

7-11-2014

Risk of Compliance: Tracing Safety and Efficacy in Mef-Lariam's Licensure

Julie Marie Gerdes

University of South Florida, jgerdes@mail.usf.edu

Follow this and additional works at: <https://scholarcommons.usf.edu/etd>

 Part of the [Other Communication Commons](#), and the [Rhetoric Commons](#)

Scholar Commons Citation

Gerdes, Julie Marie, "Risk of Compliance: Tracing Safety and Efficacy in Mef-Lariam's Licensure" (2014). *Graduate Theses and Dissertations*.

<https://scholarcommons.usf.edu/etd/5222>

This Thesis is brought to you for free and open access by the Graduate School at Scholar Commons. It has been accepted for inclusion in Graduate Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact scholarcommons@usf.edu.

Risk of Compliance: Tracing Safety and Efficacy in Mef-Lariam's Licensure

by

Julie M. Gerdes

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Arts
Department of English
College of Arts and Sciences
University of South Florida

Major Professor: Carl Herndl, Ph.D.
Julie Stagers, Ph.D.
Ambar Basu, Ph.D.

Date of Approval:
July 11, 2014

keywords: risk communication, pharmaceuticals, technical communication

Copyright © 2014, Julie M. Gerdes

Acknowledgments

I am very grateful to my committee members, who each contributed a unique perspective to this project. I am also indebted to Dr. Remington Nevin, who not only contributed expert insight into this complicated case that he has been following for years but also graciously shared primary sources from his collection. Without these documents, this study would not have been possible. On a personal note, I must also thank my parents, Jim and Marie Gerdes, and my person, Catherine Ruprecht, for always picking up the phone or jumping on a plane to support and encourage me.

Table of Contents

List of Figures	ii
Abstract	iii
Introduction	1
Technical Communication, Praxis, and Pharmaceuticals	1
Literature Review.	4
Distributed Agency.....	9
Research Design.	16
Early War on Malaria: History of Malaria Response (1500 BC-WWI)	17
Quinine: Humans' First Synthesized Antimalarial.....	18
Chloroquine.	23
Chapter 1: Vietnam Era Research.....	25
Topoi as Response to Fluid Rhetorical Situation	25
Promising Chemical: Medicinal Chemistry 1971	27
Human Trials: WHO Bulletin 1974	31
Experimental Drug: Pharmacology and Chemotherapy 1979.....	35
Chapter 2: NDA Research Findings	42
Safety and Efficacy	44
Dosages	46
Discussion.....	51
Rhetoric of Pharmaceutical Compliance.....	51
Roche Labels and Medication Guide	52
Label as Afterthought.	52
Drug Packaging.	53
Post-Marketing Communication	57
Public Definition of Safety.....	57
FDA Response.....	57
Implications.	60
References.....	62

List of Figures

Figure 1: Drug Research Process	7
Figure 2: Distribution of malaria in the United States, 1882-1935. (Report for Certification and Registration of Malaria Eradication from United States of America published by PAHO/WHO, December 1969).....	8
Figure 3: NDA summary of adverse effects, p. 15	47
Figure 4: (left) FDA label request in NDA response, 2 May 1989 (right) Roche response to request, 2 January 1990.....	52
Figure 5: First approved Lariam label, 1989	53
Figure 6: Precautions section of 1990 Lariam insert	55
Figure 7: 2013 FDA “black box warning” on mefloquine chloride label.....	59

Abstract

The Walter Reed Institute of Army Research developed the antimalarial drug mefloquine then collaborated with Hoffman-La Roche to produce the drug under its brand name “Lariam,” after Food and Drug Administration (FDA) approved licensure in 1989. For over twenty years, the Army used this pill as its “drug of choice” for soldiers deployed to endemic regions until 2009, and in 2013 the Food and Drug Administration warned that the drug’s neurotoxic effects could be lasting, if not permanent. The sociopolitical exigence of developing a new biochemical antimalarial drug rushed the development and licensure processes, and the modern craving for certainty in the New Drug Application (NDA) process led to a biomedical disaster—economically, politically, and interpersonally. In this paper, I present the factors contributing to uncertainty and heightened exigence in the development of what I call “mef-Lariam” in a nod to Latourian hybridization. By tracing the history of the drug’s development process, I argue that definitional stasis around the NDA genre’s terms *safe* and *effective* undergird a dangerous ontological orientation to medicine that privileges an ethic of expediency. Finally, I argue that actor-network theory can help medical rhetors apply a more ethical, multiple view of medical research that could prevent the future licensure of toxic pharmaceuticals.

Introduction

The truth, or at least what my family, the State Department, the Fulbright Organization, and I have determined as the truth is that the psychotic break, the hallucinations, the amnesia— it all was an extreme side effect of the Lariam, the anti-malarial drug that was a prescription of choice in those days. It's got a reputation for doing things like what happened to me, as well as much worse.

—David MacLean, guest on This American Life, NPR

Technical Communication, Praxis, and Pharmaceuticals

Mefloquine hydrochloride was the result of a major Army-run Vietnam-era malaria drug discovery program that began in 1963, and it received Food and Drug Administration (FDA) licensure under the brand name “Lariam” in 1989. In 2013, the malaria prophylaxis received the strictest warning that the FDA puts on drugs, and pharmaceutical company Hoffman-La Roche (Roche) stopped manufacturing the drug. The FDA’s “black box warning” explained that the drug’s neurotoxic effects might be lasting, if not permanent. While this case is not consistently framed as a “crisis,” it has received significant media attention, with the publication of David MacLean’s memoir *The Answer to the Riddle is Me*, *New York Times* articles, National Public Radio segments, and a *60 Minutes* special. Most of these outlets find ready victims but struggle around the construction of a perpetrator, alluding to Roche, the FDA, and the drug itself, but many of them come back to the technical documentation that accompanied the pill. In fact, the

FDA's own response, as serious side effects were reported, was to rectify the wrongdoing by turning to the prescription labels, revising and increasing warnings.

Latourian actor-network theory can reveal agency in a historical crisis case by bringing to the surface the actants that contributed to said crisis. The flattened network of actants involved in the FDA licensure of mef-Lariam reveals that sociopolitical exigence rushed the development process, scientific stakeholders' narrow definition of "effective" excluded concerns of mental health and noncompliance, and the New Drug Application prioritized a positivistic view of efficacy over effectiveness and safety. Ultimately, the lack of definitional stasis around the terms "safe" and "effective" among NDA stakeholders including lab scientists, pharmaceutical developers, and regulations officers as well as a sloppy translation of those terms to public audiences led to the premature licensure and marketing of Lariam.

The main contributing factors to the FDA licensure of mefloquine were (1) sociopolitical exigence that rushed the development process, (2) a narrow definition of "effective" that excludes concerns of mental health and likelihood of noncompliance, and (3) the deprioritization of safety in NDA masked by euphemistic warnings. These factors are not particularly problematic at development stages and during the construction of scientific facts and experiments within research contexts, and in fact they are particularly unique to emerging drugs. However, in the drug development practice, as with most scientific innovation, there is a point at which research findings are translated to recommendations and policy. In the case of mef-Lariam, an inexplicit definition of "effective" allowed for an ethic based on efficacy and expediency, motivating researchers prevented regulatory writers from accurately translating findings from medicinal chemistry labs and clinical trials into precautions and warnings on pharmaceutical labels for public consumer audiences.

Consumers are met with pharmaceuticals daily. Casual patients heed warnings of side effects and weigh the risks of taking and not popping pills for particular conditions, deciding whether the pain pill that induces wooziness and prohibits driving will be worth skipping out on a late trip to the store or whether the blood-thinning ibuprofen is a better option than wine for a headache, knowing that combining the two is a bad idea. Recent outbreaks of antiquated and preventable illnesses like polio and measles illuminate public weariness of side effects, with the vaccination debate making a case for rhetorical intervention in medical risk communication.

The romantic and widespread view of western biomedicine is that it evolves with technological advances and responds to emerging disease. However, as with any field, medicine is plagued by a number of situational factors like policy, regulation, approval boards, etc. At the consumer level, drugs appear as little miracle substances. Take them and feel better. Take them and prevent feeling bad. The assumption is that Science has proven the drug's safety and value. However, behind the scenes in drug discovery are in-depth analyses and discussions over how findings should be interpreted and presented. Developers adjust dosages and observe results use the best equipment they can access or create within time and budget constraints. Often, stakeholders disagree about what particular data sets from the field mean and negotiate how they should be translated into policy and consumer recommendations. This thesis follows the case of one drug, revealing the complimentary roles of kairos and exigence in the drug discovery and production processes to examine how sociopolitical exigence leads to a lack of definitional stasis among stakeholders (biochemists, FDA regulators, and physician/patient consumers) around the terms "safe" and "effective" in new drug applications and licensure.

Literature Review. Recent literature in the field of technical communication indicates a turn away from current traditional practices to new considerations of culture and power (Longo, 2000; Scott, Longo & Wills, 2006; Roberts, 2006; Mirel, 2002). This move is crucial to the scholarship as it responds to the claim of J. Blake Scott, Bernadette Longo, and Katherine V. Wills (2006) that “hyperpragmatism continues to dominate technical communication research and teaching, even coopting those practices that could be transformative” (p. 8). As they note, Carolyn Miller’s work on revealing and critiquing the extremist logical positivist approach to technical writing since the early twentieth century has been fundamental in bringing technical communication back to the humanities (Miller, 1979, p. 17). In fact, as Longo argues in her historical book *Spurious Coin* (2000), when viewed as “cultural artifacts,” technical documents are uniquely situated to reveal institutional power structures.

In an analysis of Nazi memos, Steve Katz (1992) highlights the ability of well-written technical documents to obscure a lack of ethos. He points out that a document can be rhetorically sound and functional within its own discourse community to explain that it will nevertheless adapt the ethics of the organization that it is representing. He calls this “not an anomaly nor a problem in technical writing only, but a problem of deliberative rhetoric” (p. 258), citing Aristotle’s distinction of deliberative rhetoric as that which aims to get work done for the future. Katz distinguishes the tendency to embrace the basing of a moral standpoint on expediency and technology as “predominant in Western culture” (p. 258). As a manifestation of human character, he argues, ethos defines technical writers’ ethics. When an organization’s ethics are epistemologically based on a search for objective “Truth,” then its morals tend to adopt similar foundations in an ethic of expediency.

Technical communication in medicine is no exception to this argument. In fact, the role of regulatory agencies is to check this ethic of expediency in drug development. While not necessarily immoral—prophylactic drugs emerge to prevent death and illness—this ethic represents an epistemology that privileges speed and objective efficacy over effectiveness and safety. Perhaps for this reason, the primary regulating body of food and drugs in the West, the FDA, focuses on the topoi *safe* and *effective*. While these terms invoke the morality of the original Hippocratic Oath, an ethic of expediency underlies them, and consequently allows rhetors to wrap them into the trope of an objective *efficacy*. This becomes apparent when the document leaves the context of the organizations that subscribe to this ethic as the basis of their communication, in other words, when it leaves the realm of Western science and technology. The safety and effectiveness of mef-Lariam are questioned by the public patient's sense of morality. Proponents of the drug within the FDA and WRAIR react to the public's perception that this is an unsafe antimalarial in divergent ways, from continuing to back the pill's biochemical ingenuity to questioning the military's field prescription, thus revealing their individual ethic.

As a subdiscipline, the rhetoric of medicine has gained traction within rhetoric, and recent studies have focused on medical technologies (Graham, 2009), multiple ontologies in medicine (Mol, 2002; Graham & Herndl, 2013), and feminist theory (Koerber, 2005; Hausman, 2013; Condit, 1994). However, it is important to remember that the practice of medicine in an institution-driven western system relies most primarily on policies and public health campaigns that dictate normative solutions to threats of disease. Some scholarship within technical communication circles has begun this work of engaging with real practice in the field through case studies of public health responses (Gong & Dragga, 2008; Ding, 2013; Danisch &

Mudry, 2008), and this work needs to continue to complement theories of technical communication, particularly in regard to medicine.

As a technoscience, medical campaigns mix pure sciences (e.g. chemistry) and applied sciences (e.g. public health). Thus, campaign failures carry with them a nearly infinite number of culprits; while lawsuits often attack medical *malpractice*, doctors might turn the finger towards bad policy or protocol. Rarely, however, do public responses to failures in medicine go back as far as research communities, taking the effectiveness of drugs and instruments for granted. A debate that focuses on proximal causes ignores underlying assumptions about the construction of facts in scientific discourse. Meanwhile, a case study approach to researching problems in medical communication allows researchers to understand then circumvent a surface-level debate over proximal causes and instead unfold the root of agency by analyzing the texts that construct and illuminate social networks.

From a modern standpoint, malaria prevention in nonimmune travelers is a biochemical affair. Sporozoites in the plasmodium-infected female Anopheles mosquito enter into the human bloodstream, setting off a sequence of events that lead to malarial infection. Thus, if pharmacologists can synthesize a compound that inhibits the heme polymerase that malaria parasites release to infect host cells, they have prevented malaria at the cellular level (Hawley, Bray, Mungthin, Atkinson, O'Neill & Ward, 1998). Medicinal chemists experience uncertainty in terms of structural formulas, derivatives, and synthesis while pharmacologists experiment with bioavailability, excretion, and toxicity. One transition in scientific ontology happens when a drug passes from experimentation with theoretical compounds to experimentation with animals and humans. Another transition happens at the regulatory level as medical officers translate pharmacology reports into dosage approvals and endorsements. Governing agencies like the

American Centers for Disease Control (CDC) then translate these findings into recommendations for public audiences (See Figure 1).

