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Microscopic Allies: Examining and Tackling Legal and Regulatory Barriers to the Development of Phage Therapy

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MICROSCOPIC ALLIES: EXAMINING AND TACKLING LEGAL AND REGULATORY BARRIERS TO THE DEVELOPMENT OF PHAGE THERAPY

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INTRODUCTION

In the course of discussing environmental law and policy, the relationship between human beings and the microenvironment—the ever-present microscopic realm encompassing the ecology and habitat conditions of microbial organisms such as bacteria, protozoa, and viruses—is often overlooked.[1] Nonetheless, human activities have a definite and significant impact on the microenvironment, which often leads to repercussions that influence our health, economy, and quality of life.[2] One way law and policy impact the microenvironment is through the regulations placed on medicine aimed at combating disease-causing or otherwise harmful microorganisms.[3] Of particular note are our current policies regarding antibiotic medicine.

In the United States and wider Western world, traditional penicillin-derived antibiotics have long been the medicine of choice when dealing with bacterial infections and diseases.[4] However, due to the overuse and misuse of antibiotics, many disease-causing microbes are evolving to resist antimicrobial medicines, posing a problem for the medical community and society at large.[5] One possible solution to this problem is the development of phage therapy.[6] A technique developed in the Soviet Union,

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[1] *See* Charles Cockell, *Environmental Ethics and Size*, 13(1) ETHICS AND THE ENVIRONMENT 23 (2008).

[2] Charles S. Cockell & Harriet L. Jones, *Advancing the case for microbial conservation*, 43(4) ORYX 520, 520–21 (2009).

[3] *See id.* at 521.

[4] Donna Duckworth & Paul Gulig, *Bacteriophages: Potential treatment for bacterial infections*, 16(1) BIODRUGS 57, 58 (2002).

[5] C. Lee Ventola, *The Antibiotic Resistance Crisis Part 1: Causes and Threats*, 40(4) PHARMACY & THERAPEUTICS 277, 277–78 (2015).

[6] Duckworth & Gulig, *supra* note 4, at 57–58.

phage therapy involves the use of bacteriophages—viruses which prey exclusively on bacteria—to treat bacterial infections.[7] This method of treatment has many advantages: bacteriophages are plentiful and evolve faster than the bacteria they prey upon, making any bacteria unlikely to develop an immunity to such treatment, and produce few negative side effects.[8] However, with few exceptions, phage therapy is not approved for use in humans in Western countries,[9] and only three U.S. states currently allow its limited use.[10] Additionally, funding for phage therapy research and clinical trials is insufficient and difficult to obtain since the patentability of bacteriophage products—a complex and lengthy process to begin with—has recently been called into question.[11] Researchers have even commented that the largest hurdle to developing phage therapy is regulatory.[12]

In this Note, I argue that the current regulatory scheme enforced by the United States Food and Drug Administration ("FDA") hinders the useful research and development of bacteriophage medicine, a technology that is sorely needed to better promote a healthy and sustainable microenvironment. Thus, the pertinent FDA regulations must be amended in order to accommodate and promote the greater exploitation of bacteriophage products for medical use in humans. In order to determine what such an amendment might look like, I will examine the federal laws and FDA policies that prove to be such a hurdle to the development of phage therapy.

I will also examine the policies of three U.S. states that allow the use of phage therapy—Washington, Oregon, and Texas—to see what the experiences of these states might teach. Furthermore, I argue that more

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[7] *Id.*

[8] Sara Reardon, *Phage therapy gets revitalized*, 510 NATURE 15, 15–16 (June 5, 2014), http://www.nature.com/news/phage-therapy-gets-revitalized-1.15348 [https://perma.cc/LX5Z-RWYG].

[9] Callum Cooper et al., *Adapting Drug Approval Pathways for Bacteriophage-Based Therapeutics*, 7(1209) FRONTIERS OF MICROBIOLOGY, at 1 (2016).

[10] Doris Faltys, *Evergreen Researcher Dr. Kutter Announces 'There's a Phage for That'*, THURSTON TALK (Aug. 3, 2013), http://www.thurstontalk.com/2013/08/04/evergreen-researcher-dr-kutter-announces-theres-a-phage-for-that/ [https://perma.cc/4HRH-LZRP] (noting that Oregon and Washington allow naturopaths to use phage therapy); ANNA KUCHMENT, THE FORGOTTEN CURE: THE PAST AND FUTURE OF PHAGE THERAPY 115–18 (2011) (noting Texas allows licensed physicians to use Phage Therapy).

[11] Vincent Fischetti et al., *Reinventing phage therapy: are the parts greater than the sum?*, 24(12) NATURE BIOTECHNOLOGY 1508, 1509 (2006).

[12] Isabelle Huys et al., *Paving a regulatory pathway for phage therapy*, EMBO REPORTS (Oct. 18, 2013), https://www.researchgate.net/profile/Minne_Casteels/publication/258055371_Paving_a_regulatory_pathway_for_phage_therapy_-_Europe_should_muster_the_resources_to_financially_technically_and_legally_support_the_introduction_of_phage_therapy/links/53faf1260cf20a454970296a.pdf [http://perma.cc/JK8N-5GSN].

states should adopt policies promoting the medical use of bacteriophages. This will increase awareness and acceptance of phage therapy, both among the general public and the scientific community, and ultimately precipitate its regulatory accommodation by the FDA—a necessary step toward fully exploiting bacteriophage technology.

