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Globalization of Clinical Research and Assessment of Global Access to Treatments Approved between 2006-2015

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This is to certify that the doctoral study by

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2019

Abstract

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MPH, Johns Hopkins University Bloomberg School of Public Health, 2006

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BS, Wheeling Jesuit University, 1989

Doctoral Study Submitted in Partial Fulfillment of

the Requirements for the Degree of

Doctor of Public Health

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Abstract

Globalization in clinical research and development has increased since the 1990s. Products approved in the United States (U.S.) and European Union (EU) include increasing numbers of research participants from low- and middle-income countries. The purposes of this quantitative correlational study were to investigate the lag time, or drug lag, between U.S. approval and the approval of selected drugs in all countries that hosted their pivotal clinical trials. The study population was limited to products approved first in the U.S. between 2006 and 2015. The health capability model and research for health justice framework were the theoretical frameworks for the study. Data were collected from public reports and websites of the U.S. Food and Drug Administration (FDA), European Medicines Agency, National Institutes of Health, local ministries of health, National Association of Securities Dealers Automated Quotations, New York Stock Exchange, the World Bank, and a subscription-based report from Springer Publications. Data were analyzed descriptively, with inferential statistics performed via Wilcoxon and chi-square tests. Independent variables were FDA approval year, drug indication, FDA review type, orphan indication, host country World Bank income category, sponsor market capitalization, and sponsor headquarters country. The dependent variable was drug lag, in months. The U.S. to EU drug lag was significantly shorter than U.S. to last host country drug lag. Lower host country income was also associated with longer drug lag. Reducing drug lag may create justice for research participants, improve health outcomes, and yield positive social changes.

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Dedication

I dedicate this project to my mother, Carolyn Griffin Escandon (1938-2013), who served as my first and most influential of mentors in the virtues of honesty, respect for persons and human rights. Also, for his participation, guidance and encouragement of this project, I remember and dedicate this project to Dr. Ernest Ekong. Finally, for his courage both in recognizing that some in his profession were acting unethically, and to shine a light on the practice at a time when he must have known he would receive deep criticism, I dedicate this project and its inspiration to Harry Beecher, MD (1904-1976) of the Massachusetts General Hospital.

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I'd like to acknowledge my wife, Galyn Burke for her patience, support and interest in this project throughout every phase of its development, all of which have been positive forces. Also, Dr. Donald Goodwin, as my doctoral study chair and adviser, I owe a great deal for his interest, his reviews and comments and thoughtful and pragmatic advice throughout. Thanks, as well to Dr. Ernest Ekong for his reviews, his interest and enthusiasm for my project. I would also like to thank my peers and other professors and reviewers throughout the process at Walden, especially Dr. Richard Palmer and Dr. Debo Awosika-Olumo. I have learned a great deal from all of you and the diversity of opinions and experiences has definitely enriched this project and my personal and professional perspectives.

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Section 1: Foundation of the Study and Literature Review

The number of clinical trials of new drugs has increased significantly since 1962, the year the U.S. Food and Drug Administration (FDA) began requiring well-controlled clinical trials to gain U.S. marketing approval (U.S. FDA, 2018b; Kinch, Haynesworth, Kinch, & Hoyer, 2014). Furthermore, U.S. spending on prescription drugs has increased more than 130-fold, from $2.5 billion in 1960 to nearly $330 billion in 2016, making the United States the largest revenue market for prescription drugs in the world (Hartman, Martin, Espinosa, Catlin, & The National Health Expenditure Accounts Team, 2018; Liljenquist, Bai, & Anderson, 2018). The need for clinical trial data to support and accelerate new product approvals in the United States, European Union (EU), and Japanese markets has created a competitive environment for recruitment of human subjects into clinical trials (Weigmann, 2015). To address this need for trial participants, sponsor companies have shifted, since the 1990s, from domestically conducted trials to global trials, increasingly including countries from the developing world (U.S. FDA, 2017a; Viergever & Li, 2015). Today, ex-United States participation is significant, as 93% and 72% of the pivotal trials supporting the FDA approvals granted in 2015 and 2016, respectively, included participants from outside the United States (U.S. FDA, 2017a, 2017c).

The first passage of the Prescription Drug User Fee Act (PDUFA) in 1992, has transformed the FDA into a more predictable and transparent regulatory agency (U.S. FDA, 2012). Clearer approval requirements and adherence to legally mandated timelines for completion of new drug application (NDA) reviews has resulted from PDUFA (U.S.

FDA, 2012). In the 25 years since PDUFA passage, the FDA has effectively eliminated concerns in the United States over *drug-lag*, a term which refers to the discrepancy between availability of approved drugs, particularly between the United States, EU and Japan (Venkatakrishnan et al., 2016; Wardell, 1973; Wileman & Mishra, 2010; Yonemori et al., 2011). PDUFA has since been refined and renewed five times, most recently in 2017, and its main guarantees are a decision on new drug approval within 6 or 10 months depending on priority, establishment of an applicant user fee and investment of those fees in technology upgrades, and hiring additional review personnel and development of more efficient procedures across the agency, enabling more reviews to be completed annually and ultimately granting access to a greater number of new approved drugs (U.S. FDA, 2012, 2017d).