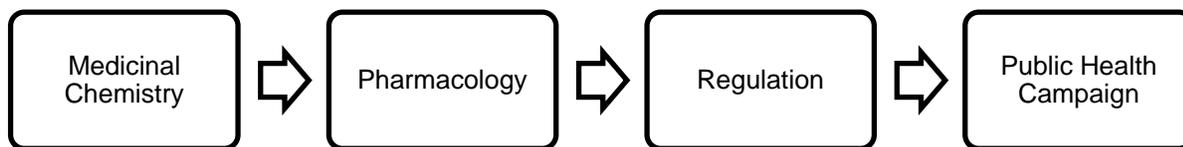


Figure 1: Drug Research Process

Functionally, these roles overlap but allow subject experts to focus on sets of achievable tasks. Ideologically, however, these breaks tend to segment pure and applied sciences, with medicinal chemistry authors writing about internal biochemical interactions and pharmacologists writing about external corporal results of those interactions. According to this model of division, sociological factors emerge at the regulatory and especially the public health phases of a drug's development, far removed from the initial chemical conception of it.

However, a divided model of conceptualizing drugs in this way wrongly establishes medicinal chemistry as a practice without social context. No matter how much institutions distinguish biology as a natural science and studies of the humanities as social, at its core, the separation is a false binary. Latour (1999) blows out the contradiction of modernity, problematizing the nature/culture dichotomy, which fails to account for the proliferation of acting hybrids (combinations of Nature and culture) that make up our sociopolitical landscape and constitute decisions about how people use science, which is never really pure because it is also “made” in sociopolitical contexts. This false binary resonates in the halls of contemporary institutions as “pure” science separates itself from social sciences and the humanities. In fields of health and medicine, this iteration actualizes itself in the health/medicine divide, with “public health” officials doing the social work of distributing the pure medicine that biochemists develop.

The impossibility of this divide is perhaps nowhere as important to note and warn against as it is in global health. Not only is public health fundamentally a rhetorical practice rife with behavior change models (how do we persuade people to act on behalf of their health) but it also relies on the contradiction of modern medicine. Public health solutions to malaria demonstrate the hybrid nature of doing healthcare; pure chemistry has not been able to eradicate the parasite at universal rates. On the one hand, environmental action reliant on widespread use of DDT eradicated malaria from the U.S., suggesting that the solution to the environmental problem was found. But even in a western context, eradication did not occur at even rates, and southern states were last to experience relief (see Figure 2).¹

Furthermore, in the U.S. and Europe, the parasite continues to adapt and thrive in economically marginalized global regions. So, while seemingly scientific answers have worked in

contexts that support the dominant western approach to health, development organizations have moved to social and cultural answers in other contexts, often assuming the logic “if *we* educate *them* (of the science), *they* will change their behavior and malaria will end.” Dutta (2008) developed the culture-centered approach to health communication that “questions the

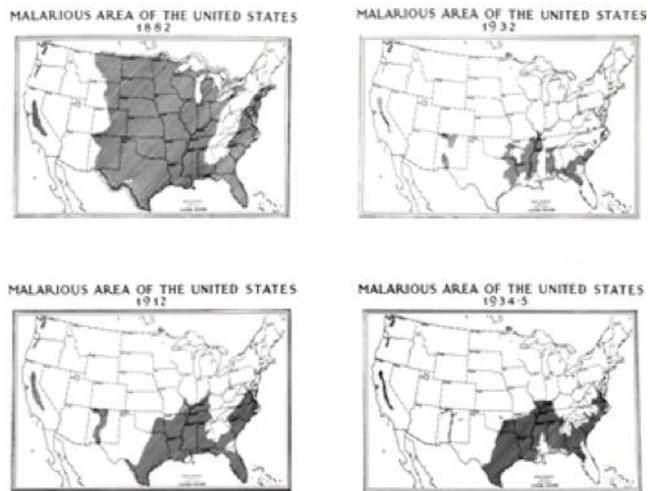


Figure 2: Distribution of malaria in the United States, 1882-1935. (Report for Certification and Registration of Malaria Eradication from United States of America published by PAHO/WHO, December 1969)

¹ The “Global South,” a trending term proposed to replace “third world” and describe marginalized countries of the southern hemisphere, is reminiscent of the colloquial “Dirty South,” referencing the agrarian region of the American South that has traditionally suffered from fewer job opportunities and political capital in the American system.

constructions of culture in traditional health communication theories and applications, examines how the latter have systematically erased the cultural voices of *marginalized* communities in their construction of health, and builds dialogical spaces for engaging with these voices” (p. 4). This approach helps explain the violent marginalization that results from basing an entire network of policy on the foundations of a dominant perspective of western biomedicine that rests on a positivistic view of biochemical fact.

Distributed Agency. Claiming, “we have never been modern,” Latour (1979) emphasizes the need for bridging the gap between social and life sciences; a gap that helps the life sciences maintain authoritative roles as experts of matter and thus divert blame to those who use or interpret the facts they reveal. By distinguishing “pure” fields like medicinal chemistry from applications of them, social context is removed and emergent facts are seemingly universal until disproven. One way in which this ontology is harmful and inaccurate is that it presents a kind of pure science that is void of uncertainty.

In the pharmaceutical science, what really happens in the research communities that develop the biological knowledge to produce new drugs is represented by publications with titles such as, “A Process *Similar to* Autophagy Is Associated with Cytocidal Chloroquine Resistance in *Plasmodium falciparum*” (emphases mine) (Gaviria et al., 2013). In research article titles, modifiers distance hard fact from preliminary research, and limited methods are revealed, even openly presented. Debate over the efficacy of animal testing for human biomedical responses, messy international clinical trials, loose reporting, favoritism in observation based on tangentially related studies, and a culture of competitive research grant proposing to institutes like those that comprise the National Institutes of Health all point to a field enveloped by uncertainty.

In fact, most biomedical journal articles report descriptive accounts of observations in specific contexts but don't presume to project generalizations as main objectives. That's the policy maker's job. Collins and Evans (2002) establish a Third Wave of Science Studies that "turns...on a normative theory of expertise" (p. 249). Without removing different kinds of understanding from the network, they emphasize that the expertise of scientists is different from that of the policy maker, which in turn differs from that of the public. As actants that are part of the network, contributing to the artifact that is mef-Lariam neurotoxicity, these experts receive varying degrees of information, especially amidst variables such as dosages and half-lives that are adjusted frequently during clinical trials, making stasis difficult.

At different points in time during the drug development process, one actant may take the reins as more agentive for progressing the project, but ultimately, the agency of public acceptance, policy, regulation, and medical research is distributed across a network rather than passed from one player to the next. When a basketball team loses on a missed buzzer beater, announcers and spectators may shame the shooter for her inaccuracy, but teammates and coaches will account for the moments leading up to the shot that put them in a shootout situation, counting every turnover and lackadaisical practice and attributing the loss to infinite factors. Networked agency accounts for a team of expertise. It can also lead to finger pointing in different directions, as victims of some perceived wrong-doing seek proximal causes to blame.

While the discursive transition of uncertainty into certainty for the sake of a modern Science is not inherently problematic for the way that it functions in regulatory documentation, one only has to follow the network down the line a bit farther to see the considerable long-term problems for all stakeholders of positioning that certainty at the center of policy decisions and packaging it to public audiences as Science. While a Public use collapses ideas of safety with

effectiveness and efficacy. By proposing that the drug was effective, the FDA is assumed to be supporting its safety, for a drug that is deemed unsafe will not be taken and thus cannot be effective. The FDA's conflation of safety with effectiveness isn't important in the realm of biological systems theory or even on the lab bench or in animal experimentation. However, once that definition reached praxis, wherein patients experienced hallucinations and other side effects, noncompliance deemed that a lack of safety was causal to a lack of effectiveness.

Aside from questions of expertise and legitimacy, other complications arise along the way in the journey from lab to regulation to pillbox label. At every turn, one diversion in the Deleuzian line of flight could result in a vastly different outcome. If a project is unfunded, new knowledge fails to emerge, but if a project is highly anticipated, then all knowledge about it is privileged early, and perceived progress is pushed forward as fact. If we pull out of the war that necessitated a new, inexpensive antimalarial, the Army research program shuts down, leaving nonmilitary travelers (business travelers, Peace Corps volunteers, etc.) to use alternatives. Such a move could also mean that academic researchers take over the project, spend more time justifying their work to the International Review Board and to funding agencies, and all clinical trials are run under a different code of ethics and definition of efficacy, giving researchers the chance to recognize neurotoxicity. Organizations like the IRB and NIH are able to police the progress of research projects before they leave the institution, requesting that the scientist move closer and closer to certainty before pharmaceutical companies move to production. It's important for technical communication scholars, whose work concerns ethics and representation and whose skills include discourse analysis and network mapping, to intervene in productions and applications of technical documents, particularly in the complicated network of medical

regulatory issues working with the various stakeholders around what Wilson and Herndl (2007) call “boundary objects.”

Once research is transcribed into a material object (e.g. a capsule), institutions compensate for uncertainty about processes within biological systems at microlevels by flooding the public with recommendations, treatment plans, policies, procedures, contraindications, dosage guidelines, regulations, side effect warnings, and pamphlets. These post-production texts manage a lack of empirical knowledge that starts in the lab and that are unacceptable by a public of non-experts. Anticipating these issues, researchers focus on reaching the most comprehensive results possible. However, limitations, both epistemological (wherein researchers don’t know better, especially in a unique rhetorical situation) and sociopolitical (e.g. pressure to stick to project timeline, budgetary restraints), prevent researchers from achieving ideal levels of certainty. On the one hand, for medical breakthroughs to be passed quickly in a capitalist structure, they must be monetized. Pharmaceutical companies rely on the outbreak of highly exigent diseases and conditions to keep their wheels rolling. Meanwhile, research in public institutions moves much slower, waiting on red tape and adhering to regulations. Capital for this work in academic contexts, while tied to an economic gain, is more overtly about publications and scholarly reputation.

Technical communication scholars can use artifacts from across the drug discovery process to illuminate the rhetoric of compliance and to consider the role of institutional policy documents. The field might also begin considering the dual role of medical labels as product packaging for consumers and informants for expert advisors such as physicians. As actants in the biomedical network move from R&D to communicating that development, they must consider

the necessary transition of science from uncertainty in the lab to hard fact in regulation and policy to ethically provide the transparency that would benefit a wide range of end users.

Science studies and Latour's quasi-objects bring us closer to a functioning take on societies and on the functionality of nonhuman and human actors in society construction. Quasi-objects allow philosophers to provide "social explanations for hard scientific facts" (Latour, 1993, p. 55), and this is the approach that malarial health and its hard science products need to avoid the dualist/dialectic merry go-round ride malarialists have been stuck on.

This project refers to mefloquine chloride's material form as "mef-Lariam" in this allegiance to the quasi-object that Latour develops. As a material object circulating in a dualist policy society, Lariam forces patients to choose: be on the side of Nature, and comply with antimalarial policy or be on the side of culture, and deviate from policy, turning your back on Science to face the risks. As a quasi-object, mef-Lariam allows patients to consider the messiness of biomedical science, and it accepts the capitalist pharmaceutical enterprise as well as laboratory uncertainties that arise during drug development and policy decisions. Quasi-objects consider expertise as shades of degree, and they allow for varied approaches to solutions. In fact, malaria historian Gordon Harrison (1978) classified early approaches to foreign malarial endemics as hinging on a definitional divide, writing, "Whereas [Ronald] Ross and [U.S. military medic William Crawford] Gorgas thought of malaria control in medical terms and sought above all to drive *Anopheles* from the vicinity of human habitations, (Angelo) Celli, an intellectual, historian, and passionate social reformer, saw it essentially as a social problem" (p. 170). While parasitologists continue to see disease prevention as an offensive attack on infectious disease carriers, public health advocates see medicine as a means of defending innocent persons against said attack. However, this reduction of the problem only comes on the

outside of the black box. In practice, parasitologists understand that their approaches are problematic, if for no other reason than malaria's propensity to build resistance to their developments. Nevertheless, the work of malariologists in mitigating these risks as they manifest is extremely relevant in keeping up with the disease and maintaining ethos in the present environment of intercontinental travel.

The "world risk society" that Beck (1992) claims new modernity lives relies on the framing of risk as monocausal; there must always been a root cause leading to risk, regardless if its human or not. However, plasmodium parasites, ever adapting, ever changing in context as well as physiological makeup, deny a singular cause. As long as biochemists target a particular therapy for a particular version of the parasite, they will always be just beyond the reach of a solution. Like a child catching lightning bugs in a jar, she will never succeed by opening the jar to catch one at a time; the threat of escape arises with every opening. Instead, if the child wants to capture all lightning bugs in an area, she must find a way to attract all the bugs with one sweep, luring them into the jar. The malaria parasite is always outsmarting Science, and this characteristic may be the most threatening aspect of it. Latour (2003) responded to Beck's "remodernization" by explaining, "for Beck and his group the proofs have to be in the *substance* of the phenomena they study, for me only in the *collective interpretation* given to phenomena which, all along, have never been modern" (p. 39, emphasizes his). He draws a line between Beck's focus on substance and his own on interpretation. The issue with dealing with risk plus any version of modernity is that in Beck's version of society, risks associated with an environmental, medical, or other industrial issue, are products of developments and changes *within* these specific industries. However, an ANT approach to modernity posits risks as interpretations of interpretations made by or presented to various actants. ANT doesn't presume

to offer a better way of handling risk factors but rather a more realistic way of seeing them as subjective interpretations.

In *Pandora's Hope*, Latour (1999) describes the translation of individual actors to a collective actants with the example of the popular “guns don’t kill people, people do” argument.. He debunks this logic by explaining, “you are another subject because you hold the gun; the gun is another object because it has entered into a relationship with you” (p. 179). Replacing Latour’s gun with medicine clarifies the nonmodern position on biomedical technologies. When a medicine, or for that matter, a parasite, enters into a subject, the two become a third actant. Illness itself is a quasi-object; it does not exist without a human host. As an isolated and fixed *thing*, if it were possible to exist as such, mefloquine chloride is purely a technology. It is science that happens when $C_{17}H_{16}F_6N_2O$ combines. But when combined with a human subject, this compound binds to brain receptors and inhibits polymerase (we think), preventing plasmodium falciparum from entering the blood stream. The human brain without mefloquine is not the malarial brain with it. Mefloquine is nothing but a set of elements without the human brain. The two combined lead to a new agentive collective, and all of the moving parts and shifting goals of this collective must be accounted for in order to move past a circular debate about whose fault mefloquine suicides belong to. Moving the technology and the human subject away from isolated mechanisms and into varied and constantly changing variables would allow policy makers to understand shared responsibility. In fact, this collective itself is the very basis for clinical trials; testing the collective as one and observing the effects, and this topic will prove crucial to the case.