I also argue that the model for legalizing phage therapy used in Texas is preferable to the model used in Washington and Oregon. This is because the Washington and Oregon model places phage therapy—and the onus for developing bacteriophage medicines—in the purview of "naturopathic physicians,"[13] who are ill-regarded by the medical establishment—often thought to practice pseudoscience—and who are ill-equipped to actually research and develop efficacious bacteriophage medicines.[14] Not only does this model stymie the development of efficacious bacteriophage remedies, but it may also serve to associate phage therapy with pseudoscientific, naturopathic remedies in the eyes of many medical professionals, including researchers and physicians.[15] Such discredit would hamper any efforts to bring phage therapy into the discourse of the mainstream medical establishment. Meanwhile, the preferable Texas model, which allows licensed medical professionals to use bacteriophages as a supplement to, but not in lieu of, established medical techniques, does not discredit phage therapy by associating it with naturopathic pseudoscience; instead, the model treats it as a legitimate medical technique.[16] Furthermore, the Texas model places the onus for researching and developing bacteriophage medicines in the hands of capable professionals, and fosters a complementary relationship between phage therapy and conventional antibiotic drugs that improves the efficacy of both treatment methods.[17]

Ultimately, it is my contention in this Note that, while the regulation and maximum exploitation of bacteriophage medicine will require the FDA to change its regulatory policy on bacteriophage medicine, state-level legalization of the medical use of bacteriophage medicine has the potential to bring about greater cultural and scientific awareness and acceptance of phage therapy, which could in turn induce the FDA to regulate phage

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[13] *See* Faltys, *supra* note 10.
[14] *See* Julianna LeMieux, *A Naturopath's Human Experiment Ends In Death*, AM. COUNCIL ON SCI. AND HEALTH (Mar. 23, 2017), https://www.acsh.org/news/2017/03/23/naturopaths-human-experiment-ends-death-11039 [https://perma.cc/G9DG-FFTM].
[15] *See* Faltys, *supra* note 10; *see also* Timothy Caulfield, *Naturopaths and the creep of pseudoscience*, TORONTO STAR (Dec. 15, 2013), https://www.thestar.com/opinion/commentary/2013/12/15/naturopaths_and_the_creep_of_pseudoscience.html [https://perma.cc/H4EB-KW4A].
[16] 22 TEX. ADMIN. CODE §§ 200.1–.3 (2003).
[17] *Id.*

therapy. Thus, in order to speed the regulatory acceptance of phage therapy, more states should legalize the use of phage therapy within their respective territories. However, states must take care when doing so, as the details of how they legalize the use of phage therapy may prove laden with consequential implications. For an example, I reference the differences between the Texas and the Washington-Oregon models, and urge states to draw inspiration from Texas rather than Washington and Oregon.

I. OVERVIEW

The bacteriophage was discovered in 1915 by British bacteriologist Frederick Twort, and independently reported in 1917 by French microbiologist Félix d'Herelle, who commented that such viruses commonly appeared in the stool of dysentery patients soon before they began to recover.[18] George Eliava soon recognized the medical potential of bacteriophages, met with d'Herelle in Paris, and in 1923 founded the Eliava Institute in Tbilisi, Georgia (then a part of the Soviet Union), dedicated to the development of bacteriophage technology for medical use.[19] Although Eliava was executed as an Enemy of the Soviet People in 1937,[20] the Soviet Union nonetheless embraced his bacteriophage research.[21] The institute bearing his name continues his research into bacteriophage medicine, uninterrupted even into the modern day.[22]

While the use of antibiotic medicines derived from penicillin flourished in the Western world after the discovery of penicillin in 1928 by Alexander Fleming,[23] bacteriophage medicines enjoyed widespread use behind the Iron Curtain.[24] Soviet and other Eastern Bloc researchers put great effort into developing bacteriophage cures for numerous bacterial diseases.[25] However, without the resources available to researchers in Western Europe and the United States, Eastern Bloc research into bacteriophage medicine lagged behind the research and development of antibiotics

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[18] Leonard Norkin, *Felix d'Herelle, the Discovery of Bacteriophages, and Phage Therapy*, VIROLOGY (May 20, 2015), https://norkinvirology.wordpress.com/2015/05/20/felix-dherelle-the-discovery-of-bacteriophages-and-phage-therapy/ [https://perma.cc/UR2V-PUA5].
[19] *Id.*
[20] *Id.*
[21] Reardon, *supra* note 8.
[22] *Id.*
[23] Rustam Aminov, *A brief history of the antibiotic era: lessons learned and challenges for the future*, 1 FRONTIERS IN MICROBIOLOGY 134, 2 (2010).
[24] Lawrence Osborne, *A Stalinist Antibiotic Alternative*, N.Y. TIMES (Feb. 6, 2000), http://www.nytimes.com/2000/02/06/magazine/a-stalinist-antibiotic-alternative.html [https://perma.cc/Y9W7-TV5Z].
[25] Reardon, *supra* note 8.

derived from penicillin, and did not proliferate to nearly the same extent as penicillin-derived antibiotics.[26]

With the end of the Cold War, and the accession of several former Warsaw Pact nations to the European Union, Eastern Bloc bacteriophage research became available to Western European researchers.[27] The European Union is already beginning to capitalize on this inheritance by establishing and financing the Phagoburn program, a clinical study dedicated to developing and testing bacteriophage medicine for wound treatment.[28]

While such developments are encouraging, the main focus of this Note will be on the United States and its relationship with phage therapy. In recent years, the United States—as represented by both private corporations within the nation and relevant agencies within federal government—increased its interest in bacteriophage technology.[29] In 2006, the FDA and the United States Department of Agriculture ("USDA") approved the use of bacteriophage products to prevent harmful bacteria from contaminating foodstuffs.[30] However, the FDA has not yet approved the medical use of bacteriophage products in humans.[31]

Meanwhile, at the state level, there has been movement toward allowing the use of bacteriophage medicines.[32] Notably, Washington's and Oregon's laws allow for "naturopathic practitioners" to use any medical technique which has gained legal acceptance somewhere in the world.[33] Researchers interested in phage therapy have taken advantage of these laws to develop and use bacteriophage medicines.[34] One such researcher

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[26] *See* Osborne, *supra* note 24.
[27] Reardon,*supra* note 8.
[28] *Id.; About Phagoburn*, PHAGOBURN, http://www.phagoburn.eu/about-phagoburn.html [https://perma.cc/XJR6-66UG] (last visited Jan. 21, 2018).
[29] *Positive Developments from Clinical Studies and FDA Approvals Pushing Biotech Stocks to New Highs*, PR NEWSWIRE (Oct. 18, 2017), https://www.prnewswire.com/news-releases/positive-developments-from-clinical-studies-and-fda-approvals-pushing-biotech-stocks-to-new-highs-651428793.html [https://perma.cc/98ED-GTAA] (noting AmpliPhi Biosciences Corporation's publication of preclinical data entitled "Activity of Bacteriophages in Removing Biofilms of Pseudomonas Aeruginosa Isolated From Chronic Rhinosinustis Patients").
[30] Zach Mallove, *Phages: A New Means of Food Safety?*, FOOD SAFETY NEWS (May 21, 2010), http://www.foodsafetynews.com/2010/05/phages-a-new-means-of-food-safety/#.WK5BPfnytPY [https://perma.cc/SC3M-5GMR]; EBI Food Safety, *FDA Extends GRAS Approval LISTEX(TM) to all Food Products*, PR NEWSWIRE (July3, 2007), http://en.prnasia.com/releases/global/FDA_Extends_GRAS_Approval_LISTEX_TM_to_All_Food_Products-3917.shtml [https://perma.cc/V7HY-WADU].
[31] Cooper et al., *supra* note 9, at 1.
[32] Faltys, *supra* note 10.
[33] *Id.*
[34] *Id.*

