Bacterial resistance to antibiotics poses a serious health threat. Since research into new antibiotics is not progressing at the same rate as the development of bacterial resistance, widespread calls for alternatives to antibiotics have been made. Phage therapy is an ideal alternative candidate to be investigated. However the success of phage therapy may be hampered by a lack of investment support from large pharmaceutical companies, due to their narrow spectrum of activity in antibiotics, very large costs associated with clinical trials of the variety of phages needed, and regulatory requirements remaining unclear. Intellectual property is difficult to secure for therapeutic phage products for a variety of reasons, and patenting procedures vary widely between the US and the EU. Consequently, companies are more likely to invest in phage products for decontamination or veterinary use, rather than clinical use in humans. Some still raise questions as to the safety of phage therapy overall, suggesting the possibility of cytotoxicity and immunogenicity, depending on the phage preparation and route. On the other hand, with patients dying because of infections untreatable with conventional antibiotics, the question arises as to whether it is ethical not to pursue phage therapy more diligently. A paradigm shift about how phage therapy is perceived is required, as well as more rigorous proof of efficacy in the form of clinical trials of existing medicinal phage products. Phage therapy potential may be fulfilled in the meantime by allowing individual preparations to be used on a named-patient basis, with extensive monitoring and multidisciplinary team input. The National Health Service and academia have a role in carrying out clinical phage research, which would be beneficial to public health, but not necessarily financially rewarding.

Antimicrobial resistance is a major international public health threat, which can severely limit treatment choice in clinical settings, making infections more difficult or even impossible to treat. The severity of the threat is such that there are even suggestions of a return to pre-penicillin days, in the absence of adequate countermeasures. The development of new classes of antibiotics is not keeping pace with the speed at which bacteria are developing resistance. Reports of antibiotic-resistant bacteria isolated in hospitals already exist.

In the late 1960s and early 1970s, the success of antimicrobial medicines created an illusion that infectious diseases had been defeated. Since that time, bacterial infections have made a worrying comeback, and as a consequence, strategic documents were issued by the WHO. In April 1998, the House of Lords Select Committee on Science and Technology published the report, *Resistance to Antibiotics and other Antimicrobial Agents*, which recognized the severity of the situation. In response, the Department of Health published a decisive strategic plan, which defined eight action areas, one of which was ‘to encourage the development of new and novel agents/technologies to detect, prevent and treat infection to overcome resistance.’

As long ago as 2000, this UK Antimicrobial Resistance Strategy and Action Plan stated very clearly that...
alternatives to antibiotic treatment must be sought in the fight against antimicrobial resistance. The UK Government has recognized the predicament and has clearly encouraged the development of alternative agents, which encompasses phage therapy.

**The Ethics of Phage Therapy**

To date, no debate about the ethics of phage therapy based on bioethical theories has been published. Attention has been focused on presenting positive evidence of human and animal case studies and on possible reasons why phage therapy has at times failed and may do so in the future. With court cases and public pressure forcing licensing authorities and governments to enable fast-track licensing schemes for drugs treating HIV, MS and cancer, it is interesting why no similar scenario has been seen regarding phage therapy. A major reason is the absence of convincing evidence of phage safety and efficacy in humans in the form of modern double-blind clinical trials.

In the UK, there is no national data published reflecting the mortality rate due to bacterial infections other than *Staphylococcus aureus* (including MRSA) and *Clostridium difficile*. There is also a lack of available national statistics representing the morbidity and mortality associated with bacterial strains untreatable with antibiotics. Such data, if collected, should highlight the reality of casualties due to an absence of alternatives to the currently available antibiotics. Governments may be understandably reluctant to collate and publish such figures; however, pressure groups of patients may force decision makers to invest in alternatives to currently available therapy options.

The Declaration of Helsinki states: “In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published.”

Considering reports that phage therapy has been widely successful even when used as a last resort in infections non-responsive to antibiotics, a question arises: Is it even ethical to continue not pursuing phage therapy in the UK? Phage therapy was suggested as a treatment option in the context of the recent *E. coli* O104 outbreak, which resulted in many fatalities. No clinical trials on any therapeutic options for patients affected by the Shiga toxin-induced hemolytic uremic syndrome were available at the time of the outbreak, and some of the chosen therapy may have been harmful, yet phage therapy was not even considered. Notably, given the circumstances of the outbreak, the use of an unapproved medicinal product such as phage would have been allowed under EU legislation.