Lastly, the divided nature of health and medicine Lastly, the divided nature of health and medicine extends violently to create a stigma around mental health issues, wherein health

professionals are only now beginning to make headway on legitimizing concerns of mental health, albeit these attempts are more often turning to neurorhetorics, framing various disorders as neurologic (Jack, 2010).² By using ANT to bring agentic actants to the surface, it's possible to see what actants were denied agency, failing to enter the network in policy decisions. It's also possible to see what factors motivated the development process at significant nodes, namely points in time. If decision makers like the medical officers and label designers are presented with the agentic factors motivating particular decisions, then presumably they will be able to make decisions from an ethics of healthcare. At minimum, awareness of the larger networks in which actants are making decisions would hold them accountable for the ethics to which they prescribe.

Research Design. Latourian ANT establishes a flat framework for laying out the network and elucidating artifacts that define the actants involved in the case. As a historiography, this project relies on surfacing the historic documents that serve as legitimization and legal justification for policy decisions and thus informed medical recommendations. Coming out of sociology and typically an ethnographic practice, ANT urges, "We have to be as *undecided* as the actors we follow" (Latour, 1987, p. 175, emphasis his). This work doesn't do much digging into private artifacts but rather looks at the common artifacts that scientific, regulatory, and ultimately public stakeholders accessed and cross-referenced themselves. Beyond

² In the 2010 *Rhetoric Society Quarterly* special issue on *Neurorhetorics*, scholars debate the role of neurorhetorics in which Jordynn Jack calls on readers to consider the very rhetorical use of the prefix neuro-, writing, "the articles in this issue argue for an expanded definition of neurorhetorics that acknowledges these impulses [to investigate neural underpinnings of rhetorical topics like pathos and persuasion], but also upholds the importance of critical and rhetorical perspectives on discourses involving the brain" (p. 405). Jack's work on the rhetorical framing of autism as a function of neurology rather than as a legitimate illness of its own right. Increasing medicalization of mental conditions threatens the legitimacy of lived experiences among patient populations, and rhetoricians have seen an opportunity to intervene in the negotiations between neuroscience and expression. Unfortunately, such divides tip the scales towards an increasingly divided view of medicine that attributes crises to proximal causes.

narrative case mapping, I apply a discourse analysis approach to determine points at which uncertainty defined the mefl-Lariam discovery project in documents that scientists used to communicate within their discourse communities, namely chemotherapeutic and pharmacological research journal articles. I then analyze the New Drug Application (NDA) submitted by Hoffman-La Roche to the FDA. Firstly, however, my goal is to retell the story of mefloquine's development and distribution through a nonmodern lens.

Lawrence Grossberg (2010) conditions the work of cultural studies, a discipline that aims to deeply contextualize discourse, as “messy.” This work is no exception. Part of doing the work of tracing is justifying what gets included in the network. If done right, this occurs naturally as artifacts discursively present actants. As Latour writes in *Science in Action*, “From now on, the name of the game will be to leave the boundaries open and to close them only when the people we follow close them” (p. 175). Of course, my analysis maps my own interpretation and has both the insight and limitations of an outsider. After presenting a historical background of the case in narrative form below, I use chapters one and two to present discourse analyses of primary journal articles that document mef-Lariam's emergence in the community and the New Drug Application that led to FDA licensure, respectively.

Early War on Malaria: History of Malaria Response (1500 BC-WWI)

The history of malaria has been fairly consistent— by and large, it is a wartime disease confronted by wartime research programs. The parasite has adapted to the biochemical responses we've thrown at it, and yet researchers continue to take largely the same approach to preventing malarial disease. The parallel networks of malaria and of biomedical malarial research have followed mostly straight-line trajectories.

Malaria's historic impact on global societies has been devastating, to say the least. If I am to trace the *relevant* factors in this case, that is, the actants that speak, and those that are spoken about and demonstrate agency in the flattened network of antimalarial efforts, I must go back as far as the earliest documentation of the disease, where the actants begin to taper out. The history of medical discourse is rife with war metaphors, political complications, and inequity. These figures represent the positivist view of biomedicine that has defined the field at least since Plato likened rhetoric to cookery and philosophy to medicine in *Gorgias*, implying that medicine and philosophy led to Truth. The science wars progressed the paradox of what Richard Bernstein (1983) calls "Cartesian anxiety," but for biomedicine, this positivism goes a long way back.³ Malaria is one of the oldest and most frustrating infectious diseases for medical scientists and practitioners alike. Egyptian papyrus manuscripts presumed to be written by Hippocrates circa 1500 BC suggest malaria among diseases he documented (Russell, 1955; Garnham, 1966; qtd. in Harrison, 1978, p. 265). The disease that Hippocrates documented was identified by periodic fever in swamp and marsh areas (Meshnick & Dobson, 2001, p. 15). Chimpanzees and African ancestors were known to have chewed leaves of the *Vernonia amygdalina* shrub, which possesses secondary compounds that relieve malaria, and other common botanical materials like clove, nutmeg, and onion help destroy plasmodium (Shah, 2010, p. 88).

Quinine: Humans' First Synthesized Antimalarial. The network of malarial reactions in dominant western biomedicine goes back to quinine. Heralded as a miracle cure and naturally occurring, quinine set out on a line of flight that, upon articulation, could have set off a number of possibilities for defining early American healthcare. Had the fact that it was natural and

³ For more on this conversation, see Thomas Kuhn's *Structure of Scientific Revolutions*.

harvested from tree bark been seen as the grounds for its success, or had it existed in a context of other natural remedies, the system of synthetic chemical material development might have developed with less anthropocentrism. Nonetheless, the anthropocentrism that does arise from biomedical research, wherein researchers create and test chemicals that are seemingly “out there” waiting to be tested, is a good place to start the process of tracing in ANT. In the western model of healthcare, man and science are most agentic. Thus, tracing the man-chemical hybrids illuminates one line of quasi-object agency.

Meanwhile, bark from the cinchona tree possesses the complex alkaloid quinine, which poisons malarial parasites (Shah, 2010, p. 89). Jesuits in South America lauded the bark’s success against disease and brought it back to malaria-ridden Europe in the 1630s (Rocco, 2003). Of course, at the time, the medicine was considered “anti-Catholic” because of its Jesuit association, so it took fifty years to become commonplace in England. Widely distributed by the 1800s, quinine has been attributed as motivating Britain’s success in its attack in Ghana in 1874 and thus bringing European imperialism to Africa (Curtain, 1998; Brantlinger, 1985; qtd. in Shah, 2010, p. 89). Unfortunately, reserves of the bark were limited, and cinchona seeds didn’t make it to Europe until the Dutch smuggled them and spent thirty years tending to their cultivation in Indonesia (Shah, 2010, pp. 92-93). Both Dutch and British politics prevented early widespread distribution of quinine, with the British producing and selling understrength packets on the streets of India and failing to provide levels close to those required for treatment in the country (Shah, 2010, p. 95).

In the States, malaria was first reported by Jamestown settlers in the early 1600s. It became the subject for preventative medicine as the first military hospital department arose in 1775 and began developing germ theory (Ockenhouse, Magill, Smith, & Milhous, 2005, p. 12).

By the 1830s, when soldiers defending white settlers were engaged in fighting the Seminoles in Florida and experiencing exceptionally often fever, doctors were prescribing high doses of quinine (Ockenhouse, Magill, Smith, & Milhous, 2005, p. 12). During the Civil War, Union troops previously unexposed to malaria suffered from fever as they moved into southern regions, even delaying the seizure of Vicksburg, Mississippi for fear of anticipated high soldier mortality rates in the woods and swamps involved in traveling through the region.

Although the U.S. had identified the cause of fever breakouts in the Civil War and southern states as a parasitic infection called malaria and begun environmental measures to eradicate it, the very eradication of the disease prevented immunity for travelers. As such, malaria in the 20th and 21st centuries has become a traveler's threat. Nothing inherent about malaria is "African" or "Asian," but the lack of it through large-scale capitalist and technical insecticide campaigns in western countries have made the disease appear as if it characterizes these global regions and thus their inhabitants.

When the 1898 War with Spain, a country that was endemic at the time, led to deployed soldier camp outbreaks of uncertain disease, the U.S. Military established an investigatory board under the leadership of Major Walter Reed to inspect and research soldier disease. Some speculated that typhoid fever was the culprit, but the team determined that typhomalaria did not exist uniquely, and more importantly it established justification for microscopic testing of malaria back in the U.S. In 1900, Walter Reed investigated yellow fever in Cuba with Carlos Finlay under COL William Crawford Gorgas to determine the significance of mosquito transmission to preventative measures. In response, they quickly and successfully implemented a comprehensive plan to eradicate yellow fever in Cuba. However, as a much more complicated

disease, malarial parasites would be more difficult to fight. Insecticides, netting, and swatters helped American citizens fend off malaria until its Pacific involvement in World War I.

Quinine remained the only malarial drug prescribed by western countries until the 1940s. Until the mid-20th Century, malaria was a concern of great exigence for western doctors and scientists, but it fell out of vogue once no longer endemic in the U.S. and Europe. At the same time, as the epoch of colonization slowed, so too did the concern for developing malaria prevention and treatment methods.

Postcolonial and subaltern studies can help explain the nature of that health inequity that played a role in the necessity of WRAIR to take over the research side of developing mef-Lariam; a project is typically reserved for researchers paid by the pharmaceutical company responsible for manufacturing a pill. Partly because of the Kefauver Harris Amendment of 1962, which required increased proof of efficacy for FDA approval, and party because there was little money to be made in developing a medicine for low-income countries, the only exigence for doing so came from the organization that needed to protect its members' bodies from the foreign threat while in combat. In what Spivak (1988) refers to as "epistemic violence," western biomedicine remains a tool for the rich. As a preventable disease, malaria most prominently plagues developing nations along the Equator, mirroring the habitats of the persistent HIV/AIDS endemic. Epistemic violence can help explain not only this phenomenon, but also the rhetorical exigence of an situation in which soldiers were at risk of failing to maintain their authority as physically strong and resilient-bodied Americans in the context of a war in which international politics dictated America's need to help out a South Vietnamese population vulnerable not only to Communism but also disease

German microbiologists realized that synthetic dyes could be used as stains in the lab. Happenstance discoveries, in fact, are common in science; the popular school lesson of the “discovery” of penicillin— the result of petri dishes coincidentally left out to mold— is one such case. But these natural or “coincidental” occurrences need a hard lab bench to be legitimized in society. The move from observation of use of dye for staining to strategic repurposing of dye as cellular malaria treatment in the lab draws the border between nature and science. Although the synthetic dye was a biochemical manipulation, it was considered instrumental to a larger cause, much the same way that the cinchona bark was a common tree material until it became a means of fever prevention and ultimately a political bargaining tool.

Those “happenstance” discoveries do not jive with the positivistic science in a vat model, so they are immediately transported to the lab to begin the process of instrumentalization, which requires not only measurement and observational data sets but also a place within the sociopolitical landscape. Institutional exigence determines the transferability of soft science into hard fact. The desire, in the growing free market economy, to develop commercial pharmacology, paired with the political power of antimalarials in war time, allowed scientists to consider novel approaches to prevention and bring chance observations into the lab to be tested and Scientificized (black boxed). As Latour (1987) notes, “the paradox of the fact-builders is that they have simultaneously to *increase* the number of people taking part in the action- so that the claim spreads, and to *decrease* the number of people taking part in the action- so that the claim spreads *as it is*” (p. 207). The building of atebriene required just one fact maker’s observations of methylene blue but many persons confirming, passing along and building off of its synthetic derivatives to not only legitimize the fact but also to move Bayer — and Germany— to the top of

the list of up and coming malarial research giants, thus providing a basis for legitimizing their work in the future.

Particularly effective on staining plasmodia, methylene blue successfully cured two malaria patients, making them the first subjects of synthetic drugs (Meshnick & Dobson, 2001, p. 19). A popular dye company, Bayer became a leader in pharmaceutical manufacturing, and they developed plamoquine and mepacrine (atabrine) in 1925 and 1932, respectively (Meshnick & Dobson, 2001, p. 19). In 1934, a Bayer scientist developed resoquin, but deemed it too toxic for use and consequently synthesized its derivative, sontoquin.

Chloroquine. When the Japanese seized Java during World War II and effectively took over the global quinine supply, American, British, and Australian scientists collaborated to develop new synthetic drugs. They tested and judged toxic resoquin, and continued to test 16,000 other compounds.

This failure to develop a drug based on its toxicity is common in biochemistry; however, the later distinction as the “resoquin error” points to the balancing act that science is forced to play with risk. Without a “measure” for risk, best judgment suffices to determine what drugs are followed up with and which are put on the shelf. While mefloquine wound up being too toxic to release, resoquin was not toxic enough to later convince policy makers that they should have abandoned the compound. A scientist might throw up their hands and claim “I can’t win with these people,” alluding to the companies and policy makers requesting a final material product ready for market. On the other hand, developing a model for risk assessment that considers publics, rather than policy makers, as its main audience could get risk *makers* to bring more voices into their network, assessing the implications of their science from multiple perspectives.

Upon capturing North Africa, where the French were doing clinical trials on sonotochin, the Allies rekindled their interest in resochein. Johann “Hans” Andersag took atabrine and replaced its acridine ring with a quinoline ring to develop “chloroquine” that did not discolor skin and eyes (Krafts, Hempelmann, & Skòrska-Stania, 2012, p. 3). The drug went on to become the leading antimalarial worldwide (Meshnick & Dobson, 2001, p. 20). At the time of discovery, Andersag made a salt from the compound and called it “resochein,” but its toxicity shelved it at Bayer for over 10 years, which was considered a major mistake (Krafts Hempelmann, & Skòrska-Stania, 2012, p. 4). Eventually a form of chloroquine was put in cooking salt and heralded by the WHO in the 1950s and 60s.