is Dr. Elizabeth Kutter, who runs the Evergreen Phage Lab in Olympia, Washington, and whose experimental use of phage therapy has found some success.[35] Texas law, meanwhile, allows licensed medical practitioners a "reasonable and responsible degree of latitude" to offer their patients "complementary and alternative medicine[,]" as long as there is scientific evidence that such treatment will yield a reasonable potential for therapeutic gain.[36] This provision has been interpreted to give licensed physicians the ability to use bacteriophage medicines as a supplement to, but not in lieu of, conventional medicines and remedies.[37] As in Washington and Oregon, this allowed researchers and physicians to develop and utilize bacteriophage medicines.[38] Two such individuals are Dr. Ryland Young, head of the Center for Phage Technology at Texas A&M University, and Dr. Randall Wolcott, whose wound treatment center in Lubbock, Texas has been using bacteriophage medicines to treat patients' wounds since 2007.[39]

II. BENEFITS OF PHAGE THERAPY

In discussing the advantages of using bacteriophage medicines over the exclusive use of conventional antibiotic medicines, we cannot avoid discussing the drawbacks associated with these established medical techniques. Conventional antibiotic medicines revolutionized the relationship between humans and the microenvironment, especially with regard to disease-causing bacteria.[40] However, the overuse and misuse of traditional antibiotics led to the evolution of strains of drug-resistant bacteria.[41] One prominent example of this is Methicillin-resistant *Staphylococcus aureus* ("MRSA").[42] These virulent strains of the *S. aureus* bacteria—which is known to cause a diverse number of debilitating, disfiguring, and even fatal ailments[43]—have, through natural selection, evolved a

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[35] *Id.*
[36] 22 TEX. ADMIN. CODE §§ 200.1–200.3 (2003).
[37] KUCHMENT, *supra* note 10, at 115–18.
[38] *Id.*; Faltys, *supra* note 10.
[39] Azeen Ghorayshi, *Mail-Order Viruses Are The New Antibiotics*, BUZZFEED NEWS (Feb. 2, 2015), https://www.buzzfeed.com/azeenghorayshi/mail-order-viruses-are-the-new-antibiotics?utm_term=.gx9r14KJ3#.ed4QJgEj2 [https://perma.cc/H2SV-LDHZ].
[40] Lecia Bushak, *A Brief History Of Antibiotic Resistance: How A Medical Miracle Turned Into The Biggest Public Health Danger Of Our Time*, MEDICAL DAILY (Feb. 17, 2016), http://www.medicaldaily.com/antibiotic-resistance-history-373773 [https://perma.cc/5JGX-7W2J].
[41] Ventola, *supra* note 5, at 277–78.
[42] *Id.* at 280–81.
[43] Ananya Mandal, *Staphylococcus Aureus and Disease*, NEWS-MEDICAL (May 2005),

resistance to numerous brands of traditional antibiotics, including all of the penicillin-derived brands.[44] Due to this resistance, MRSA is notoriously difficult to treat in humans, and often able to spread to patients in hospitals themselves.[45] The Centers for Disease Control ("CDC") estimate that 11,285 people are killed by MRSA annually.[46] In the United States, the antibiotic drug Vancomycin—a non-penicillin-derived antibiotic—is currently used as a treatment against MRSA.[47] But it too is losing its efficacy as strains of *S. aureus* are beginning to develop resistance to this drug as well.[48]

Moreover, MRSA, while possibly the most notable example of antibiotic resistant bacterial infection, is far from the only such pathogenic bacteria, and its pattern of evolving ever-increasing resistances is hardly unique.[49] Indeed, new strains of antibiotic-resistant pathogenic bacteria continue to emerge periodically.[50] Recently, for example, a Nevada woman died from an infection caused by an unusually resilient strain of *Klebsiella pneumoniae* which proved to be resistant to 26 different antibiotic medicines.[51]

To deal with such virulent strains of pathogenic bacteria, doctors have been forced to turn to especially potent antibiotic drugs.[52] One of the most common such drugs is polymyxin E, also known as Colistin.[53] However, Colistin is used only as a drug of last resort because of its highly negative side effects.[54] Although an effective antibiotic, Colistin is also a

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http://www.news-medical.net/health/Staphylococcus-Aureus-and-Disease.aspx [http://perma.cc/9S8J-9PVE].

[44] Ventola, *supra* note 5, at 277–81.

[45] *Id.* at 281.

[46] *MRSA Fast Facts*, CNN (June 9, 2016), http://www.cnn.com/2013/06/28/us/mrsa-fast-facts/ [http://perma.cc/Z7RG-CP33].

[47] Scott Micek, *Alternatives to Vancomycin for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections*, 45 CLINICAL INFECTIOUS DISEASES s184 (2007).

[48] *Id.*

[49] *See* Ventola, *supra* note 5.

[50] Huys et al., *supra* note 12.

[51] Sara Zhang, *A Woman Was Killed by a Superbug Resistant to All 26 American Antibiotics*, THE ATLANTIC (Jan. 13, 2017), https://www.theatlantic.com/health/archive /2017/01/a-superbug-resistant-to-26-antibiotics-killed-a-woman-itll-happen-again/513050/ [http://perma.cc/X8EY-4CC5].

[52] Brent Bambury, *An American Woman Just Died From a Superbug Resistant to 26 Different Antibiotics*, CBC RADIO (Jan. 20, 2017), http://www.cbc.ca/radio/day6/episode-321-women-s-march-on-washington-hamilton-s-one-last-time-jerry-maguire-circus-fare wells-and-more-1.3941806/an-american-woman-just-died-from-a-superbug-resistant -to-26-different-antibiotics-1.3941881 [http://perma.cc/WYP6-9E6D].