Even if this approach is deemed too risky, the exceptionally good track record and safety profile of topically used phage virtually begs for further exploration of therapeutic use.

Following the bioethical concept of non-maleficence, after Beauchamp and Childress who direct physicians to refrain from harming a patient regardless of intent, it could be debated whether, and under which circumstances, patients should have phage therapy made available to them. The concept of beneficence encompasses weighing the risks of using a given treatment vs. the benefits, and phage therapy should also be considered under this directive. The next logical step is to explore what the limitations are to bringing therapeutic phage products to the patient.

**Safety of Phage:**

**Safety of Phage Preparations**

There is an implied understanding that phages are inherently safe, using the argument that phages are abundant in the environment and we are already exposed to them constantly, both topically and enterically. An additional argument is that they have been used so extensively for therapeutic purposes in some parts of the world with virtually no reports of harm, indicating that negative effects must be subtle or at least relatively minor. Additionally, Barrow and Soothill (cite Ochs, 1971) pointed out that phages have been used to test antibody function in immunodeficient patients, implying that phages are non-toxic and seeing no evidence to the contrary. Even taking these arguments into account, it is surprising that no phage cytotoxicity studies have been published, and any assumptions as to whether phage may be safe or not should be challenged and verified by scientific experiments. According to Pirisi (2000), Du Bow summed this up concisely: “What we think we know about phages has to be verified and then deemed reproducible, safe and effective” under therapeutic conditions.

There are further examples of phage being “generally considered as safe”:

- When some vaccines were found to have been contaminated with phage in the 1970s on a very large scale, an Executive Order was issued to permit the continued use of the contaminated vaccines. No ill effects were reported.
- In 2006, the US FDA designated a mixture of *Listeria monocytogenes* phages for use in ready to eat foods as GRAS (Generally Recognized as Safe). This provides another argument to support the safety of phage.

However, phage therapy may entail single or repeated use of concentrated phage preparations with high titers in a patient, administered by a variety of routes, which is quite different to ingesting the quantities contained in food products. There is also a clear distinction to be made between IV use, which has seldom been implemented, and topical applications of phage at relatively low concentrations, for which there is a great deal of experience.

Not all phages are safe to humans under all circumstances. For example, phage-associated conversion of *Tox* Streptococcus pyogenes into *Tox* bacteria in vivo has been described in the literature, with the concern that genes for other phage-associated toxins like botulinum, shiga and diphtheria toxins may be transferrable by particular related phages. It needs to be emphasized, however, that it is generally temperate phages that can induce these toxins, and a very different type of phages—professionally
lytic phages—are used for phage therapy. Additionally, in modern phage therapy, complete genome sequencing of each phage can help with avoiding use of phages which carry toxin or virulence genes, or have mechanisms to acquire these attributes by recombination with resident prophages and carry them on to other hosts.

It is also important to differentiate between the safety of a specific phage and the safety of a particular phage preparation. In the early days of phage therapy, several authors reported cases of insufficiently purified phage preparations or the presence of chemical contaminants and attributed treatment failures to this problem. Thus, the safety and sterility of the phage preparations must be ensured sound design and Good Manufacturing Practice. Past treatment failures are a reminder that any claims of safety need to be corroborated by scientific evidence.

**Cytotoxicity and Safety of Phage**

It is surprising that there appear to be no comprehensively conducted in vitro cytotoxicity experiments for phage, designed similarly to routine cytotoxicity testing of chemical compounds. The reasons may be that phages are assumed to be ‘clinically safe’, due to a lack of reports of adverse effects during human and animal experimentation and possibly decades of reported human phage therapy mainly in Georgia, Russia and Poland. A lack of in vitro cytotoxicity studies also extends to lack of data on phage cytotoxicity in wound models. It needs to be borne in mind that therapeutic phage would be locally applied in concentrations of approximately $10^9$ phages per milliliter, at volumes of several milliliters, to cells which are involved in a very complex immune system involving cytokines and other biochemical messenger systems; any minor interference by phage preparations in the wound healing and graft-take processes could potentially affect clinical outcomes significantly.