Chloroquine rose quickly to popularity. It was touted as a cheap miracle drug, taking over the role of aspirin in Africa, and doctors advised persons to take chloroquine at the onset of any degree of fever, even before a malaria diagnosis (Shah, 2010, p. 102). Unfortunately, its success was also its downfall. The WHO’s medicated salt program has been considered as a contributor to widespread chloroquine resistance. Unfortunately, by the mid-1960s, *plasmodium falciparum* (*p. falciparum*), the more serious of the two most common strains of malaria, had become resistant to widely used chloroquine treatments. This kind of resistance was first observed in 1957 in Thailand, then in 1959 along the Colombian-Venezuelan border and in 1978 in Kenya and Tanzania (Sheehy & Reba, 1967; Baird, 2004; Campbell, Collins, Chin, Teutsch, & Moss, 1979; Croft, 2007, p. 170), but chloroquine was the best antimalarial American medicine had developed.

Chapter 1: Vietnam Era Research

Topoi as Response to Fluid Rhetorical Situation

The rhetorical situation in which any rhetor operates is contingent on a number of factors, least of which is exigence. Scholars Bitzer (1968) and Vatz (1974) argued whether rhetors enter into or create discursive situations, bringing attention to the term “exigence,” Consigny (1974) gets closer to the definition of exigence that is closest to what’s at play in the WRAIR Malaria Drug Discovery Program. By claiming that the antimony between Bitzer and Vatz stems from their incomplete consideration of rhetorical practices, Consigny makes the case for rhetoric to function as an art, with real constraints that can be overcome with the use of commonplaces.

Exigence depends entirely on the interpretations of actions and discourse. For instance, from a dominant western biomedical vantage point, the word “malaria” invokes an enemy in the form of a rare and dangerous parasite. On the other hand, for some settled bantu tribes in sub-Saharan Africa whose bodies had become immune to the parasite’s deadly hemozoin, the disease signified a weapon that protected them from migrant enemies. Viewing rhetoric as an art with certain constraints not only supports its role in medical interventions but also carves out a space for ethical considerations about said interventions. It also explains how seemingly indeterminant but fatal health situations are met with such an array of responses globally. To respond to this fluid nature of the rhetorical situation in medicine, the U.S. FDA makes use of commonplaces, or topoi, in an attempt to create stasis among invested stakeholders throughout the drug development process, leaning on the terms “safety” and “efficacy.”

Developing Exigence in Practice

On January 15, 1973, President Nixon announced plans for a ceasefire that would bring troops home from Vietnam to airport protests in a country divided on their involvement in the War. While the soldiers, many of them drafted, put themselves in immediate danger on the front lines, for most, their biggest risk came from a second war that Americans were fighting—the war on malaria. During the Vietnam War as well as every previous military engagement in endemic regions, more Americans died from malaria than from bullets (Irwin, 2012, p. 3). Given high mortality rates from the parasitic infection in the Southwest Pacific during World War II, military medics were strict about preventative care by the time troops deployed for Vietnam, and they required all deployed personnel to take chloroquine.

As more soldiers fell ill to infection with *p. falciparum* malaria in Vietnam, Congress responded by reinstating a Malaria Drug Discovery Program the Walter Reed Army Institute of Research (WRAIR) in Bethesda, Maryland. U.S. Army Surgeon General George Sternberg founded WRAIR in 1893 as the Army Medical School, and its primary focus has been the development of preventative medicine for infectious disease (WRAIR, 2014). At this site, researchers would test nearly 3,000 compounds for potential new drugs between 1963 and 1976 (Maugh, 1977). Exigence for reaction was formed from two principle events: the Vietnam War and the observation of chloroquine resistance. The logic underlying this reaction was the binary “develop a drug or die,” insisting that the best and in fact only response rested on the success of the program in unveiling a compound. The dominant biomedical assumption that disease is a biochemical problem and thus must be funded as so led to the funding of a multi-million dollar project whose product ultimately got taken off the market and blacklisted. The plasmodium parasite has been creating a rhetorical exigence probably since before humans roamed the planet,

but the artful use of war and heroism tropes angled the situation so that the exigence could only be met with one rhetorical response. In other words, by framing the situation as a biomedical risk emergency, the funding of a large-scale, high-speed biomedical research project was perfectly fitting.

Carolyn Miller (1992) frames this as the “centrality of kairos to the rhetoric of science” (p. 310). As she points out, timing and opportunity play essential roles in our understanding of scientific discourse as event whose appropriateness shifts. The DoD’s discursive decision to implement the Drug Discovery Program came at a kairotic moment of rhetorically created and sociopolitically motivated exigence.

Promising Chemical: Medicinal Chemistry 1971

Latour’s first chapter in *Science in Action* is entitled “literature,” in which he starts with the most basic, earliest start to the construction of a black box, “when someone utters a statement, what happens when the others believe it or don’t” (p. 21). In the case of mef-Lariam, an entire country of scientists, politicians, and military men were eager to believe promising leads in antimalarial discovery, so rather than extremist dissenters, domestically, mef-Lariam researchers had to deal with scientific yes-men. Collectively, readers of this early literature largely agreed on both the science and the foci of medicinal chemist reports, the first genre to document antimalarial compounds. On purpose of these texts was to establish a baseline for what the FDA would eventually use as terms of approval. As a compound, the literature needed to establish efficacy as grounds for moving forward with safety tests.

During this initial discovery period, publications were written for an audience of discourse community members, all aware of the limitations of transferring “pure” biochemical science into applied drug manufacturing and prescription. The article’s writers, at this point, are

only concerned with the black boxes of chemistry. WRAIR test results show that their compound demonstrates antimalarial properties. They are not concerned with the history, funding, or controversial prison trials related to the WRAIR results. As inputs, these tests result in valuable outputs.

The first publication to document mefloquine was a 1971 article supported by the Office of the Surgeon General of the U.S. Army Medical Research and Development Command. The project started in chemistry discourse communities, presented at the Southeast Regional American Chemical Society Meeting and then published in the *Journal of Medicinal Chemistry*. Written by two postdocs and their PI at a University of Virginia lab, these scholars used results they obtained from WRAIR to present a study on the development of the 4-quinolone compound.

The initial paragraph of this article opens with a reference to previous studies, mentioning that compounds in a series being pursued had “consistently shown only moderate or slight antimalarial activities against *Plasmodium bergeri* in mice, and they were also moderately phototoxic,” referencing a 1968 publication in the same journal (p. 926). The paragraph continues to elaborate on the development of the current research based on reconfiguring of elements in the 4-quinoline-methanol that demonstrated increased antimalarial success. The paragraph ends by justifying pursuit of this compound when it “proved to be curative at 20 mg/kg and relatively nonphototoxic” (p. 926).

The document’s first nod at “safety” comes in the integration of the root *toxic*. Because of the tendency of previous antimalarial agents and the general mechanisms of similar compounds to produce phototoxicity, this focus on skin reactions became the precedence for evaluating safety in the late 1960s and well into the 1970s. It’s also important to note that phototoxicity reports as well as proof of efficacy in this article (specifically in a footnote about the curative

levels) reference back to WRAIR studies. As the leaders in the charge to find an antimalarial, WRAIR science was the authority, and it furthered its voice in scientific communities when articles like this refer back to it. Latour (1987) writes that “attacking a paper heavy with footnotes means that the dissenter has to weaken each of the other papers” (p. 33), but in this case the weight of WRAIR papers is equivalent to countless smaller references. Because the global epidemic didn’t lend itself to profit and thus wasn’t well funded for university or pharmaceutical researchers, the Army had an ironic monopoly on malaria research in the States. Thus, dissenters within the medicinal chemistry discourse community would have a hard time attacking their results; the only mice studies funded in the nation.

Following the paragraph introduction, explanatory paragraphs and chemical compound line drawings walk the reader through the process of chemical reduction to the resultant bis(trifluoromethyl)- \square -(2-piperidyl)-4-quinolinemethanol that would become mef-Lariam. Midway through the article, after mentioning the most promising result that was prepared on a large scale, the researchers approach concerns of safety, writing, “Because of the suspicion formerly held that there might be a relation between phototoxicity and uv absorptivities, these values have been assembled in Table II” (p. 927). The article concludes with a section of highly technical language describing what is labeled as “experimental results” completed with apparatuses and a spectrograph.

Uncertainty abounds in biochemical research; as a “pure” modern science, the field operates like a game of logic, and trial-and-error largely dictates results. The use of “might” here and modifiers throughout the article points to the uneasy but exciting steps that the UVA scientists took to get to their result; “addition of 2-PyrLi gave the pyridyl ketones 9a-9d, but only 9a,b were obtained in good yields” (p. 926, with letter/number combinations pointing to

mathematic equations on the same page). This is reflective of the cooking allusion that Plato makes in the *Gorgias*, wherein he likens rhetoric to flattering cookery. What Plato's modern divide fails to consider is how akin to cooking medicine actually is. In a review of clinical protocols in drug development, practitioners Bell and Walch and technical communication scholar Katz (2000) argue that while Plato dismisses rhetoric as deceitful, Aristotle's introduction of the art into his "pharmacy" is more accurate for the process of drug development.

In this early paper, formations are "reasonably interpreted," and interpretations "may be significant." Additionally, "it was feared [by the authors] that the PyrLi addition might be impeded by steric effects of the 5 substitute" and they muse that "possibly this overreduction was facilitated by the appreciable release of steric strain" (p. 927). The chemists constantly balance concerns about the unpredictability of steric effects (atomic spatial arrangement of chemical reactions) and make adjustments to their model, much like a chef would add a pinch of salt to temper sweetness or a baker might throw in baking soda to get their goods to rise in a second batch. Early biochemical papers in antimalarial research show simultaneous vulnerability and hopefulness. Over 300,000 compounds were synthesized and tested in the WRAIR campaign alone, and 2 emerged. Trepidation marked this program, and the writing that documents it show the finger crossing that chemists did with presumably every promising start. There was not one moment before the drug's black box that declared, "this is it! We found our compound!" That came later, after the ready-made science was packaged.

In terms of the equipment used to get to the black box, many rhetoricians of science have considered the effect of technology on not only science but on society as a whole, particularly post-WWII. By and large, the research that these UVA chemists present is only possible with the development of named equipment, which they reference in a footnote but is now more often

included in a methods section. In this study, the chemists treat equipment in much the same way they treat the WRAIR test results— as a given necessity whose material conditions are unquestioned. In reality, the equipment is another network imbued in sociopolitical constraints.⁴

Human Trials: WHO Bulletin 1974

After the publication of these findings, the WHO bulletin published the first human test results of mefloquine in a 1974 article by K. H. Rieckmann, Director of the Center for International Health at Rush University in Chicago; G. M. Trenholme and R.L. Williams former Majors of the Medical Corps at WRAIR; P.E. Carson, Chairman of the Department of Pharmacology at Rush University; H. Frischer, Director of Clinical Hematology and Red Cell Genetics Laboratories at Rush University; and R. E. Desjardins, Major in the Medical Corps at WRAIR. This interdisciplinary and cross-institutional group laid out a three-page description of their 17-person preliminary study in the *Bulletin of the World Health Organization*, a monthly peer-reviewed, open-access public health journal primary interested in developing countries.

In the article, the team presents the problem with current chloroquine-resistant antimalarials as, at least partially, stemming from side effects and medication schedules:

Protection of persons against falciparum malaria may be difficult in areas where chloroquine-resistant strains are common. Currently available drugs are often ineffective in preventing or suppressing malaria infections. Undesirable side-effects, the possible selection of resistant bacteria, and awkward medication schedules further limit the use and value of some drugs or drug combinations. During recent investigations with mefloquine (WR 142 490), we found that a single dose of the drug had a prolonged

⁴ For more on the discussion on the rhetoric of technology, see Miller (1998) and Winner (2010).

suppressive activity against a strain of *P. Falciparum* showing pronounced resistance to chloroquine and pyrimethamine. Preliminary results obtained with this 4-quinolinemethanol compound are described in this report. (Trenholme, Williams, Desjardins, Frischer, Carson, Rieckmann, Canfield, 1975).

As the only introductory paragraph in the piece, the piece begins, as most research projects do, with an introduction to the problem, identifying the justification for the new medicine. However, the results focus on the effectiveness of malaria prevention⁵, which, after many failed attempts, was a crucial first step. In early studies, the distinction between therapeutical and prophylactic capacities of was important; those that proved only capable of treating were thrown out of the pool early. Similarly, the research money that had gone into chloroquine only for plasmodia to outsmart it scared malariologists. To stay on top of the next wave of drug-resistant parasites, the newest drug would need to prove it could knock off the most recent violent offender. Otherwise, they feared, they would be facing a seemingly wasteful drug development project when a new strain came about in a few years, resistant to WRAIR's pill.

The results in this paper were very promising. First, the single volunteer exposed to malarial mosquitoes two days after taking mefloquine never developed parasitaemia, nor did the four volunteers bitten 14-16 days after drug administration. The article reports that in testing three individuals exposed to the parasite 21 days after taking mefloquine, "the drug suppressed parasitaemia in at least 2 and possibly all 3 of the individuals, but it did not prevent the

⁵ Annemarie Mol introduces the problem with conceptualizing illness as singular and segmented in *The Body Multiple*. In the case of mefloquine, side effects and medication schedules are mentioned in some contexts but sidelined in others. Considering a drug for its individual purposes, while serving individual stakeholder needs, opens gaps through which valuable connections can be lost and unseen.

development of patent infections” (p. 176). While the results demonstrated that the prepatent period with mefloquine extended to a mean of 29 days versus the mean of four control volunteers, which was at 10 days, the focus of the preliminary study was already moving towards establishing a half life. The experiment showed that the drug would work for 14-16 days, which was crucial as the daily doxycycline, an antibacterial FDA approved in 1969 that was beginning to show promise, posed many potential problems as a main malaria prophylaxis (Magill, 2013).