Sponsoring company pursuit and prioritization of registration in the most predictable and lucrative markets adheres to sound business principles and business ethics, particularly for companies funded by the public capital markets (Hartman et al., 2018; Poitras, 2009). Investigational drugs however, because they have possible salutary but also unknown potentially harmful or fatal effects, warrant consideration by both business and medical ethical standards (Emanuel, Wendler, & Grady, 2000; Poitras, 2009). Because new drug testing in the present globalized setting involves participation of individuals in altered states of health in many different parts of the world, questions of whether, when, and how companies seek drug approval in all participating countries is important knowledge in determining whether equity and global social justice for research participants and their communities are assured or if inequities exist. Quantifying any

time-lag between FDA approval and drug approval in each country participating in clinical trials is especially important in diseases where the treatment or curative window is narrow or finite, such as with cancer (Prasad, Kumar, & Mailankody, 2016; Wileman & Mishra, 2010; Yonemori et al., 2011). Should gaps in availability be found and/or a consistent pattern of covariates contributing to "drug-lag" for developing countries be identified, this may indicate possible exploitation of clinical trial participants from different regions and an opportunity to reduce or eliminate that potential.

Fundamental medical ethical principles and public health ethics seek to create a clinical research environment free of the social concern of patient exploitation (Council for International Organizations of Medical Sciences [CIOMS], 2016; Freedman, 1987; Freedman, Weijer, & Glass, 1996; Kass, 2004; National Bioethics Advisory Commission [NBAC], 2001a). Twentieth century medical research provides several examples of ethical transgressions following publication of court proceedings, ethical guidelines, and best practices, sometimes by decades (Beecher, 1966; Emanuel et al., 2000). Therefore, concerns and identified inequities related to the recent rapid globalization of clinical research are valid, considering these historical delays in adopting best ethical practices. Many ethical transgressions could potentially be addressed by a better definition of the responsibilities of the physician-investigator and development of international regulations better specifying the allocation of responsibilities to physician-investigators and research sponsors (Banerjee, Hollis, & Pogge, 2010; CIOMS, 2016; Prasad et al., 2016; Pratt & Loff, 2014; Schafer, 2010; Joint United Nations Program on HIV/AIDS [UNAIDS], 2012; World Medical Association [WMA], 2013). Just as the United States, EU and

Japan have largely successfully eliminated drug-lag for their populations, the benefits of PDUFA and cooperation between the United States, EU and Japanese regulatory agencies should consider the access and well-being of all participants from all countries that contribute trial data deemed pivotal for drug approval when making policy (NBAC, 2001b; Nuffield Council on Bioethics [NCOB], 2005; Prasad et al., 2016; Venkatakrishnan et al., 2016; Wileman & Mishra, 2010). To date, a tabulation and analysis of new drug approvals in all countries participating in pivotal clinical trials relative to FDA approval has not been performed. The knowledge gained by this analysis can assist in identifying specific countries or regions where local approvals lag behind FDA approval. Further, measurement of the time length of approval lags and identification of covariates associated with approval lag will be important to regulatory agencies, researchers, and sponsors conducting trials in affected regions. This knowledge can also assist in identifying which sponsoring companies prioritize expedient global approvals, a factor that can be included in existing scorecards of corporate transparency and ethical research practices in the pharmaceutical and biotechnology industries (Miller, Wilenzick, Ritcey, Ross, & Mello, 2017).

In Section 1, I present the problem statement, the research questions and hypotheses and a description of the theoretical foundations of the study. I also present the literature review strategy and gaps in the current literature, discussion of the relevance of this study, and present measures which can result in positive social change based on the findings of this study. Section 1 of this study introduces the globalization trend in clinical trial participation since the 1992 passage of Prescription Drug User Fee Act (PDUFA)

and the practical and ethical implications of conducting human subject research across a diversity of social, cultural, and economic geographies and demographics. I present a multipart literature review, including a description of the role of the physician-investigator, a brief history of modern clinical research, foundations of medical ethics in moral philosophy, contemporary research ethics and notable transgressions, a history of the FDA, phases of drug development, and current FDA regulations and recent FDA modernization. Historical articles and cases in medical ethics have also been included in the literature review, as are the processes and time-frames for adoption of principles codified in key ethical guidelines such as the Nuremberg Code, the Declaration of Helsinki, CIOMS and the World Health Organization (WHO) guidelines, and the Belmont Report (CIOMS, 2016; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016; U.S. Department of Health & Human Services, Office for Human Research Protections [OHRP], 2016; WHO, 2017; WMA, 2013).