There is a further potential issue that is not generally considered. Phages are structures within the 1–100 nm size range and could be seen as nanoparticles. It may be useful to study phages in a similar way to nanoparticles, investigating surface charge, aggregation and nanotoxicity. The migration and incorporation of similarly sized nanoparticles into mammalian cells has been investigated and may offer an increased insight into how phage could operate in a complex system and further evidence of the safety at therapeutic doses.

**Immunogenicity**

Phage, when administered intravenously, may evoke an immune response, which may be stimulated by some component in the phage preparation and/or by the phages themselves. Bacterial products remaining in the preparation were sometimes suggested to have possibly contributed to phage therapy failure in the past. At the same time, there are indications that using sterile-filtered crude phage lysates may actually improve treatment outcomes by stimulating the immune response. In fact, immune system stimulation is the directed purpose of the Staph Phage Lysate marketed in the US by Delmont Labs since the 1940s for veterinary staphylococcal skin infections.

Repeated exposure to the same phage strain may also activate the adaptive immune system and result in antibody production, decreasing the efficacy of a particular phage for its intended pathogenic target. It is unknown whether purified phage can elicit allergic reactions, though immune responses can eliminate phage under certain conditions. While crude lysates may actually improve treatment outcomes by stimulating the immune response, in contrast purified phage preparations may have some immunosuppressive function; both types can modulate cytokines.

Whether or not any kind of effect of phage on the immune system is desirable, it is debatable whether intravenous phage therapy will be accepted as a serious therapy option until clear evidence has been presented exploring the nature and extent to which systemic phage administration affects the human immune response.

**Can Human Phage Therapy be Profitable?**

For a pharmaceutical product to be profitable, the income generated from it must exceed the initial investment. For phage therapy both the profit and the investment factors remain unknown. To bring a new licensed drug to the market can cost as much as $400–800 million, which can constitute a hindrance to any new drug development. Since no licensed phage product for human therapy has yet reached the Western market, the costs remain unknown.

The pharmaceutical industry has not displayed much interest in phage therapy. The reasons for the low level of interest are closely related to the reasons for the lack of new antibiotics. The return on investment from new antimicrobial agents is less than that from other drug classes. They are only required for short courses, rather than as a continuous therapy as required for chronic conditions. Due to aging populations, drug discovery efforts are largely focused on medicines that treat chronic medical conditions, which commonly occur in the elderly.

The tendency in recent years has been for pharmaceutical companies to focus most of their research on improving well-established structures, rather than attempting to discover structurally novel compounds, and this is particularly true in terms of antibacterial agents. There is a tension here between the interests of public health and of the pharmaceutical industry. Limiting the use of the new, high-priced broad-spectrum antibiotics is in the interest of public health, to discourage resistant bacterial strains from developing. To this end, it is important to continually introduce new drug formulations but to enforce prescribing protocols. The appropriate measures of antimicrobial stewardship to extend the useful life of antibiotics have a downside: they discourage the more widespread use of newly developed, more expensive antimicrobials, which in turn negatively impacts sales. It may be more in the interest of patients to develop selective antibacterial agents, specific for a small group of pathogens, rather than more broad-spectrum antibiotics; however this would also limit the indications and the market of such product. For these reasons some large pharmaceutical companies have indicated that they are limiting or entirely abandoning anti-infective research, except...
for anti-HIV agents, which are more profitable.

A range of companies specializing in bacteriophage have appeared or become established in recent years, demonstrating that there is growing commercial interest in phage therapy. However, the companies currently undertaking research and development regarding the use of phages are all small to medium-sized enterprises, rather than the large multinational companies traditionally associated with drug development. A prominent example of this is Amplipher Biosciences/Biocontrol Ltd. UK, which is facing high regulatory hurdles, the need for substantial financial investment and the prospect of having to finance controlled clinical trials. With such high investment cost at stake, phage therapy investors will want to protect their intellectual property (IP) on any phage product. The issues around IP are discussed in more detail elsewhere. In short, private companies will be reluctant to invest in a product that may be difficult, or impossible, to patent. To add to this challenge, the US and EU patenting pathways differ.