The discussion section of this introductory public health article presents the background of developing this drug off the basis that a 4-quinolinemethanol showed potential in a previous study “conducted at our centre many years ago” (p. 376) but displaying “phototoxic side-effects” that prevented its further development. The authors explain that the funding of the program allowed further research in the 4-quinolinemethanol class, and explained that, in a study of one such compound, WR 30 090, “no appreciable phototoxicity or other side-effects were observed” (p. 376). By the fourth paragraph of the discussion section, the researchers get to the present study, claiming that the administration of mefloquine in nonimmune volunteers was “well tolerated” in single doses.

Here again, the observation of phototoxicity in SN-10 275 is the focus of risk in 4-quinolinemethanol compounds. Because of the nature of scientific experimentation, which relies either on innovation or further development of previous research, the continued focus on phototoxicity made sense, just as future foci on neurotoxicity will make sense following mefloquine’s fall. Impossible to predict all long-term drug complications, uncertain scientists rely on observational data from previous work. However, this can also blind observers to other side effects, especially when the precedence is set on a very visual display such as phototoxicity, manifesting in widespread red skin rashes.

The WHO Bulletin article concludes by stating that the studies “confirm the prolonged suppressive activity of mefloquine against infection with the Viet-Nam (Marks) strain of *P. falciparum*” (p. 377), indicates a recommendation for a biweekly prophylactic dosage as well as further research on other strains, and for further research “to establish its cumulative toxicity, if any, during repeated administration.” The very last sentence of the article raises the concern of possible emergent strains of resistant malaria parasites.

By the time this program was initiated, one of the biggest fears of malaria drug research was, and continues to be, the potential of the parasite to develop resistance to new drugs. The overuse of chloroquine and consequent widespread resistance meant that research was no longer just about inhibiting heme synthesis (and trying to do so before the parasite reached the liver stage) but rather about negotiating spending on development of new drugs to suit immediate needs and acknowledgment of long-term fears that those new drugs might lead to a cycle of drug evasion by the slippery parasite (and in the case of mefloquine, resistance by *p. falciparum* has been confirmed in southeast Asia, particularly on Thailand’s borders with Myanmar and Cambodia as well as southern Vietnam (Arguin, P.M. & Tan, K.T., 2013). The nonmodern reality of biomedical research is perhaps nowhere more apparent than in clinical trials, where researchers cross their fingers and hope that their theories materialize into viable solutions. In this setting is the closest human biomedical research can get to approaching claims of certainty; through observed responses and measurements, one can see a drug’s effect— if a patient doesn’t develop malaria, which can be evaluated through blood serum samples as well as observed physical symptoms— then it can be deemed effective.

Measuring safety this way, however, is more problematic in that side effects beneath the surface, moving through neurons and into folds of the brain, go unseen and may not manifest for

years. If equipment is available for evaluation of particular toxicities, the researcher must know to test for it. In the case of early mefloquine testing, there was a great deal of trepidation concerning not only resistance but also toxicity. The potential for neurotoxicity was glossed over completely or tied in with general safety concerns.

Discourse to a wide scientific audience about WR142,490 as an early and promising compound has begun to demonstrate the community's underlying ethic of expedience, wherein the exigence for the drug is not promoted as a defense against a disease but rather as a material entity that will promote the WRAIR research program and the science that at this point it had invested eight years into developing. The tension underlying the push to produce a response and to validate the program's worth was high, and it set the tone for how clinical trials and definitions of efficacy were being established.

Experimental Drug: Pharmacology and Chemotherapy 1979

By the time that the *compound* had become an *experimental antimalarial drug*, it had a number of voices in chemistry backing it. The WRAIR authors refer readers back to the studies that Latour (1987) says are “in reserve, ready to bring with them the many technical supports [the authors] need to make [their] point firm” (p. 36). The expert voices that these scientists use are benign and uncontested, but as with the original article by Lutz, Ohnmacht, and Patel (1971), they are uncertain at times, particularly about the steric effects of the synthesis process. It seems that by 1979, these concerns have been worked out.

In 1979, mefloquine made it into the first section of Volume 16 of *Advances in Pharmacology and Chemotherapy*. Under the chapter “New Experimental Antimalarial Drugs,” written by Robert. S. Rozman and Craig J. Canfield, both of the WRAIR Division of Experimental Therapeutics, this section includes drug-specific subsections on

quinolinemethanols, phenanthrenemethanols, quinazolines, and drugs entering efficacy trials. WR 142,490 is the second of two in the quinolinemethanols description and detailed in 6 pages of the print journal. By this time, the drug had received its name “mefloquine” and the compound had been further studied, isolated, and characterized in *Journal of Medicinal Chemistry* articles.

A method of quantifying the drug in blood was also reported in a 1977 pharmaceutical journal paper, and it was subsequently tested in mouse and monkey models with Malaysian and Vietnamese *P. falciparum* strains as well as New Guinea and Vietnamese *P. Vivax* strains. Test results focused on curative abilities at various amounts (2.5-5.0mg/kg) given orally and rate of administration (once, 3, and 7 days). Another focus was on comparison between strains, particularly chloroquine-resistant and chloroquine-sensitive strains. The “preclinical efficacy and biology” section continues to outline the methods for developing chloroquine-resistant *p. Berghei* and concludes with a paragraph on the intercalation mechanism of antimalarials with DNA, stating that “mefloquine has been shown not to bind significantly to DNA” (p. 13).

One primary concern about efficacy that emerges here focuses on the variable of *p. falciparum* strains. Because there are infinite numbers of malaria strains and their derivatives, a significant challenge for malariologists has been keeping up. Research results are always limited to the strains to which scientists subject their testing models. While researchers can be fairly confident that results will transfer for similar strains from close geographic areas, resistance is common and unpredictable, so the move from lab to use in endemic areas is always unpredictable and based on a certain degree of uncertainty. The strains themselves are often named after areas from which they come, furthering the stigma of places in which malaria is a threat to local populations. Discursively associating a disease strain with the name of a country is a transparent and easy nomenclature system but it brings with it the burden of Othering. Here,

the naming serves as a means of defining efficacy within this discourse community, and the definition has no apparent connection to patient consumption but rather focuses on parasitic reaction. Although the drug is in clinical testing phases, internal biological functions of human body+protozoa have agency over the definition of efficacy, and quasi-objects like perception+compliance are left out. This isn't a surprising move, logically, but it helps to define how the ethics of efficacy are winning out over the ethics of patient safety without overtly denying "safety" from considerations.

In fact, safety was clearly brought forward as a secondary concern. After the chemistry and efficacy section, content under the heading "preclinical toxicology" outlines results in animal models of rats and beagle dogs under varying amounts of daily drug dosages. At high levels (150 mg/kg/day), death occurred in both species. Toxicity reports at lower levels indicated lymphocytopenia "with no other adverse effects" in the rat and "occasional diarrhea and emesis, and depletion in lymphoid tissues and/or inflammatory changes in the liver characterized by vacuolar degeneration" (p. 13) in the dog. The article also reports on studies that tested animal models for 52 consecutive weeks and found minimal issues. Lastly, it looks at varying levels in pregnant female rats and males for fertility, finding that at 100mg/kg/day, mefloquine "produced some anomalies" (p. 14) that didn't occur at dosages of 10mg/kg/day. One sentence concludes the section to indicate that no phototoxicity was found in mice given mefloquine.

As compared to the first publication, in which phototoxicity was given significant attention, the authors here have moved on to focusing on other side effects, constructing an updated definition of safety that revolved around dosages. For the pharmacology community, it is with dosages that ideas about safety and efficacy merge. Adverse effects ("safety") are described according to administration amounts and frequencies ("efficacy") so as to reach an

agreeable dosage that is both safe and effective. Of course, variants of adverse effects aren't overtly measured in the same scale, nor do the authors discuss causation for effects in the gastrointestinal and central nervous systems, instead treating them as inevitable but tamable byproducts of the compound.

The final section of the article on "clinical studies" references Phase I human trials by Trenholme et.al. (1975) and Clyde et.al. (1976). In the first, the authors note, "transient dizziness and nausea were reported for 4 out of 8 volunteers receiving [single doses of] either 1750 or 2000 mg" (p. 15), but there were no signs of phototoxicity. In the second, weekly doses of 250 and 500 mg over eight weeks produced no side effects, as were doses of 500 mg every two weeks for six to eight weeks. Meanwhile, monthly doses of 100 mg for two or three months produced "mild epigastric discomfort but no vomiting or diarrhea after each dose" (p. 15). The authors mention a 1-year tolerance study wherein they reference personal communication but no significant information about methods other than weekly doses is given.

In this paper appear reports from across the field and across time. At this point, the concern over gastrointestinal problems is response to those presented in the dog model. The fact that no adverse effects are observed is constructed from the lack of previously observed or measured results. As the biochemical model moves into the category of experimental chemotherapy, mef-Lariam's side effects become more and more factish, with declarative language and more citations. Here, toxicity has moved away from just observed skin rashes and nausea and on to more quantitative measures like BUN levels. The first mention of dizziness appears, once, at the time that the drug moves closer to material development and regulatory phases, where stakes are higher and more names are on the line if the drug were to carry with it significant issues. At the time of this publication, the WRAIR drug discovery program is no

longer active, and the promise of its compound 142,490 is beginning to gain significant steam, having appeared in over 200 peer-reviewed articles. While there was an ethical responsibility to be very transparent in addressing previous concerns in the community, there was little apparent impetus to seek out concerns outside of those, which would include neurotoxicity.

Rozman and Canfield refer back to Trenholme's work in 1975 to present Phase II (human) clinical trials. In two paragraphs, the writers summarize successful findings from the original source. The authors then claim that "the radical curative activity of mefloquine was confirmed in a field trial in Thailand with patients who had naturally acquired falciparum malaria," citing a different 1976 study. The article ends by stating that the drug was "well tolerated orally in doses up through 1500 mg for 1 day or in 500 mg weekly doses for 52 weeks" (p. 17).

This move to field acquisition and trials is crucial to revealing the diverse experience of malarial acquisition; however, it's a much different test than a study on nonimmune inmate volunteers in a controlled environment. Rather than confirming lab results, it provides additional and different results. Nevertheless, it becomes more difficult to refute the curative efficacy of the drug as different environments and tests are added to the list of potential references to cite and present to broader and broader audiences. While the number of participants and methods of monitoring them are not necessarily expanding, the kinds of studies and number of researchers involved are increasing. By this point at which the drug is still experimental but Phase II clinical trials have been undergone, it's at the point in which Phase III clinical trials would begin. The efficacy of curing parasitemia has been demonstrated on mouse, dog, monkey, and inmate volunteers at various dosages, and the drug has been deemed safe according to all the criteria that researchers knew to look for— phototoxicity and naseua. This report is positive throughout.

Conclusions refer back to the study previously reported in the same article, but they remove the citation, moving the small-scale field study out of its questionable context and into the realm of fact. Still, the use of simple past tense implies that the finding is the result of one or many studies and not a recurring phenomenon (simple present) or even a sure occurrence that can be anticipated in the future (future).

Quinolinemethanols are just one of three classes of compounds presented in the antimalarials chapter of the journal. Between the three, mefloquine is one of eight WRAIR compounds, included two that were classified as having entered efficacy trials. In both of these early-stage compounds, very small scale clinical trials (N=13-45) documented lack of phototoxicity and nervous system side effects like “an increase in vivid dreams” (p. 35) and “some mild mental ‘fuzziness’” (p. 37). These findings come in the first of seven chapters in the journal, followed by chapters dedicated to anxiety therapies, anesthetics, antitumor agents, and anticancer activity by colleagues from WRAIR as well as places like childrens hospitals, cancer institutes, and even a department of veterinary pathology at the University of Sydney in Australia, among many other international institutions. The advisory and editorial boards are similarly diverse, with members of both residing across Europe and the States and working in academic, private research institute, and hospital settings.

The implied audience, thus, is a diverse one of early-stage experimental researchers. Introductory explanations suggest that chemists and pharmacologists readers work at the cutting edge of compound discovery rather than within a particular applied subject such as malarial research. This construction of audience provides an example of how the divide between pure and applied science is made. Contributions to this volume are considered meant to inform about what is happening at the level of innovation; those working in applied sciences are to interpret and do

something with the facts that these early purists provide. Of course, those focused on antimalarials at these early levels would be able to allude to findings of toxicity and nervous system side effects from other trial drugs, but isolating one compound as the most promising to present to a regulatory audience erases concerns from similar trials.

Chapter 2: NDA Research Findings

The FDA's New Drug Application (NDA) is the genre where medicinal chemistry and pharmacological researchers aspire to persuade readers to believe in the safety and efficacy of their product. In this space, pharmaceutical companies enter into a conversation with other expert communities not for the purpose of developing their science but rather of developing regulations for public consumption. The NDA is the technical sales pitch, where drug developers put forth their best research. Here, discovery has ended, as far as the hopeful rhetor is concerned.

After Phase I and II clinical trials by WRAIR, the Army partnered up with Swiss pharmaceutical company Hoffman-La Roche to market WR 194,490, which the company named Lariam. Unfortunately, the details of this partnership are not public (Croft, 2007). In 1985, a review of recent chemotherapy and vaccination trends published in the *British Medical Journal* name Lariam as a "highly effective compound" discovered ten years prior and "synthesised and tested by a pharmaceutical company, and clinically assess in Brazil, Thailand, Zambia, and other countries" and already being distributed (Bruce-Chwatt, 1985, p. 1073). By 1986, there was concern over mefloquine resistance in Thailand Indonesia (Irian Jaya), but the drug was considered promising nonetheless, with no serious side effects reported in 800-person global trials reported by WHO (Hoffman, 1986, p. 194). This same article would report that 14.7% of these 800 trial participants experienced "dizziness" and 0.9% reported neuropsychiatric changes. In 1986, the drug was only commercially available to Switzerland (Hoffman, 1986, p. 195).