[53] *Id.*

[54] *Id.*

powerful nephrotoxin and neurotoxin, which has a tendency to cause severe kidney and nerve damage, sometimes leading to the failure of these organ systems.[55] Additionally, powerful multipurpose antibiotics such as Colistin or Vanomycin also pose a risk to beneficial bacteria endemic to the human body, including those that make up our gut flora.[56] This presents serious health concerns to patients, as culling such symbiotic bacteria would deprive these patients of their beneficial effects—such as their aid in the process of normal digestion.[57] In the vacuum left by the symbiotic bacteria's absence or diminishment, antibiotic resistant pathogenic bacteria can establish themselves in the fertile areas of the human body that are normally inhabited by our bacterial symbiotes, thus giving such pathogens a stronghold in the human body from which to grow.[58] However, for all the associated risks, even Colistin is beginning to lose its efficacy against certain virulent strains of bacteria, as it too was unable to combat the aforementioned strain of antibiotic resistant *K. pneumoniae* bacteria.[59]

Thankfully, research further east has yielded some encouragement. Researchers at the Eliava Institute are also looking into the treatment of antibiotic resistant bacteria using bacteriophage medicine, with promising results.[60] Using phage therapy techniques on mice infected with MRSA, researchers have managed to synthesize a treatment that is 97% effective in the infected mice.[61] This demonstrates one of the main advantages that phage therapy has over traditional antibiotic medicine: while bacteria are often able to develop resistance to traditional antibiotics, bacteriophages evolve much more quickly than the bacteria they prey upon.[62] As viruses, bacteriophages have short generation times and high mutation rates, allowing them to evolve quickly to meet new environmental conditions.[63] Furthermore, this high rate of evolution has led to the emergence

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[55] Herbert Spapen et al., *Renal and Neurological Side Effects of Colistin in Critically Ill Patients*, 1 ANNALS OF INTENSIVE CARE 14, 14–15 (2011).
[56] *See* Reardon, *supra* note 8.
[57] Maryn McKenna, *Antibiotics: Killing Off Beneficial Bacteria . . . for Good?*, WIRED (Aug. 26, 2011), https://www.wired.com/2011/08/killing-beneficial-bacteria/ [https://perma.cc/VG4Q-YGZ8].
[58] *Id.*
[59] Bambury, *supra* note 52.
[60] Zuzanna Kaźmierczak et al., *Facing Antibiotic Resistance: Staphylococcus aureus Phages as a Medical Tool*, 6(7) VIRUSES 2551, 2559 (2014).
[61] *Id.* at 2555.
[62] Carol Potera, *Phage Renaissance: New Hope against Antibiotic Resistance*, 121(2) ENVIRONMENTAL HEALTH PERSPECTIVES A49–50 (2013).
[63] KEITH LEPPARD ET AL., THE EVOLUTION OF VIRUSES, INTRODUCTION TO MODERN VIROLOGY 272–73 (2007).

of innumerable strains of bacteriophages.[64] Indeed, scientists estimate that "[a] pinch of soil or drop of seawater, for example, contains many millions of bacteriophages" and that "[p]hages are probably the most diverse things on the planet."[65] Some researchers even speculate that bacteriophages outnumber all other organisms put together.[66] Thus, it is unlikely that bacteria could develop any natural resistance to bacteriophage medicines, as they are able to with conventional antibiotics.[67]

In addition, bacteriophage species tend to be highly specialized, preying exclusively upon one strain or species of bacteria.[68] This means that bacteriophages pose little to no threat to the beneficial bacteria within the human body, unlike many conventional antibiotic drugs—especially very potent drugs such as Colistin and Vanomycin.[69]

III. CONCERNS WITH PHAGE THERAPY

For all of its potential benefits, some scientists have apprehensions about the use of phage therapy. Notably, there is scientific concern with the use of lysogenic (also known as temperate) bacteriophages in phage therapy.[70] This particular group of bacteriophages is able to alter the genetic material of a host bacterium without destroying it.[71] This ability means lysogenic bacteriophages have the potential to actually turn nonpathogenic, benign bacteria species into pathogenic, harmful bacteria.[72] The risks associated with the creation of a new disease-causing bacteria are potentially severe.[73] Though it is difficult to say with certainty how a new species or strain of bacteria would behave, there is every

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[64] Reardon, *supra* note 8.
[65] John Travis, *All the World's a Phage: Viruses That Eat Bacteria Abound—and Surprise*, SCIENCE NEWS (July 12, 2003), http://www.phschool.com/science/science_news/articles/all_worlds_phage.html [http://perma.cc/8UTF-MB8U].
[66] *Id.*
[67] *Id.*
[68] Reardon, *supra* note 8.
[69] *Id.*
[70] Duckworth & Gulig, *supra* note 4, at 61.
[71] Xavier Wittebole et al., *A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens*, 5(1) VIRULENCE 226 (2013); *see also* Harald Brüssow et al., *Phages and the Evolution of Bacterial Pathogens: from Genomic Rearrangements to Lysogenic Conversion*, 68(3) MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEW 560, 574–75 (2004).
[72] Duckworth & Gulig, *supra* note 4, at 61.
[73] *See id.*

possibility that such new bacteria could be highly virile and deadly.[74] In addition to spreading genes that make previously benign bacteria pathogenic, lysogenic bacteriophages could actually spread genes that increase microbial resistance to antibiotic medicine.[75] For this reason, lysogenic bacteriophages are typically not used for phage therapy.[76] To avoid this risk entirely, the use of lysogenic bacteriophages in bacteriophage medicines could be banned outright by appropriate regulatory organizations without greatly hindering the development of bacteriophage medicines using non-lysogenic (lytic) bacteriophages.[77]

Lytic bacteriophages also pose potential risks to human health, albeit less severe than those posed by lysogenic bacteriophages.[78] Lytic bacteriophages can cause patients harm by exposing them to bacterial endotoxins.[79] Certain pathogenic bacteria contain substances that are toxic to humans within their cell walls, collectively known as endotoxins.[80] When lytic viruses break open (or, *lyse*) infected bacteria during normal viral reproduction, these endotoxins can be released.[81] If many of these endotoxin-containing bacteria are broken open within the human body, these toxins have the potential to cause symptoms ranging from very minor[82] to potentially life-threatening.[83] However, this reaction, known as the Herxheimer reaction, is not unique to phage therapy.[84] It has been observed to happen in the course of conventional antibiotic treatment, which also destroys bacteria cells and releases their endotoxins.[85]