Patenting of phages that have been isolated from the environment (not modified) is currently possible, but it provides limited IP protection. Investing in a product without full IP and particularly patent protection is unlikely to be financially viable. In addition competitors may easily isolate similar phages from the environment. For these reasons some companies are exploring other avenues, such as patenting specific phage sequences, pursuing novel concepts like using phage deficient in their lytic system, using genetically engineered phage as a vector for lethal genes, or molecules, employing phage products such as cell hydrolyases, also known as lysins, or modified phage products. Formulação of delivery systems may offer another avenue for IP protection, for example dressings, skin graft material or sutures impregnated with phage.

The need for high financial investment, coupled with the absence of a guarantee of a market, means that phage therapy may be considered inherently financially unattractive. If phage product development if solely left up to the private sector, future research efforts may be focused on finding phage products aimed at providing financial returns, rather than combating infectious disease.

Profitable phage products may not necessarily be those intended for human therapeutic use, but for decontamination or for veterinary use, as the cost of bringing a product to the market would be low compared with the extensive clinical trials required for licensed human medicines. Public-private partnerships and involvement of the National Health Service (NHS) may be required to let phage live up their full potential in combating the crisis of antibiotic resistance.

**Regulatory Agency Approval**

Phage-based products intended for clinical use are still not explicitly covered by existing regulatory guidelines; however, ListshieldTM, a product for spraying onto ready-to-eat meat and poultry products, was successfully given full Food Additive approval by the US FDA in 2006, while a European anti-Listeria phage product was given GRAS (generally regarded as safe, no objection) status by the US FDA, also in 2006.

There has been much debate how regulatory agencies would and ought to regulate therapeutic phage. Should phage be considered a ‘biological medicinal product’ (Commission Directive 2001/83/EC) or, as suggested by Verbeken et al., an ‘advanced therapy medicinal product’ (Commission Directive 2003/63/EC)? For the former, clinical trials will need to be conducted for each phage strain, while the latter is based on manufacturing processes focused on various gene transfer produced bio-molecules, with legislation making allowances that “it may not be possible to perform conventional clinical trials” (Commission Directive 2003/63/EC).

The question of how to legally classify phage products is important. This is not purely an academic debate within the phage community, as the outcome of this argument may make the difference between phage therapy becoming a successful mainstream treatment option or not. The crux of the debate lies in whether the emphasis should be placed on process controls or on characterizing each single phage strain used for therapeutic purposes. If process controls are the determining factor, updating phage cocktails with more effective phage would become much easier and cheaper. Otherwise a clinical trial with all its cost implications might need to be conducted after each phage cocktail modification.

Kutter and Sulakvelidze pointed out that updating with new strains is not unprecedented in the West and suggested therapeutic phage could be treated similarly to influenza-vaccines in terms of regulation. The authors report that in the former Soviet Union only the ‘principal’ phage preparation and manufacturing and quality control protocols needed official approval; a similarly flexible approach in the West would foster the success of phage therapy. The advantage of allowing licensing of therapeutic phage products as a biotechnology product would be that it would allow for continuous changes of phage strains in response to evolution of dominant antibiotic-resistant bacterial strains and allow phage preparations to have maximum clinical effectiveness.

With Listshield the FDA allowed updating of the host strains as well as substitution of similar well-characterized phages. There is hope that a similar approach will be taken by regulators when it comes to licensing human phage therapy products.

**Absence of Rigorous Proof of Efficacy: Funding for Clinical Phage Research**

Despite an overwhelming number of reports that phage has been used successfully for a multitude of infections, there remains an urgent need for double blind, placebo-controlled studies. Factors discussed previously, particularly hurdles involving licensing issues and lack of patentability of most phages, are most likely to discourage investors. Clinical trials are cost intensive, requiring years of resources and qualified support, but without them phage therapy has little chance of success.