Lariam⁶ would not officially marketed and distributed to U.S. troops for three years, and U.S. dosages would be slightly different from those of European pills because of the FDA's pressure on Roche to revisit their dosing regimens.

Still, successful integration of the drug to the Swiss, a so-called first-world market, provided a model for global use and might have proven the exigence to continue distribution on a wider scale. It also meant that American public health stakeholders would be eager to begin using the drug themselves so as to stop subjecting nonimmune American travelers to risk of malaria armed only with outdated drugs. The use on the global market meant that the project was too far along to go back, for if Swiss travelers were using the product of American research, then why would U.S. regulation delay our own use?

The structure of the NDA reveals the priorities of the FDA audience and the degree to which the applicant can mask uncertainties in the process of presenting findings that the agency seeks and values. Similar to the accepted understanding that newspapers prioritize issues that they anticipate their readership to be most interested in and bury those stories that may have broad international implications but are unlikely to attract local readers, the NDA touches on the most pertinent concerns of its readers first. In this case, a narrow focus maintains the argument that mefloquine has the ability to inhibit parasites in red blood cells and it calls attention to what would have been a malarial expert's interest in the compound's ability to inhibit these parasites outside of the red blood cells (i.e. in the liver).

⁶ The drug was being used in Thailand for clinical drug testing, a typical colonial move by pharmaceutical companies that export clinical trials hosted in western countries to economically underprivileged countries for experimentation on human subjects.

Safety and Efficacy

Hoffman-La Roche first submitted “Lariam” for FDA approval on February 19, 1986 and made amendments to the document in 1987, thrice in 1988, and once in February 1989 before its approval for licensure on May 2, 1989. In a letter from then director of the Office of Drug Evaluation James M. Bilstad to then La Roche Drug Regulatory Affairs Jeannie-Marie Skinner, the FDA requested supplemental copies of final printed labeling, which was approved in its draft stage but apparently still undergoing adjustments on La Roche’s end. Additionally, the FDA asked for advertising copy for the agency’s records as required by law. In this letter, Bilstad acknowledges that “adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft labeling... Accordingly, the application is approved” (FDA, 1989, p.1).

The labels, according to this sentiment, serve the purpose of recommending usage. This regulatory purpose is overlooked when the labels become the primary communication about safety for prophylactic patients, who unlike pain patients do not question the efficacy of recommended dosages but might look to the label for information on safety and side effects, which would affect not the efficacy of the drug (its ability to do its job) but its effectiveness (its ability to work in context, along with factors like perception and compliance).

As a successful NDA, at minimum, the mef-Lariam application passes FDA standards. At maximum, it might serve as a model for future drugs. The structure of the document itself is not particularly surprising as far as technical reports go. The focus for the first 14 pages explains the findings of ten clinical trials worldwide. They are not inherently persuasive in the way that grant proposals are framed, with justifications, implications, methods and specifications and instead blow up the findings— they answer: what does the drug do and what are its limitations? Each

study briefly lays out the title, dosage, summary of methods and results, followed by a comment section of what Roche sponsors understand from the findings.

The mefloquine NDA contains 16 pages of medical officer's review at its core, with much more supplementary information that accompanies it. After an initial letter from the FDA to Roche, the medical officer's review begins with brief identifying information then presents a page and a half on recommended dosages for treatment/prophylaxis, indications for use, and manufacturing and controls, before reporting on parasitology, toxicology, and pharmacology findings in prophylaxis and treatment studies. Ultimately, the medical officer approves the drug but with some reservations.

The strategy, here, is to divide and explain. With so much content and so many orientations, it seems that the institutional field has decided to frame risk as one category of consideration alongside efficiency and usage. This classification, while speaking to experts of each separation, fails to communicate a unified subject with multiple lines of flight. Instead, it relies on dividing expertise to the point that they exist side-by-side but fail to communicate with one another.

That's not to say that this categorization and focus on multiple experts is not warranted—the pharmaceutical and regulatory structures are too complicated for one to be expert of all things. However, at some point, there needs to be oversight of all of these components together. A master rhetor that can put the various parts together as a whole to present to one regulatory committee would move from an idealized image of a drug as having multiple effects to a more realistic image of a drug as *being* multiple.

Dosages

The opening section of the mefloquine NDA presents parasitologic findings associated with the compound. Resistance to the primary strains of malaria is documented using *p. berghei*, or the equivalent of *p. falciparum* developed for use in mice experimentation.⁷ In each section, findings refer to this *p. berghei*, which is an accepted variable for this kind of research.

Of course, the documents serve an incredibly rhetorical purpose. They request approval. Rather than asking the audience to put their money in the form of physical cash on the line, they ask for regulatory capital, for the FDA to put its credibility on the line. At their roots, grant and new drug applications are similar requests and often cater to similar organizational audiences.

While the toxicology section serves to present adverse effects, the entire document contains places in which things could go off the rails. Toxicology is the significant risk here, but the NDA fails to present comprehensive sections laying out the corporal effects of the drug, much like the significance and background sections of the grant genre. It might be implied that expert readers will understand the contexts of the clinical trials and the justification for applying for the drug's licensure despite apparent central nervous system effects like dizziness, but dedicating a section of the NDA for this role would clear up the findings to secure stasis around the terms on which drug approval hinges.

On pages 15-16, a table and handful of paragraphs lay out the findings of adverse effects. Under prophylaxis (as opposed to treatment), researchers compile the results of 114 total

⁷ Monika Cwiarka (2011) calls attention to the linguistic functions of reification and phenomenological functions that neurobehavioral scientists use when communicating results based on lab mice. She questions the very practice of conflating animal and human reactions in behavioral studies. Here, WRAIR researchers use mice to determine protozoan inhibition but also consider side effects based on this model, which might be helpful in exploratory observations but certainly cannot fully predict human reactions.

volunteer reactions and include syncope, nausea, vomiting, extrasystoles, and dizziness, reporting that between 0 and 3 of 114 suffered from the first 4, and, under “dizziness,” using just a question mark with the footnote “the numbers are unknown. The sponsors stated only ‘several’” (see Figure 3).

NDA 19,591

-15-

Summary of adverse effects

A. Prophylaxis

Adverse Effect	Number Affected/Total Number	% Affected
Syncope	1/114	0.9%
Nausea	0/114	-
Vomiting	3/114	3%
Extrasystoles	1/114	0.9%
Dizziness	?"	-

*The numbers are unknown. The sponsors stated only "several".

Figure 3: NDA summary of adverse effects, p. 15

The treatment section, B, tested a total of 469 volunteers, of which 21% experienced dizziness. Under said section a note indicates that “some of these symptoms are part of the disease process, it is therefore difficult to say exactly what is drug induced. This notwithstanding, the high rate of dizziness reported deserves evaluation” (p. 15).

The “final comments” section starts immediately with major concerns on part of the author, medical officer Celia J. Maxwell, M.D. She notes that the drug was compared against itself rather than against current treatment and that the prominence of dizziness in high dosages is a major concern. In the correspondence between the medical officer at the FDA and the drug regulatory affairs manager at Roche, the FDA has some confusion about the implications of reported adverse effects that are overlooked in its approval. Given that this was the only

compound that the decade-long WRAIR program produced as a safe and effective possibility, and that there weren't extensive reports of side effects (which may have indicated that the side effects were idiosyncratic or the result of the malaria disease itself), agency seems to exist, at the moment of licensure, in sociopolitical exigence to get the drug to market.

The chief concerns for new drug licensure hinge on demonstration of "safety" and "efficacy." Opening language that deems the drug "safe and effective" mirrors that of the Kefauver Harris Amendment of 1962, which required more stringent measures to prove safety and efficacy of drugs on the heels of the "thalidomide tragedy" in which thousands of babies were born with birth defects or stillborn because of loose clinical trial terms that resulted in the distribution of over 20,000 nausea tablets with incredibly high dosages (Kim & Scialli, 2011).

The amendment established new regulations for proving that consumer drugs were safe and effective before going to market. While this amendment is credited with lowering the numbers of hokey drugs (Kim & Scialli, 2011), it also meant that pharmaceutical companies became picky about choosing which conditions to take on because of the additional costs that the measures would require. Some have criticized the amendment for being a knee-jerk Congressional response to a medical disaster (see Krantz, 1966, which claimed that the amendment "had its origin in the hysteria and panic of the thalidomide tragedy, it was nurtured and developed in the pandemonium of the biased hearings before the Kefauver Committee of the Senate, and through the pressure of an impetuous Administration, was enacted into law" (p. 78)). By and large, though, the resultant checks on drugs have been celebrated as a victory for consumer safety advocates.

Kefauver-Harris amendments centered on particular definitions of "safe" and "effective." Cicero's stasis theory might bring forward the crux of arguments for safety and efficacy; by

questioning these definitions, one can bring forward the assumptions about safety. In the case of mef-Lariam, safety didn't consider neurotoxicity.

Attached to these 15 pages are four chemist reviews from 1986, 1987, 1988 and 1989 completed by the Division of Anti-Infective Drug Products. Each review was no more than two pages and similar in format. The first two reviews were completed by John W. Taylor, Ph.D. while the latter two were both completed by Wilson H. De Camp, PhD. Each follows genre conventions of introducing the drug and dosage recommendations then making reviewer remarks and conclusions. In 1986, Dr. Taylor remarked that “apparently about 1981, Roche discovered that the drug exists in 5 polymorphic modifications and revised the granulation process to generate a more bioavailable product containing the polymorphic ‘E’ crystalline drug,” alluding, presumably, to the FDA medical officer’s criticism that most clinical trials were with a different formulation of the mefloquine chloride compound than was later presented. The bioavailability that Taylor mentions might also refer to the funding that Roche received to make a more affordable drug as a result of the 1983 Orphan Drug Act, which provided incentives for companies willing to invest in rare or “orphaned” disease, of which malaria was included (Wellman-Labadie & Zhou, 2010) Taylor’s conclusion in this first review is that “the application is non-approvable per 505(b)(1)(d) of the Act.” According to the FDA (2014), section 505(b)(1)(d) of the Federal Food, Drug, and Cosmetic Act corresponds to “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug.”

Remarking that the requisite responses were sufficient but that dosages differing from the proposed and those in use in France and Switzerland needed to be explained and accounted for on labeling, Taylor writes that the “application is approvable from the standpoint of manufacture

and control” in the second chemist’s review. He also provides language to be inserted in a letter to Roche requesting additional Army research information. The third chemist’s review is a reply to the second, referring to the application’s approval “from a manufacturing and controls standpoint” but indicating in the conclusions section that “labeling remains NOT APPROVABLE” (emphasis original).

The final chemist’s review is what translated to the final letter of the drug’s approval. Here, De Camp agrees to approve “all items except Labeling,” writing that telephone conversations communicated the necessary changes. Amidst known dosing issues that would prevent effectiveness and compliance and announced trepidation over what might be going on in the drug’s interaction with the central nervous system, mef-Lariam was approved and marketed to the public.

Discussion

Rhetoric of Pharmaceutical Compliance

The FDA's New Drug Application (NDA) consists not only of lab and clinical results but also of the consumer label, which also necessitates approval for commercial use. Through journal articles and scientific discourse, medicinal chemistry and chemotherapy researchers, from those in the WRAIR lab paid by the U.S. Army to those in the field paid by Roche, agree that there is at least some degree of uncertainty about the effects of mef-Lariam for prophylactic use on a large-scale nonimmune human population. How does that uncertain risk get communicated outside of scientific discourse communities? Under the intention of providing information for, by default, a health illiterate public audience, writers scrape off the layers of risk and uncertainty to get to and deliver a prognosis: if you are in x situation, you should do y.

In this work, the public becomes defined as anyone outside of the core stakeholder group formed around a particular task, and that public conflates a Fulbright poet fellow traveling to India with a local Army medic who has lived in Viet Nam and treated malaria all her life. Mef-Lariam's uncertainty was accepted among Roche, WRAIR, and FDA stakeholders but never translated to prescribing physicians much less patients. Given "Army culture" of silencing soldiers in the face of hierarchical rank systems, soldiers were encouraged to take what they were given and not speak up about side effects. Consequently, patient fear resulted in noncompliance. It is important for technical communication scholars, particularly those interested in the communication of health and health risks to publics, to note where this translation work happens.

Immediately after the FDA approved licensure of Lariam, it began getting distributed to international travelers. The audience for information communication about the drug transitioned from the FDA to lay consumers. Following medical packaging protocols, Hoffman La Roche distributed pamphlets of information along with the drug. Intended to inform patients of side effects and drug usage, the pamphlets are important texts for understanding medical composition and communication. In fact, these labels would become the source of blame in what would become referred to as a scandal.

Roche Labels and Medication Guide

Label as Afterthought. Mef-Lariam was approved for licensure on the basis of its reviews of safety and efficacy, and although public communication was a necessary component of the regulation process, the labels had no bearing on the company’s ability to get the drug approved. In correspondence by FDA officers to Roche, the FDA indicated that additional labels were needed “for administrative purposes” for the then-approved drug (see **Error! Reference source not found.**). In other words, the focus of the NDA and a drug’s ability to get passed, on this case, relied on the intercommunication between expert communities and not on the communication between these expert communities and patient publics. In fact, the drug is well documented as receiving FDA licensure in 1989, but the labels following up on this request were not received until 2 January, 1990.

