{86.

Laxminarayan, R. and G. M. Brown (2001, 9). Economics of antibiotic resistance: A theory of optimal use. *Journal of Environmental Economics and Management 42* (2), 183{206.

Lin, D., B. Koskella, and H. C. Lin (2017, 8). Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World Journal of Gastrointestinal Pharmacology 8* (3), 162{173.

Loc-Carrillo, C. and S. T. Abedon (2011). Pros and cons of phage therapy. *Bacteriophage 1* (2), 111{114.

Luepka, K. H., K. J. Suda, H. Boucher, R. L. Russo, M. W. Bonney, T. D. Hunt, and J. F. Mohr III (2017, 1). Past, present, and future of antibacterial economics: Increasing bacterial resistance, limited antibiotic pipeline, and societal implications. *Pharmacotherapy 37* (1), 71{84.

Oechslin, F. (2018). Resistance development to bacteriophages during bacteriophage therapy. *Viruses 10* (7), 351{372.

Ostrom, E. (1990). *Governing the Commons: The Evolution of Institutions for Collective Action*. Cambridge: Cambridge University Press.

Verberken, G., J.-P. Pirnay, R. Lavigne, S. Jennes, D. De Vos, M. Casteels, and I. Huys (2014). Call for a dedicated European legal framework for bacteriophage therapy. *Archivum Immunologiae Et Therapie Experimentalis 62* (2), 117{129.

Viscusi, W. K. and P. H. Born (2005). Damages caps, insurability, and the performance of medical malpractice insurance. *Journal of Risk and Insurance 72* (1), 23{43.

Wiebe, R. H. (1967). *The Search for Order: 1877{1920*. New York: Hill and Wang.