As the interest of the pharmaceutical companies is necessarily in maximizing their short and medium term profits, it may be the case that they will under-invest
in novel techniques/treatments that bring better clinical results when these new treatments are not profitable on a sufficiently short timescale (i.e., not fast enough). It is surely the role of a nationalized health service with a remit to prioritize patient outcomes, to identify and step into such gaps, either by providing ring fenced funding or at least by co-ordinating research, otherwise opportunities for the development of beneficial new technologies may be missed.

As the NHS is publicly funded, one way for phage therapy to gain a foothold in the UK would be to secure NHS funding and work within the structure of the NHS, possibly using unlicensed phage preparations on a named-patient basis under the emergency clause. In the future the potentially strongest driving force behind phage therapy may become the public, provided phage therapy is appropriately lobbied. This may be difficult as individual researchers may not have the resources to start PR campaigns and patient groups may be unaware of the potential of phage therapy. However mainstream media, popular science publications, science blogs and other internet-based media may help in communicating the urgency of finding alternatives to antibiotics and facts about phage therapy.

**Paradigm Shifts**

Phages are biologically active particles, genetically changeable, with very narrow activity spectra and display entirely different pharmacokinetics to antibiotics. As with any paradigm shift, the ‘old’ antibiotic paradigm—the concept of using chemicals to treat bacterial infections, is needed to explore the new paradigm—that of phage therapy. Yet, although the outcome—the killing of bacteria—is similar, the means by which this is achieved is entirely different. The kinetics of phage therapy are very different from antibiotic pharmacokinetics and these differences have a dramatic impact on the use of phage, compared with antimicrobials.

There is a serious risk that if these differences are not reiterated to healthcare professionals, to peers and particularly to licensing authorities and accounted for when attempting phage therapy, the nature and potential of phage may be misunderstood and phage therapy may fail a second time in the West. In practice this may be overcome by treating therapeutic phage preparations in the same way as a restricted antibiotic, by dispensing to individual patients only on specialist consultant microbiologist advice, after rigorous testing of suitability.

**Conclusion**

Phage therapy has undoubtedly huge potential, but whether it will be fulfilled will depend on a variety of factors. The multi-national pharmaceutical companies may be reluctant to invest in phages that maybe difficult to patent or, if patented, may provide limited IP protection. It is most likely that the pioneers in phage therapy will remain in the ranks of academia and small spin-off companies, which may mean lengthy delays before phage therapy reaches mainstream therapeutics.

Therapy with phages that are hard to isolate or those with a narrow spectrum may be seriously hampered by the absence of available strongly lytic phages. This may be remedied by international collaborations, the building of national phage libraries and using phage cocktails. Licensing authorities would need to be convinced of the benefits of regularly updating phage mixtures; alternatively, phage may be used in unlicensed form on a named-patient basis in collaboration with physicians.

Successful phage therapy is likely to require a certain minimum infrastructure, which private companies or academia alone may not easily provide. Bacteria would need to be isolated from the patient, rapidly identified, and screened against available approved phage cocktails or individual phage strains, to ensure maximum clinical efficacy. On the basis of these results, a specialized phage cocktail might then be mixed and formulated into a medicinal product in an aseptic suite, as is already done for intravenous antibiotics and chemotherapeutics in hospital pharmacy departments. Within a large hospital environment, particularly with close ties to academia, an appropriate infrastructure, which may require effective cooperation between scientists, clinicians and other healthcare professionals, already exists. From a public health perspective it could be justified that public money be spent on bringing phage therapy for key antibiotic-resistant bacteria into extensive clinical trials. This may need to be done, at least in the UK, by collaborations between the NHS, academia and private phage companies.

Phage preparations may need to be treated like restricted antibiotics, dispensed on a named patient basis with consultant microbiologist involvement. Adequate phage prescribing and administration may need to be monitored by microbiologists and pharmacists, and excellent communication with the rest of the healthcare team would be essential.

Failing to pursue the avenue of phage therapy may become ethically unacceptable, when weighing risks against benefits. However, it appears that pharmaceutical companies are unlikely to invest in phage therapy for various reasons. It will need to become unacceptable in the public eye for patients to routinely die of infectious diseases that might have been curable with phage.