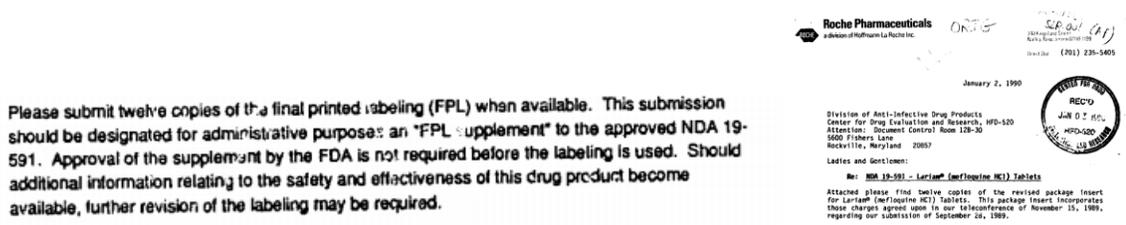


Figure 4: (left) FDA label request in NDA response, 2 May 1989 (right) Roche response to request, 2 January 1990

The divided nature of this process, in which some parts are examined by certain experts and others are looked at separately and as auxiliary demonstrates not only regulatory perception of medicine but also that of the public. Nonmodern scientists are okay with uncertainty for the purpose of discovery within their own discourse communities, but translating scientific efficacy as effectiveness to a regulatory audience prohibits poor clinical research from accurately and ethically communicating patient risk to publics.

Drug Packaging. The design of pharmaceutical packaging itself questions rhetor's intentions and audience expectations. As the product of a commercial endeavor, the label reflects a brand's economic goal of consumption. As a regulatory document intended to prevent lawsuits, its style resembles that of any user agreement; that is, it's not read in depth by casual users.

Nevertheless, the mef-Lariam insert provides valuable insight into Roche's construction of modern science. At the moment in which the writers move from addressing an audience of fellow scientists in the NDA to that of which they are addressing non-scientist audiences, dizziness from unknown but concern-worthy causes become "adverse effects" and correlations between mental health patient demographics and reports become warnings of causal drug interactions for select populations.

FDA medical officer Dr. Celia Maxwell's initial concerns expressed in the NDA that the presented studies were problematic because "mefloquine was



Figure 5: First approved Lariam label, 1989

compared to mefloquine' for efficacy as opposed to the current standard of treatment" is reflected in the insert line under contraindications that reads, "use of this drug is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds." The hesitancy about the reliability of the original data is translated into a guideline, but passive voice prevents the reader from access to the causality for the contraindication referenced. Furthermore, Roche covers its bases regarding the FDA's concern without providing any guidance for lay or expert readers. Because mefloquine is a 4-quinolinemethanol, a much different compound than other antimalarials that were currently on the market, it would be unlikely for consumers to know their sensitivity to it or to similar drug compounds. So, while Roche *covers* lab uncertainty, it fails to *communicate* the uncertainty itself to its public audience, indicating that its primary audience is the small group of FDA stakeholders to whom they are responding.

Dr. Nevin Remington, MD, MPH, a former Army epidemiologist and Preventive Medicine officer, writes, "From my perspective, the original warning of encephalopathy, and certain symptoms being 'prodromal' to a more serious event, suggests to me that the sponsors were fully aware of the drug's neurotoxicity from the time of the drug's initial licensing" (personal communication). The word "prodromal" appears in the precautions section, which continues in the push/pull manner of audience analysis and response, although it seems to allude more overtly to neurologic concerns, possibly responding to the "dizziness" conversation held during the licensure process. Particularly fascinating is the fact that the drug was developed by Army researchers and deemed one of two best options coming out of a military funded program for the purpose of use in deployments, yet the first warning the insert advises against operating heavy machinery (albeit buried three quarters into the document) (see Figure 6). In this section, the conflict that authors have between the lived reality of nonmodern science and the understood

expectation of Scientific certainty becomes clear. Authors collapse the divide between prophylaxis and treatment uses when reporting findings, failing to distinguish which of the two “have been reported during the use of Lariam,” and thus getting around the field report that researchers had only indicated “several” cases of dizziness. In the following sentence, however, they specify that for prophylactic use, neuropsychiatric side effects “may be considered prodromal to a more serious event.”

PRECAUTIONS: General: Caution should be exercised with regard to driving, piloting airplanes and operating machines, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported during the use of Lariam. During prophylactic use, if signs of unexplained anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued.

Figure 6: Precautions section of 1990 Lariam insert

In his memoir about his experience with Lariam that led to crippling amnesia, former Fulbright scholar in India David MacLean pieces together stories from his mother and colleagues about minor episodes in which he had acted uncharacteristically angry, had uncontrollable vomiting, and even once inexplicably blacked out while on mef-Lariam. After a series amnesiac event, he returns to the States and in his local physician’s office, the doctor reported that, “these events all seemed to be prodromal to the larger episode.” MacLean continues, “I had him define *prodromal* for me: ripples before the tsunami” (p. 101). Later in the memoir, MacLean would write about his fear that the serious event could be “prodromal” to an even more serious one. Although the term rests on a degree of comparison, syntactically, it does not provide a superlative in terms of degree or temporality. There is no teleological conclusion to the “serious events” here, and the term, albeit helpful as a pre-consumption warning, becomes useless for post-affected users or their advocates.

MacLean's work also provides insight into the other term in the precautions that Nevin points out: encephalitis. Mef-Lariam's interaction with the brain is complicated because, as the early journals demonstrate, it can be difficult to observe and measure, especially if one is not looking for it. Bioengineers have been particularly interested in the role of the blood-brain barrier (BBB) for targeting drug delivery for a number of syndromes, particularly those infections like meningitis that are able to cross the incredibly robust BBB. As a traditionally impermeable defense system, this cell canal instills awe and fear among scientists who want to manipulate it for good while aware of its high sensitivity. MacLean explains his understanding of Lariam as "very good at crossing the blood-brain barrier" (p. 143). He elaborates on the ability of Lariam to become neurotoxic as it "pools in the brain" (p. 143) because of its interference with protein gap junctions, a theory that has emerged recently, over twenty years after the drug went to market. According to his research and experience:

Scientists type these junctions by their size, and Lariam affects two very specifically sized ones. One is found in the areas that process information from the eyes, and the other is in the vestibular system, the system that processes all the data from your senses and establishes your balance and body's response to them. Lariam can nestle into these protein gap junctions and scatter the data that passes through them, like putting your thumb over a hose's spray. (p. 143)

Of course, as he acknowledges, this hypothesis about mef-Lariam is extremely difficult to prove because of the nature of studying the brain—a patient would have to be dead to analyze the drug's role. Of course, none of this is communicated to the patient in the original insert, and the product labels become the source of blame and rectification for miscommunication about the neurotoxic effects of the drug. In other words, when stakeholders could not communicate the

nonmodern science of uncertainty, it was the communication i.e. the documentation itself that inherited that shortcoming, protecting the real culprit of faulty Science.

Post-Marketing Communication

Public Definition of Safety. Once mef-Lariam was prematurely put to market, military rhetorics allowed the rouse to continue for some time. Ultimately, media coverage, relying on consumer reports and highly public incidences removed the toxic prophylaxis drug from the shelves, although mefloquine chloride is still administered under its generic name. Although lab biochemists define terms by instrumental means, the public consumer defined those same terms through narrative. Only needing the evidence of their own experiences, public patients began deeming the drug unsafe. As a result, compliance decreased significantly. In fact, one study found that 61% of soldiers prescribed daily doxycycline were compliant with their regimen whereas only 38% of service members on weekly regimens were compliant in Afghanistan, where there were 58 cases of malaria among military service members in 2010. Furthermore, 20% of those surveyed did not receive medication information from a healthcare professional (Brisson & Brisson, 2012; Nevin, 2012). An unconsumed prophylactic drug is completely ineffective in preventing malaria. Thus, the public's definition of effective hinges on the public's perception of its safety, not on clinical findings centered on malaria prevention.

FDA Response. The FDA, nevertheless, responded to reports of neuropsychiatric events associated with mef –Lariam by *adding* warnings to public communication strategies. In a British study of 1214 travelers taking mefloquine between 1993 and 1995, 333 reported neuropsychiatric adverse effects (Barrett, Emmins, Bradley & Clarke, 1996). This study used self-reporting questionnaires. In 2001, results of the first double-blind study of the drugs Malarone and Lariam in the Netherlands reported that new drugs were needed, as 67% of patients

experienced adverse effects when taking Lariam (Overbosch, et. al., 2001). This led to numerous studies that all reported varying degrees of neurological concerns for non-immune takers of Lariam (Potasman, Juven, Weller, Schwartz, 2002; Scлагенhauf, et. al, 2003; for a comprehensive literature review on mef-Lariam neuropsychiatric side effects see Toovey, 2009).

As these reports were surfacing within the biomedical research community, the Army held steady to its policy. In fact, in a 2004 public presentation, WRAIR Science Director MD/FACP Alan Magill (2004) declared, “military personnel will die of malaria if MQ is not available.” At that point, despite two decades’ worth of criticism about mef-Lariam side effects, the CDC still recommended it for most travelers because of its perceived efficacy. Meanwhile, the strongest alternatives, doxycycline (with only a 24-hour half-life) and Malarone (expensive and not reliable in non-immune travelers) became officially preferred for soldiers with a history of depression or traumatic brain injury. At least nineteen official reports of suicide and other death from mefloquine have been reported (Croft, 2007, p. 171), and many others have speculated about links to the drug in the Fort Bragg murders (Benjamin & Olmsted, 2005; Mischler, 2013; Fleet & Mann, 2004).

In light of the public attention that Lariam was receiving, the FDA added a policy that required that a medication guide be included for all mefloquine recipients in 2004. In 2009, the Centers for Disease Control (CDC) determined that mefloquine was neurotoxic, and the Army issued a news release stating that it would follow all FDA and CDC recommendations, stating that mefloquine was only to be used for patients unable to take doxycycline or Malarone. On July 29 2013, the FDA issued a press release with the following headline, “FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects,” further stating that “a boxed warning, the most serious warning about these

potential problems,” would officially accompany the drug due to persistent and possibly permanent neurologic side effects (see Figure 7).

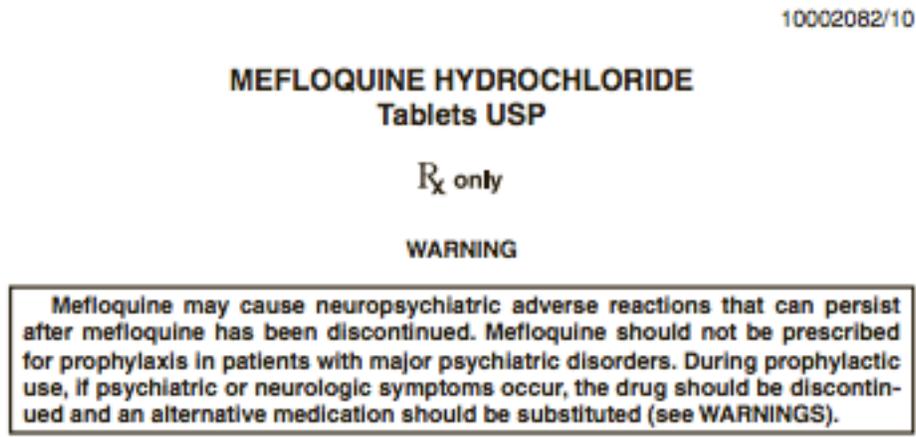


Figure 7: 2013 FDA “black box warning” on mefloquine chloride label

Following the conversation within the community, the FDA produced new requirements for amount and form of written communication to provide to prescribing physicians and consumer patients. The Lariam label, as listed in the FDA database, was revised in 1990, 1993, 1997, 1999, 2002, thrice each in 2003, 2008, and 2009, and once in 2011 before Roche stopped manufacturing the drug completely.

The Army no longer issues mef-Lariam to soldiers, and the drug is no longer marketed in the States, although mefloquine chloride remains available under generic names from seven other pharmaceutical companies, and the CDC still lists it as one of five recommended antimalarial for travelers, citing that it is a “good choice for long trips because it is taken only weekly” (CDC, 2011). Several international organizations like Medecins sans Frontieres continue to prescribe the drug as its primary antimalarial to American and other employees. Ultimately, the drug served to prevent malaria for an uncountable number of persons worldwide. It also induced neuropsychiatric problems and their side effects for countless compliant patients

and their loved ones. At the conjuncture of FDA licensure, uncertain science was only agentive in that it pushed regulatory officials to require ineffective label revisions. What was agentive, however, was the seductive promise of a chemical compound discovered by American research labs at a time of alternative drug resistance.

Implications. This entire project comes down to facing, confronting, accepting, and ultimately communicating uncertainty about biomedicine. If, in a nonmodern object-oriented ontology, we can learn to live with the notion that we will never have certainty during drug development, then it seems that we would actually become much more comfortable with communicating the degree and source of said uncertainty to key stakeholders.

Scholars in technical communication and rhetoric can serve as intermediaries in these complex communication situations. Future studies might seek to define public patient ethics to better facilitate the move from internal communication strategies to external public audiences and to achieve stasis between these audiences and their use of the topoi *safe* and *effective*. By understanding the rhetorical situation as well as principles of document design, technical communicators offer much, but they cannot succeed by simply reconstructing the black box in a new “more correct” way. Writers must enter pharmaceutical communication for the public from the black box that each drug is to understand the complications of drug development, particularly of those that interfere with the BBB. Indeed, the critique of technical communicators from an ANT perspective allows for the large-scale reconsideration of drug development communication and procedures based not on the black box of dangerous drugs and their packaging but rather on the messiness that is excused in the face of demand for said black boxes.

Tropical disease research in particular lends itself to serious engagement with themes of imperialism and global health communication. While the present study did not investigate the

sites and lived experiences of contributing clinical trials abroad, one might expand on this work with ethnographic work in these environments to further understand the cultural and sociopolitical contexts of clinical trials that are essentially outsourced when western travelers develop a need for health solutions that are unique to nonwestern workplaces. The political correctness of medical officers in their translation of “sketchy overseas reports” to undetermined findings should not be overlooked for scholars engaged in international studies funded exclusively by western technocratic nations. A more comprehensive contextualization of clinical studies from a culture-centered and nonmodern ontology would illuminate the conflicting definitions of ethics in international health campaigns.