The scientific community has also raised concerns that bacteriophages may trigger an immune response in patients which could prove harmful to the body.[86] Though bacteriophages pose no threat to our own

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[74] *Id.*
[75] Wittebole et al., *supra* note 71, at 228.
[76] Duckworth & Gulig, *supra* note 4, at 61.
[77] Wittebole et al., *supra* note 71, at 228.
[78] Maheshwar Mathur et al., *Bacteriophage Therapy: An Alternative to Conventional Antibiotics*, 51 J. OF THE ASS'N OF PHYSICIANS OF INDIA 593, 594 (2003).
[79] *Id.*
[80] Ernst Rietschel et al., *Bacterial Endotoxin: Molecular Relationships of Structure to Activity and Function*, 8(2) FASEB J. 217 (1994).
[81] *Id.*
[82] *The Herxheimer Reaction—Feeling Worse Before Feeling Better*, SILVER COLLOIDS (2012), http://www.silver-colloids.com/Pubs/herxheimer.html [http://perma.cc/L3KJ-HKJC].
[83] Mathur et al., *supra* note 78, at 594.
[84] James Hurley, *Antibiotic-Induced Release of Endotoxin: A Therapeutic Paradox*, 12(3) DRUG SAFETY 183 (1995).
[85] *Id.*
[86] Catherine Loc-Carrillo & Stephen Abedon, *Pros and Cons of Phage Therapy*, 1(2) BACTERIOPHAGE 111, 112 (2011).

cells, the body's immune system nonetheless recognizes them simply as viruses, and will naturally seek to destroy or expel them from the body.[87] Though the immune system is designed to protect the body from pathogens, not all immune reactions are beneficial to the body.[88] Indeed, some are actually harmful.[89] An allergic reaction, for instance, is one common type of immune reaction which can cause various levels of discomfort or even serious harm to the body, sometimes even resulting in death.[90] However, bacteriophage researchers have not noticed any seriously harmful immune reactions to bacteriophage medicines as of yet.[91] Rather, what has been observed is that a human immune system that has already been triggered by bacterial illnesses will also strike out at bacteriophages in the body, which can inhibit the efficacy of phage therapy in clinically significant ways.[92] Nonetheless, with more research it may be possible for clinicians to account for impediments to phage therapy caused by the immune system.[93] Additionally, even if phage therapy did lead to severe immune reactions in some cases, it would hardly be unique among medicines.[94] Many people worldwide suffer from allergic reactions to traditional antibiotics, which can cause symptoms ranging from uncomfortable rashes and blisters to life-threatening toxic epidermal necrolysis and anaphylaxis.[95]

In addition, phage therapy may be mistrusted by the wider public for its use of viruses, which could potentially prove fatal to the development of bacteriophage medicines.[96] Though bacteriophages do not prey on eukaryotic—or nonbacterial—cells, and thus do not pose a threat of attacking human cells and causing viral infection of humans, these details may be lost on certain members of the public.[97] In the words of Mzia Kutateladze, head of the scientific council of the Eliava Institute, "this is

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[87] Katarzyna Hodyra-Stefaniak et al., *Mammalian Host-Versus-Phage immune response determines phage fate in vivo,* 5 SCI. REP. 14802 at 7 (2015).
[88] *See* Ian Kimber & Rebecca Dearman, *Immune Responses: Adverse Versus Non-Adverse Effects*, 30 TOXICOLOGIC PATHOLOGY 54, 56–57 (2002).
[89] *Id.* at 54.
[90] *Id.* at 56.
[91] Loc-Carrillo & Abedon, *supra* note 86, at 112.
[92] Hodyra-Stefaniak et al., *supra* note 87, at 8.
[93] *See id.*
[94] Antonio Romano & Jean-Christoph Caubet, *Antibiotic Allergies in Children and Adults: From Clinical Symptoms to Skin Testing Diagnosis*, 2 J. OF ALLERGY AND CLINICAL IMMUNOLOGY: IN PRACTICE 3, 4, 8 (2014).
[95] *Id.* at 3–4, 7–9.
[96] *See* Reardon, *supra* note 8.
[97] *Id.*

a virus, and people are afraid of viruses."[98] While any public concerns about the risk of bacteriophages causing viral diseases would be scientifically unfounded, a public outcry against the use of phage therapy nonetheless has the potential to impede or even block its adoption.[99] Such patterns of powerful public outcry without substantial scientific backing are not new to medical science.[100] Indeed, one need look no further than the "anti-vaxxer" movement to see the repercussions that even a vocal minority can have on public policy, and the influence that such a minority can wield over policymakers.[101] Thankfully, there has not yet been any such outcry, as the public largely doesn't know about phage therapy.[102] It is possible that with adequate attempts to educate the public about the actual risks and benefits associated with phage therapy, unfavorable misapprehensions about it could be dispelled, and this obstacle to the implementation of phage therapy could be preempted.[103]

IV. CURRENT REGULATORY SITUATION

A. Federal Regulations

In the past decade or so, appropriate United States federal regulatory agencies, namely the FDA and the USDA have approved the use of several bacteriophage products for commercial use. For instance, in 2006, the FDA awarded a generally recognized-as-safe ("GRAS") status to the Micreos product LISTEX, a bacteriophage coating for cheese which kills the bacteria *Listeria monocytogenes*.[104] The USDA, meanwhile, has funded research into bacteriophage products and medicines which could combat bacterial infections of plants or livestock.[105] This research includes one ambitious project aimed at completely replacing the typical cocktail of antibiotics regularly given to farm animals in order to help them ward off infections—a practice which the USDA is concerned may lead to the advent of antibiotic-resistant pathogens which would pose a health risk