Looking for alternatives to antibiotics to treat bacterial infections would be in the spirit of the UK action plan. Whether phage therapy ultimately can play a significant role in dealing with the looming antibiotic crisis remains to be seen, but at the very least investigating it as a potential treatment option in combating bacterial diseases would be in line with government recommendations and perhaps common sense.

**Disclosure of Potential Conflicts of Interest**

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. No funding has been received for the production of this manuscript.

**Acknowledgments**

I would like to thank Dr. Neil McNair for reading the manuscript.

**Note**

Dr. Alexandra Henein died in February 2013, just after submitting revisions of
this paper. Although she had been living with scleroderma since her diagnosis in 2010, she continued to work until only a few days before her death. Her illness took her away from lab work, but she still took great pleasure in writing and in teaching. Her interest in therapeutic use of phage was long standing, being the subject of her PhD thesis in clinical pharmacy from Brighton University, and she remained convinced of its merits as she continued her work on antibiotic stewardship as a member of the Royal Pharmaceutical Society. She fought her illness with strength and bravery, and will be sorely missed by her many friends. She is survived by her husband Dr. Neil McNair, whom she married in July 2012.

References
1. Alais AJ. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res 2005; 36:697-705; PMID:16216651; http://dx.doi.org/10.1016/j. jareteh.2005.06.009
2. Soulī M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. Euro Surveillance: Bulletin Européen Sur les Maladies Transmissibles 13 2006
3. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al.; Infectious Diseases Society of America. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008; 46:155-64; PMID:18172444; http://dx.doi.org/10.1086/524891
4. World Health Organization. WHO Strategy for Containment of Antimicrobial Resistance. Switzerland: WHO, 2001
5. House of Lords Select Committee on Science and Technology. Resistance to antibiotics and other antimicrobial agents. Session 1997-98. 1998. London: The Stationary Office. pp. 1-108
6. Department of Health. UK Antimicrobial Resistance Strategy and Action Plan. London: Department of Health, 2000
7. Office for National Statistics Deaths involving Clostridium difficile, 2011. London: Stationery Office, 2012
8. Office for National Statistics Deaths involving MRSA, 2007 to 2011. London: Stationery Office, 2012
9. World Medical Association. 2008. Declaration of Helsinki, 8th (Seoul) amendment
10. Weber-Dabrowska B, Muczyk M, Górski A. Effective phage therapy on the turnover and function of peripheral neutrophils. FEMS Immunol Med Microbiol 2002; 34:135-8; PMID:12381464; http://dx.doi.org/10.1111/j.1576-695X.2002.tb00614.x
11. DeMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003; 22:151-85; PMID:1260642; http://dx.doi.org/10.1016/S0169-2046(02)00216-1
12. Projan SJ. Why is big Pharma getting out of anti-bacterial drug discovery? Curr Opin Microbiol 2005; 8:427-30; PMID:15472532; http://dx.doi.org/10.1016/j.molbiol.2005.08.003
13. Broudy TB, Fischetti VA. In vivo lysogenic conversion of T4. (Streptococcus pyogenes to T4) with Lysogenic Streptococci or free phage. Infect Immun 2003; 71:3782-6; PMID:1283469; http://dx.doi.org/10.1128/IAI.71.7.3782-3786.2003
14. Broudy TB, Scholl D, Adhya SL. The prospect for bacteriophage therapy in Western medicine. Neutro Norway Drug Discov 2003; 2:498-97; PMID:12772623; http://dx.doi.org/10.1038/ndri111
15. Penassa-Warren BJ, Warren JB, Wong SS, Misewich JA. Biological cellular response to carbon nanoparticulate endotoxin. J Phys Cosnds Matter 2006; 18:5128-30; http://dx.doi.org/10.1088/0953-8984/18/33/ s34
16. Taylor PW, Stapleton PD, Paul Luzio J. New ways to treat bacterial infections. Drug Discov Today 2002; 7:1086-91; PMID:12546840; http://dx.doi.org/10.1016/S1359-6446(02)02498-4
17. Beauchamp TL, Childress J. (2008) Principles of Biomedical Ethics.: New York: Oxford University Press
18. Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis 2004; 38:1279-86; PMID:15127541; http://dx.doi.org/10.1086/420937
19. Kutter E, Sulakvelidze A. (2005) Bacteriophages: an appraisal of their role in the treatment of bacterial infections. Antimicrob Agents Chemother 2006; 50:2087-97; PMID:16723570; http://dx.doi.org/10.1128/AAC.47.3.2087-2097.2003
20. Yacoby I, Shamis M, Bar H, Shabat D, Benhar I. Lysis-deficient bacteriophage therapy decreases endotoxin and inflammatory mediator release and improves survival in a murine peritonitis model. Surgery 2005; 137:659-66; PMID:15933632; http://dx.doi.org/10.1016/j. j.2005.02.012
21. Westwater C, Kasman LM, Schofield DA, Werner PA, Dolan JW, Schmidt MG, et al. Use of genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections. Antimicrob Agents Chemother 2003; 47:1301-7; PMID:12564662; http://dx.doi.org/10.1128/AAC.47.1.1301-1307.2003
22. Yabocb I, Shamis M, Bar H, Shabat D, Benhar I. Targeting antibacterial agents by using drug-carrying filamentous bacteriophages. Antimicrob Agents Chemother 2006; 50:2087-97; PMID:16723570; http://dx.doi.org/10.1128/AAC.00169-06
23. Fischetti VA. Using phage lytic enzymes to control pathogenic bacteria. BMC Oral Health 2006; 6(Suppl 1):S16; PMID:16934117; http://dx.doi.org/10.1186/1472-6831-6-S1-S16
24. Hanlon GW. Bacteriophages: an appraisal of their role in the treatment of bacterial infections. Int J Antimicrob Agents 2007; 30:118-28; PMID:17567613; http://dx.doi.org/10.1016/j.ian- timicag.2007.04.006
46. Parracho HM, Burrowes BH, Enright MC, McConville ML, Harper DR. The role of regulated clinical trials in the development of bacteriophage therapeutics. J Mol Genet Med 2012; 6:279-86; PMID:22872803; http://dx.doi.org/10.4172/1747-0862.1000050