References

- Arguin, P.M. & Tan, K.T. (2013). Malaria. In G.W. Brunette (Ed.), *CDC Health Information for International Travel 2014: The Yellow Book: The Yellow Book* (chapter 3). Oxford University Press.
- Baird, J. K. (2004). Chloroquine resistance in *Plasmodium vivax*. *Antimicrobial agents and chemotherapy*, 48(11), 4075-4083.
- Barrett, P. J., Emmins, P. D., Clarke, P. D., & Bradley, D. J. (1996). Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *Bmj*, 313(7056), 525-528.
- Beck, U. (1992). *Risk society: Towards a new modernity* (Vol. 17). Sage.
- Bell, H. D., Walch, K. A., & Katz, S. B. (2000). 'Aristotle's pharmacy': The medical rhetoric of a clinical protocol in the drug development process. *Technical Communication Quarterly*, 9(3), 249-269.
- Benjamin, M., & Olmsted, D. (2005). Pentagon eyes malaria drug in suicides. *United Press International*. Retrieved from <http://www.lariaminfo.org/>
- Bernstein, R. J. (1983). *Beyond objectivism and relativism: Science, hermeneutics, and praxis*. University of Pennsylvania Press.
- Bitzer, L. F. (1968). The rhetorical situation. *Philosophy and Rhetoric*, 1(1), 1-14.
- Brisson, M., & Brisson, P. (2012). Compliance with antimalaria chemoprophylaxis in a combat zone. *The American journal of tropical medicine and hygiene*, 86(4), 587-590.
- Bruce-Chwatt, L. J. (1985). Regular Review: Recent Trends Of Chemotherapy And Vaccination Against Malaria: New Lamps For Old. *British Medical Journal (Clinical Research Edition)*, 1072-1076.
- Campbell, C., Collins, W., Chin, W., Teutsch, S., & Moss, D. (1979). Chloroquine-Resistant *Plasmodium Palciparum* from East Africa: Cultivation and Drug Sensitivity of the Tanzanian I/CDC Strain from an American Tourist. *The Lancet*, 314(8153), 1151-1154.
- Centers for Disease Control (CDC). (2011, Oct. 3). Choosing a Drug to Prevent Malaria. Retrieved from <http://www.cdc.gov/malaria/travelers/drugs.html>.

- Clyde DF, McCarthy VC, Miller RM, Hornick RB. Suppressive activity of mefloquine in sporozoite-induced human malaria. *Antimicrobial Agents Chemotherapy* 1976; 9: 384-386.
- Collins, H. M., & Evans, R. (2002). The Third Wave of Science Studies Studies of Expertise and Experience. *Social studies of science*, 32(2), 235-296.
- Condit, C. M. (1994). *Decoding abortion rhetoric: Communicating social change*. University of Illinois Press.
- Consigny, S. (1974). Rhetoric and its situations. *Philosophy & Rhetoric*, 175-186.
- Croft, A. M. (2007). A lesson learnt: The rise and fall of Lariam and Halfan. *Journal of the Royal Society of Medicine*, 100(4), 170-174.
- Cwiarka, M. (2011). "How do Mice Mean? The Rhetoric of Measurement in the Medical Laboratory. In J. Leach and D. Dysart-Gale, (Eds.), *Rhetorical Questions of Health and Medicine*. (pp. 33-58). Lanham, MD: Lexington Books.
- Danisch, R., & Mudry, J. (2008). Is it Safe to Eat That? Raw Oysters, Risk Assessment and the Rhetoric of Science. *Social Epistemology*, 22(2), 129-143.
- Deleuze, G., & Guattari, P. F. (1987). *A thousand plateaus: Capitalism and schizophrenia* (Vol. 2). U of Minnesota Press.
- Ding, Huiling. (2013) Transcultural Risk Communication and Viral Discourses: Grassroots Movements to Manage Global Risks of H1N1 Flu Pandemic, *Technical Communication Quarterly*, 22:2, 126-149.
- Dutta, M. (2008). *Communicating health: A culture-centered approach*. Polity.
- FDA. (2013). FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. Safety Announcement, 7-29-2013. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm>.
- FDA. (1989). *Lariam New Drug Application*.
- Fleet, M. & Mann, J. (2004, May 20). *Military's use of malaria drug in question*. CNN Health. Retrieved from <http://www.cnn.com/2004/HEALTH/05/20/lariam/>.
- Gaviria, D., Paguio, M. F., Turnbull, L. B., Tan, A., Siriwardana, A., Ghosh, D., ... & Roepe, P. D. (2013). A Process Similar to Autophagy is Associated with Cytocidal Chloroquine Resistance in *Plasmodium falciparum*. *PloS one*, 8(11), e79059.
- Gong, G., & Dragga, S. (2008). SARS” versus “atypical pneumonia. *The Social Construction of SARS: Studies of a Health Communication Crisis*, 30, 53.

- Graham, S. S. (2009). Agency and the rhetoric of medicine: Biomedical brain scans and the ontology of fibromyalgia. *Technical Communication Quarterly*, 18(4), 376-404.
- Graham, S. S., & Herndl, C. (2013). Multiple ontologies in pain management: Toward a postplural rhetoric of science. *Technical Communication Quarterly*, 22(2), 103-125.
- Grossberg, L. (2010). *Cultural studies in the future tense*. Duke University Press.
- Harrison, G. (1978). Mosquitoes, malaria and man: A history of the hostilities since 1880. *Mosquitoes, malaria and man: a history of the hostilities since 1880*.
- Hausman, B. L. (2013). Breastfeeding, Rhetoric, and the Politics of Feminism. *Journal of Women, Politics & Policy*, 34(4), 330-344.
- Hawley, S. R., Bray, P. G., Mungthin, M., Atkinson, J. D., O'Neill, P. M., & Ward, S. A. (1998). Relationship between antimalarial drug activity, accumulation, and inhibition of heme polymerization in *Plasmodium falciparum* in vitro. *Antimicrobial agents and chemotherapy*, 42(3), 682-686.
- Hoffman, S. L. (1986). *Treatment of malaria* (No. NMRI-86-115). NAVAL MEDICAL RESEARCH INST BETHESDA MD.
- Irwin, B. (2010, Aug. 17). *Cracking the code: DoD's quest for a malaria vaccine*. Military Health System.
- Jack, J. (2010). What are Neurorhetorics? *Rhetoric Society Quarterly*, 40(5), 405-410.
- Katz, S. B. (1992). The ethic of expediency: Classical rhetoric, technology, and the Holocaust. *College English*, 54(3), 255-275.
- Kim, J. H., & Scialli, A. R. (2011). Thalidomide: the tragedy of birth defects and the effective treatment of disease. *Toxicological Sciences*, 122(1), 1-6.
- Koerber, A. (2005). "You Just Don't See Enough Normal" Critical Perspectives on Infant-Feeding Discourse and Practice. *Journal of Business and Technical Communication*, 19(3), 304-327.
- Krafts, K., Hempelmann, E., & Skórska-Stania, A. (2012). From methylene blue to chloroquine: a brief review of the development of an antimalarial therapy. *Parasitology research*, 111(1), 1-6.
- Krantz, J. C. (1966). New Drugs and the Kefauver- Harris Amendment. *The Journal of new drugs*, 6(2), 77-79.
- Kuhn, T. S. (1962). *The structure of scientific revolutions*. University of Chicago press.

- Latour, B. (1987). *Science in action: How to follow scientists and engineers through society*. Harvard university press.
- Latour, B. (1999). *Pandora's hope: essays on the reality of science studies*. Harvard University Press.
- Latour, B. (2003). Is re-modernization occurring-and if so, how to prove it? A commentary on Ulrich Beck. *Theory, culture & society*, 20(2), 35-48.
- Latour, B., & Woolgar, S. (1979). *Laboratory life: The social construction of scientific facts*. Princeton University Press.
- Longo, B. (2000). *Spurious coin: A history of science, management, and technical writing*. SUNY Press.
- Lutz, R. E., Ohnmacht, C. J., & Patel, A. R. (1971). Antimalarials. 7. Bis (trifluoromethyl)-alpha. (2-piperidyl)-4-quinolinemethanols. *Journal of medicinal chemistry*, 14(10), 926-928.
- MacLean, D. S. (2014). *The answer to the riddle is me: A memoir of amnesia*. Houghton Mifflin Harcourt.
- Magill, A. J. (2004, April 12). DoD Experience with malaria and antimalarials [PowerPoint slides]. Retrieved from timemilitary.files.wordpress.com/2012/12/magill-mq_12apr_v1-0.ppt
- Magill, A.J. (2013). For the record: A history of malaria chemoprophylaxis. In G. W. Brunette (Ed.), *CDC Health Information for International Travel 2014: The Yellow Book: The Yellow Book* (chapter 3). Oxford University Press.
- Martin, D. C., Arnold, J. D., Clyde, D. F., Al Ibrahim, M., Carson, P. E., Rieckmann, K. H., & Willerson, D. (1973). A quinoline methanol (WR 30090) for treatment of acute malaria. *Antimicrobial agents and chemotherapy*, 3(2), 214-219.
- Maugh T. H. (1977). Malaria drugs: new ones are available, but little used. *Science* 196: 415.
- Meshnick, S. R., & Dobson, M. J. (2001). The history of antimalarial drugs. In *Antimalarial chemotherapy* (pp. 15-25). Humana Press.
- Miller, C. R. (1979). A humanistic rationale for technical writing. *College English*, 610-617.
- Miller, C. R. (1992). Kairos in the rhetoric of science. *A rhetoric of doing: Essays on written discourse in honor of James L. Kinneavy*, 310-327.
- Miller, C. R. (1998). Learning from History World War II and the Culture of High Technology. *Journal of Business and Technical Communication*, 12(3), 288-315.

- Mirel, Barbara. (2002). Advancing a Vision of Usability. In Barbara Mirel and Rachel Spilka (Eds.) *Reshaping technical communication: New directions and challenges for the 21st century* (pp. 165-87). Mahwah: Lawrence Erlbaum Associates.
- Mishler, L. U. (2013). Mefloquine-induced neuropsychosis: A Commentary.
- Mol, A. (2002). *The body multiple: Ontology in medical practice*. Duke University Press.
- National Public Radio (Ira Glass). (2010, January 22). 399: *Contents unknown act 3 The answer to the riddle is me* [Podcast transcript]. Retrieved from <http://www.thisamericanlife.org/radio-archives/episode/399/transcript>
- Nevin, R. (2007). Mefloquine prescriptions in the presence of contraindications: prevalence among US military personnel deployed to Afghanistan. *Pharmacoepidemiology and Drug Safety*, 19(2), 206-210.
- Nevin, Remington L. (2012) Falling Rates of Malaria among U.S. Military Service Members in Afghanistan Substantiate Findings of High Compliance with Daily Chemoprophylaxis. *Am. J. Trop. Med. Hyg.* 87(5): 957–958.
doi: 10.4269/ajtmh.2012.12-0277a
- Ockenhouse, C. F., Magill, A., Smith, D., & Milhous, W. (2005). History of US military contributions to the study of malaria. *Military medicine*, 170(4), 12-16.
- Overbosch, D., Schilthuis, H., Bienzle, U., Behrens, R. H., Kain, K. C., Clarke, P. D., ... & Chulay, J. D. (2001). Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. *Clinical Infectious Diseases*, 33(7), 1015-1021.
- Potasman, I., Juven, Y., Weller, B., & Schwartz, E. (2002). Does mefloquine prophylaxis affect electroencephalographic patterns?. *The American journal of medicine*, 112(2), 147-149.
- Roberts, L. E. (2006). Using an access-centered design to improve accessibility: A primer for technical communicators. *Technical Communication*, 53(1), 14-22.
- Rocco, F. (2003). *The miraculous fever-tree. Malaria, medicine and the cure that changed the world*. HarperCollins Publishers.
- Rozman, R. S., & Canfield, C. J. (1979). New experimental antimalarial drugs. *Advances in Pharmacology*, 16, 1-43.
- Schlagenhauf, P., Tschopp, A., Johnson, R., Nothdurft, H., Beck, B., Schwartz, E., ... & Steffen, R. (2003). Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *Bmj*, 327(7423), 1078.
- Scott, B., Longo, B., & Wills, K. V. (2006). Critical power tools.

- Segal, J. Z. (2008). *Health and the rhetoric of medicine*. SIU Press.
- Shah, S. (2010). *The Fever: how malaria has ruled humankind for 500,000 years*. Macmillan.
- Sheehy, T. W., & Reba, R. C. (1967). Treatment of chloroquine-resistant Plasmodium falciparum infections in Vietnam. *Annals of Internal Medicine*, 66(3), 616-622.
- Spivak, G. (1988). Can the Subaltern Speak? In C. Nelson and L. Grossberg (Eds.), *Maxism and the Interpretation of Culture* (pp. 271-313). Urbana: University of Illinois Press.
- Sullivan, Pat. (2012). After the great war: Utility, humanities, and tracings from a technical writing course in the 1920s. *Journal of Business and Technical Communication*. 26(2) 202-228.
- Tigertt, W. D. (1969). The army malaria research program. *Annals of Internal Medicine*, 70(1), 150-153.
- Toovey, S. (2009). Mefloquine neurotoxicity: a literature review. *Travel medicine and infectious disease*, 7(1), 2-6.
- Trenholme GN, Williams RL, Desjardins RE, Frischer H, Carson PE, Rieckmann KH, Canfield CJ. (1975). Mefloquine (WR 142,490) in the treatment of human malaria. *Science*, 190, 792-794.
- Vatz, R. E. (1973). The myth of the rhetorical situation. *Philosophy and Rhetoric*, 6(3), 154-161.
- Walter Reed Army Institute of Research (2014). WRAIR Overview. *Walter Reed Army Institute of Research*. Retrieved from <http://wrair-www.army.mil/AboutWRAIR.aspx>
- Wellman-Labadie, O., & Zhou, Y. (2010). The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity?. *Health Policy*, 95(2), 216-228.
- Wilson, G., & Herndl, C. G. (2007). Boundary objects as rhetorical exigence: Knowledge mapping and interdisciplinary cooperation at the Los Alamos National Laboratory. *Journal of Business and Technical Communication*, 21(2), 129-154.
- Winner, L. (2010). *The whale and the reactor: A search for limits in an age of high technology*. University of Chicago Press.