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[98] *Id.*
[99] Loc-Carrillo & Abedon, *supra* note 86, at 113.
[100] Peter Hotez, *How the Anti-Vaxxers Are Winning*, N.Y. TIMES (Feb. 8, 2017), https://www.nytimes.com/2017/02/08/opinion/how-the-anti-vaxxers-are-winning.html [http://perma.cc/G7WM-9GWG].
[101] *Id.*
[102] Loc-Carrillo & Abedon, *supra* note 86, at 113.
[103] Potera, *supra* note 62, at A52.
[104] Mallove, *supra* note 30.
[105] *Viruses to Battle Bacteria*, CORNELL UNIV. (May 17, 2011), http://www.vet.cornell.edu/research/news/Bacteriophages.cfm [http://perma.cc/E9LY-XUCS].

to livestock and humans alike—with bacteriophage medicines, effectively creating a veterinary application of phage therapy.[106]

However, despite this movement toward the greater acceptance of bacteriophage products, the FDA has yet to approve phage therapy for medicinal use in humans.[107] In large part, this is because the FDA requires that antibiotic drugs be tested for efficacy and safety individually, and classes bacteriophage medicines as antibiotic drugs.[108] This individual efficacy testing is intended for conventional antibiotic drugs, which are designed to be effective against a wide array of bacteria species and strains.[109] Thus, under the current FDA regulations, different species of bacteriophages would be considered individual antibiotic drugs, and as such would need to be individually approved.[110]

However, this model is a poor fit for phage therapy. Unlike conventional antibiotics, which are able to kill a diverse array of pathogens, bacteriophages prey on specific types of bacteria.[111] As a result, phage therapy techniques often feature "multi-phage cocktails," which include numerous species of bacteriophages, to maximize the treatment's efficacy when the exact species or strain of bacteria infecting the patient is not known.[112] Indeed, researchers at the Eliava Institute have admitted that the bacteriophage injections they administer to patients are often so mixed that they do not know the exact combination of phage species that make up the cocktail.[113] While phage cocktails would be able to meet FDA efficacy standards, individual phages would not.[114]

Outside of the antibiotic context, however, the FDA has approved drug cocktails collectively rather than their individual component drugs.[115] For example, the FDA regularly approves FluMist®—a yearly live-virus influenza vaccine containing three or four attenuated flu viruses—as a whole rather than approving each individual virus.[116]

Furthermore, recent Supreme Court cases—*Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, and *Association for Molecular*

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[106] *Id.*
[107] Cooper et al., *supra* note 9, at 1.
[108] Eric Keen, *Phage Therapy: Concept to Cure*, 3 FRONTIERS IN MICROBIOLOGY 238, 238–39 (2012).
[109] Reardon, *supra* note 8.
[110] Keen, *supra* note 108, at 238–39.
[111] Reardon, *supra* note 8.
[112] Cooper et al., *supra* note 9, at 6.
[113] Reardon, *supra* note 8.
[114] Keen, *supra* note 108, at 238–39.
[115] *Id.*
[116] *Id.*

Pathology v. Myriad Genetics, Inc.—have left the patentability of bacteriophage products ambiguous.[117] First, pursuant to *Prometheus*, the application of a natural phenomenon or "law of nature," even if just discovered, cannot be patented if it lacks an "inventive concept."[118] An invention's "inventive concept" must ensure that the patent acts as more than a monopoly on the use of the natural law itself.[119] The Court further elaborated that "conventional or obvious pre-solution activity" is not necessarily sufficient to add such an element of inventiveness.[120] Second, the Court in *Myriad*—applying *Prometheus*—ruled that would-be inventors cannot claim patent protection on naturally occurring DNA patterns, because the act of discovering or isolating genetic material is not the same as inventing it.[121] Rather, inventors can only receive patent protection for synthetically created genetic patterns, such as composite DNA ("cDNA").[122] Some scholars contend that, because bacteriophages are natural phenomena possessing and distinguished by their naturally occurring genetic material, these cases leave the patent-eligibility of bacteriophage products ambiguous.[123]

Such federal regulatory hurdles present serious obstacles to the development and exploitation of bacteriophage medicines. As a matter of economics, pharmaceutical companies—who fund the lion's share of research and development of new drugs[124]—are unlikely to invest in developing products which will not yield short-term or medium-term profits.[125] Because an unapproved drug would see very little use, and because the uncertainty surrounding the patentability of bacteriophage products affords them little certainty that their intellectual property will be protected,

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[117] Timo Minssen, *The Revival of Phage Therapy to Fight Antimicrobial Resistance (AMR)—Part II: What about patent protection and alternative incentives?*, BILL OF HEALTH (Aug. 7, 2014), http://blogs.harvard.edu/billofhealth/2014/08/07/the-revival-of-phage-therapy-to-fight-antimicrobial-resistance-part-ii-what-about-patent-protection-and-alternative-incentives/ [http://perma.cc/L3PC-WRKJ].

[118] Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 71–73 (2012).

[119] *Id.* at 72–73.

[120] *Id.* at 79.

[121] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116–17 (2013).

[122] *Id.* at 2119–20.

[123] Timo Minssen, *The Revival of Phage Therapy to Fight Antimicrobial Resistance (AMR)—Part III: What About Patent Protection and Alternative Incentives?*, BILL OF HEALTH (Aug. 8, 2014), http://blogs.harvard.edu/billofhealth/2014/08/08/the-revival-of-phage-therapy-to-fight-antimicrobial-resistance-amr-part-iii-what-about-patent-protection-and-alternative-incentives/ [http://perma.cc/Y4VY-PU94].

[124] Kathlyn Stone, *Who Funds Biomedical Research*, THE BALANCE (Aug. 15, 2016), https://www.thebalance.com/who-funds-biomedical-research-2663193 [http://perma.cc/JW7E-K7DD].

[125] Alexandra Henein, *What are the limitations on the wider therapeutic use of phage?*, 3(2) BACTERIOPHAGE e24872-1, e24872-3 (2013).

pharmaceutical companies are unlikely to invest in developing bacteriophage medicines under the current scheme.[126] Thus, for phage therapy to become a reality in American medicine, the FDA must make regulatory accommodations for phage therapy.

B. State-Level Developments

Despite the stagnation at the federal level, three states thus far have legalized the medical use of phage therapy: Texas, Oregon, and Washington.[127] From these states, two distinct models can be observed. Each model implies a distinct attitude toward the medical use of bacteriophages, with implications and consequences that must be carefully considered going forward.