47. Mai V, Ukhanova M, Visone L, Abuladze T, Sulakvelidze A. Bacteriophage Administration Reduces the Concentration of Listeria monocytogenes in the Gastrointestinal Tract and Its Translocation to Spleen and Liver in Experimentally Infected Mice. Int J Microbiol 2010; 2010:624234; PMID:20652074; http://dx.doi.org/10.1155/2010/624234

48. US Food and Drug Administration (2006) Human Services, Food Additives Permitted for Direct Addition to Food for Human Consumption; Bacteriophage Preparation Federal Register /Vol. 71, No. 160 / Friday, August 18, 2006 /Rules and Regulations 47729, 21 CFR Part 172 [Docket No. 2002F–0316 (formerly 02F–0316)]

49. Thiel K. Old dogma, new tricks--21st Century phage therapy. Nat Biotechnol 2004; 22:31-6; PMID:14704699; http://dx.doi.org/10.1038/nbt0104-31

50. Withington R. Regulatory issues for phage-based clinical products. J Chem Technol Biotechnol 2001; 76:673-6; http://dx.doi.org/10.1002/jctb.435

51. Verbeke G, De Vos D, Vanechcourte M, Merabishvili M, Zizi M, Pirnay JP. European regulatory conundrum of phage therapy. Future Microbiol 2007; 2:485-91; PMID:17927471; http://dx.doi.org/10.2217/17460913.2.5.485

52. Commission Directive 2003/63/EC of 25 June 2003. Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use. Official Journal of the European Union 2003; L159:146-94

53. Sulakvelidze A. The Challenges of Bacteriophage Therapy. European Industrial Pharmacy 2011; 10:14-8

54. Payne RJ, Jansen VA. Understanding bacteriophage therapy as a density-dependent kinetic process. J Theor Biol 2001; 208:37-48; PMID:11162051; http://dx.doi.org/10.1006/jtbi.2000.2198

55. Skurnik M, Strauch E. Phage therapy: facts and fiction. Int J Med Microbiol 2006; 296:5-14; PMID:16423684; http://dx.doi.org/10.1016/j.ijmm.2005.09.002