1. The Washington-Oregon Model

The sister states of Washington and Oregon both allow for the medical use of phage therapy within their borders.[128] These two states utilize a sufficiently similar model governing the use of bacteriophage medicines, among other experimental products, that we can class them together.[129] In these states, phage therapy is one of many unconventional remedies which may be prescribed by naturopathic physicians.[130] Naturopathic physicians, or naturopaths, are practitioners who make use of naturopathic medicines.[131] Naturopathic medicine is defined under Washington law as "vitamins; minerals; botanical medicines; homeopathic medicines; hormones; and those legend drugs and controlled substances consistent with naturopathic medical practice in accordance with rules established by the [state naturopathic] board,"[132] and under Oregon law as "the discipline that includes physiotherapy, natural healing processes and minor surgery and has as its objective the maintaining of the body in, or of restoring it to, a state of normal health."[133] Naturopaths in Washington and Oregon have the legal authority to prescribe the use of medicines used

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[126] Fischetti et al., *supra* note 11, at 1509.
[127] Faltys, *supra* note 10; KUCHMENT, *supra* note 10, at 115–18.
[128] Faltys, *supra* note 10.
[129] *See id.*
[130] *Id.*
[131] Stephen Barrett, *A Close Look at Naturopathy*, QUACKWATCH (Nov. 26, 2013), https://www.quackwatch.org/01QuackeryRelatedTopics/Naturopathy/naturopathy.html [http://perma.cc/XG22-XWG7].
[132] WASH. REV. CODE ANN. § 18.36A.020 (West 2011).
[133] OR. REV. STAT. § 685.010 (1999).

extensively in other countries.[134] Certain medical doctors, such as Dr. Betty Kutter, who heads the Evergreen Phage Lab at Evergreen State College in Olympia, Washington, have taken advantage of these laws in order to research and use bacteriophage medicines on patients.[135]

However, this treatment betrays an attitude toward phage therapy rife with troublesome implications. Naturopathic medicine is ill-regarded by scientific and medical professionals, many of whom regard it as pseudoscientific.[136] Naturopathy's poor reputation is reflected in law. The FDA takes a dim view of naturopathy, and has at times considered curbing its practice.[137] Furthermore, two states, South Carolina and Tennessee, have even outright banned the practice of naturopathy within their borders.[138] By placing the development and use of phage therapy within the purview of naturopaths, the Washington-Oregon Model implicitly associates phage therapy with pseudoscientific remedies, despite the former's long history and scientific merit.

Additionally, naturopathic physicians' scientific, medical, and technical education often falls far short of what would be expected of conventional medical professionals, even in states where they are officially licensed.[139] Thus, Washington and Oregon place phage therapy in the hands of individuals who are likely incapable of effectively researching and utilizing bacteriophage medicine.[140]

2. The Texas Model

Like Washington and Oregon, the state of Texas also allows for research into and use of bacteriophages.[141] However, unlike Washington

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[134] Faltys, *supra* note 10.
[135] *Id.*
[136] Barrett, *supra* note 131.
[137] Tara Culp-Ressler, *The FDA Considers Cracking Down On Untested Alternative Medicine Treatments*, THINKPROGRESS (April 20, 2015), https://thinkprogress.org/the-fda-considers-cracking-down-on-untested-alternative-medicine-treatments-287f9b307cfc#.rupyk0p5w [http://perma.cc/N7EJ-3GJX]; *see also* Jann Bellamy, *FDA Efforts to Improve Compounded Drug Safety Upsets Naturopaths*, SCIENCE-BASED MEDICINE (July 7, 2016), https://sciencebasedmedi cine.org/fda-efforts-to-improve-compounded-drug-safety-upsets-naturopaths/ [http://perma.cc/A7B2-XDLD].
[138] S.C. CODE ANN. § 40-31-10 (2007); TENN. CODE ANN. § 63-6-205 (2009).
[139] Barrett, *supra* note 131.
[140] *See* WASH. ADMIN. CODE § 246-836-130; *see also* NATUROPATHIC PHYSICIAN CREDENTIALING, WASHINGTON STATE DEP'T OF HEALTH, https://www.doh.wa.gov/portals/1/Documents/Pubs/648011.pdf [http://perma.cc/YAD6-ZCXU] (noting the Intravenous Therapy Attestation Authorization prerequisite of "sixteen hours of training").
[141] Ghorayshi, *supra* note 39.

and Oregon, Texas does not put phage therapy in the purview of naturopaths.[142] Rather, Texas places phage therapy in the hands of licensed medical practitioners by allowing doctors to prescribe bacteriophage medicine as a supplement to, but not in lieu of, established medical techniques.[143]

Under this model, Texas fosters a complementary relationship between bacteriophage medicine and conventional antibiotic medicine, which allows each to offset the weaknesses of the other—thus improving the efficacy of both. It allows physicians to test new bacteriophage medicines without putting their patients at risk by subjecting them to an experimental remedy, as the conventional antibiotic medicine provides an anchor. Certain antibiotics have even been observed to promote phage virulence.[144] At the same time, this dual method helps to reduce the risks associated with conventional antibiotic medicine, such as the emergence of antibiotic-resistant strains of pathogenic bacteria, because bacteriophages effectively eliminate bacteria remaining after antibiotic treatment.[145] In this way, bacteriophages actually enhance the effectiveness of conventional antibiotics.[146] Indeed, some research suggests that using both methods together is actually more effective at killing pathogens than using either method in isolation.[147]

V. ARGUMENT

In an era in which once tractable pathogenic bacteria are developing resistance to our strongest conventional antibiotic medicines at alarming rates,[148] the development of new, efficacious medicines capable of controlling virulent bacterial pathogens is crucial. Because phage therapy is one of the most promising new alternatives to conventional antibiotic medicine,[149] our society should prioritize its development and full exploitation.

Reforming federal regulatory policies on phage therapy is necessary to induce the maximal exploitation of phage therapy.[150] As discussed above, pharmaceutical companies are unlikely to invest money to research

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[142] KUCHMENT, *supra* note 10, at 115–18.
[143] *Id.*; 22 TEX. ADMIN. CODE §§ 200.1–200.3.
[144] André Comeau et al., *Phage-Antibiotic Synergy (PAS): beta-Lactam and Quinolone Antibiotics Stimulate Virulent Phage Growth*, 2(8) PLOS ONE e799, at 1, 3–4 (2007).
[145] Waqas Nasir Chaudhry et al., *Synergy and Order Effects of Antibiotics and Phages in Killing* Pseudomonas aeruginosa *Biofilms*, 12(1) PLOS ONE e0168615 (2017).
[146] Aminov, *supra* note 23, at 137.
[147] Chaudhry et al., *supra* note 145.
[148] *See* Zhang, *supra* note 51.
[149] Fischetti et al., *supra* note 11, at 1511.
[150] Keen, *supra* note 108, at 238–39.

and develop a medicine which is unlikely to be approved under the FDA's current policies.[151] Thus, compelling the FDA to provide regulatory accommodation for phage therapy must be a goal and priority for the advocate of regularizing phage therapy. It may not even require great creativity to imagine what form regulatory accommodation for phage therapy would take. Indeed, if the FDA were to distinguish bacteriophage medicines from conventional antibiotics, allowing them to approve phage cocktails as a whole—similar to how the FDA treats FluMist®—bacteriophage medicines would meet FDA safety and efficacy requirements.[152] What may prove more difficult is impelling the FDA to change its policy on phage therapy so dramatically. To that end, legalizing phage therapy at the state level may prove useful.

Although state regulations are not sufficient in themselves to significantly spread or regularize the use of bacteriophage medicine, individual states can help to speed the federal regulatory adoption of and accommodation for phage therapy. By crafting legislation or regulatory policies which allow for the research and use of bacteriophage medicine within their own territory, research and treatment centers will be able to spread across the country, just as they have in Texas and Washington.[153] Through these research centers, members of the medical establishment, as well as the general population, will gain more exposure to the concept and practice of phage therapy, allowing it to enter the cultural and scientific conscience of the American people. In the event that the American people and wider medical establishment become familiar with and accepting of phage therapy, the FDA will have no choice but to respond to these cultural developments by making regulatory accommodations for phage therapy.

However, there are pitfalls which states would do well to avoid when accommodating the development and use of phage therapy. Namely, states should not put the onus for developing and using phage therapy on naturopathic physicians, as is the practice in Washington and Oregon.[154] Naturopathy is considered disreputable pseudoscience by most of the scientific and medical community, and the scientific, medical, and technical education of even state-licensed naturopaths most often falls far short of what would be expected of conventional medical professionals.[155] Therefore,

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[151] *Id.*
[152] *Id.*
[153] Faltys, *supra* note 10; KUCHMENT, *supra* note 10, at 115–18.
[154] Faltys, *supra* note 10.
[155] Barrett, *supra* note 131.

by putting the development and use of phage therapy in the purview of naturopaths, states would be placing the onus for the research and development of bacteriophage medicines on people who often lack the requisite knowledge or temperament to do so while also associating phage therapy with ostensibly pseudoscientific naturopathic remedies.[156]

The latter point is especially salient when trying to influence federal regulatory policy by raising professional and cultural awareness of phage therapy. Placing phage therapy in the purview of naturopaths risks causing many scientists, researchers, and physicians to view phage therapy as a pseudoscience, in the same vein as other naturopathic remedies, rather than as a legitimate medical technique. By causing medical professionals to associate phage therapy with pseudoscience, or even to view it as pseudoscience, states placing phage therapy in the purview of naturopaths could actually hamper any effort to impel the FDA to recognize the legitimate medical value of phage therapy, let alone to make regulatory accommodations for it.

In contrast, the Texas model provides a good alternative to the flawed Washington-Oregon model. Rather than placing phage therapy in the purview of naturopaths, the Texas model puts licensed medical practitioners in charge of developing and administering bacteriophage medicines.[157] Because licensed physicians are at the helm of the development and administration of phage therapy under the Texas model, the legitimacy of phage therapy will not suffer from association with pseudoscience, as it does under the Washington-Oregon model. Furthermore, because medical doctors are generally better medically, scientifically, and technically educated than even state-licensed naturopaths,[158] having medical doctors in command of the research and development of bacteriophage medicine will yield more fertile results than those that would be produced under the Washington-Oregon model.

The Texas model is also desirable for the complementary relationship that it builds between phage therapy and traditional antibiotic techniques. With bacteriophage medicine used as a complement to, but not in lieu of, established medical techniques, these two treatments are able not only to improve upon the other's weaknesses but also—according to some studies—kill pathogens more effectively than either method used in isolation.[159] This complementary relationship would also help lead to

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[156] *See supra* Section IV.B.1.
[157] KUCHMENT, *supra* note 10, at 115–18.
[158] Barrett, *supra* note 131.
[159] Chaudhry et al., *supra* note 145.

greater societal understanding of phage therapy. It both provides a viable look at how phage therapy could be used after cultural and regulatory acceptance, and also allows both medical professionals and society at large to get accustomed to seeing this combination of methods for fighting bacterial infection.

CONCLUSION

In order to effectively advocate for the use of phage therapy in the United States, we must first take stock of the resources at our disposal. Ultimately, change must happen at the federal level—namely, to the FDA's policy toward phage therapy—before serious headway can be made on developing effective and reliable bacteriophage remedies to bacterial infections.[160] However, the importance of state law should not be overlooked. State law is an important and relatively accessible way to influence public perception and opinion. As such, even though it alone will not be sufficient to precipitate the spread of bacteriophage medicine to every corner of the nation, it can build public opinion from the ground up, and lend momentum to the cause of normalizing phage therapy. Thus, advocates for the use of phage therapy should promote both the revision of relevant FDA regulation and the legalization of phage therapy at the state level. However, it is imperative for states to legislate in a careful and deliberate way, ever cognizant of the assumptions, implications, and consequences ingrained in the laws they create.

As humanity's understanding of the microenvironment increases, nations around the world will need to come to terms with their relationship with the denizens of that microscopic world—in law, science, and medicine alike. This relationship is complex and mutually influential; human actions play a very significant role in shaping and maintaining a healthy microenvironment, which then can impact our health and quality of life in drastic and marked ways. Key to shaping a healthy microenvironment will be developing sound policy respecting our already symbiotic relationship with the most populous and diverse denizens of the microscopic world: the humble bacteriophages. By maintaining a symbiotic relationship with bacteriophages, humanity stands to create a microenvironment hospitable to human life, and conducive to human flourishment. Phage therapy is but one example of the exciting and potentially revolutionary technologies that can result from such a concerted effort.

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[160] Keen, *supra* note 108, at 238–39.