Problem Statement

Globalization of clinical research sponsored by United States , EU, and Japanese companies has increased since the mid-1990s (Tufts Center for the Study of Drug Development, 2009). Electronic and internet technology has facilitated globalization across much of clinical medicine and medical research; and has increased the speed and capacity of information transfer, thus lowering costs to institutions and companies developing new therapies (Darrow, Sarpatwari, Avorn, & Kesselheim, 2015; Kesselheim Avorn, & Sarpatwari, 2016). Figure 1 illustrates the decline in the United States, the

plateau in the EU, and sextupling in rest of world (ROW) clinical investigators, beginning approximately 20 years ago (Coleman & Bouësseau, 2008; Drain, Robine, Holmes, & Bassett, 2014; Glickman et al., 2009; Tufts Center for the Study of Drug Development, 2009). In addition to increases in ex-U.S., EU and Japanese investigators, this globalization includes an increasing number of research participants from countries outside the United States, EU, and Japan (U.S. FDA, 2017a; Tufts Center for the Study of Drug Development, 2009).

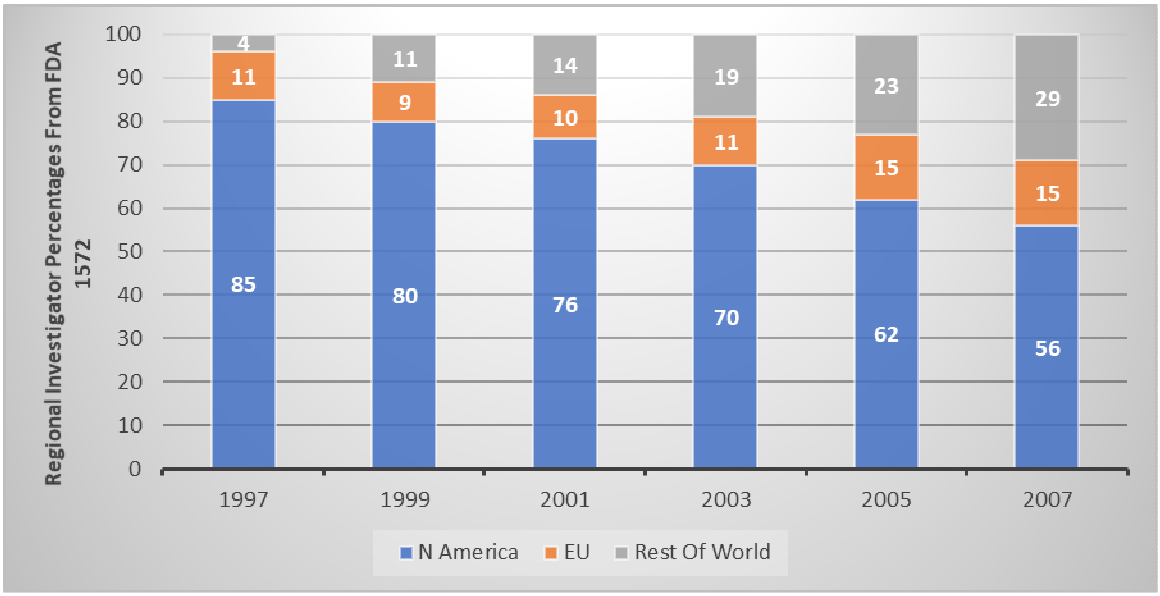

Figure 1: Clinical investigators by geographic region 1997-2007. Adapted from: Tufts Center for the Study of Drug Development, 2009.

Prioritizing approvals in the United States, EU, and Japan, the largest prescription drug markets in the world, makes business sense considering that U.S. prescription drug spending alone totaled nearly $330 billion in 2016 (Hartman et al., 2018). Analysis of applications for approval of new medications between 2004 and 2013 demonstrated that the majority of first in world approvals for new molecular entities (NMEs) are granted by

the FDA (Bujar, McAuslane, & Liberti, 2014). This corporate preference for prioritizing registration of drugs in the United States creates a potential injustice if foreign participants in clinical trials do not receive the same priority and access to NMEs as patients in the United States, EU, and Japan receive (Hartman et al., 2018). Several international guidelines require prospective disclosures of posttrial access plans for effective therapies, but debate exists on the definition of access, on a clear allocation of responsibilities for providing it, and for what duration access should be provided (CIOMS, 2016; Emanuel, Wendler, Killen, & Grady, 2004; Grady, 2005; Multi-Regional Clinical Trials [MRCT], 2016; NBAC, 2001a; Sofaer et al., 2009; UNAIDS, 2012; WMA, 2013).

The ethical concern over continued treatment for patients is relatively new in the globalized clinical research context and has been inconsistently addressed on a short-term basis by continuation of treatment in open-label extension studies or through programs such as compassionate use (CIOMS, 2016; MRCT, 2016; NCOB, 2005; Pace et al., 2006; WHO, 2017; WMA, 2013). However, in all but a few countries, sponsors are not required to continue treatment indefinitely, nor are they required to seek approval in all countries that provided research participants (Chieffi, Barradas, & Golbaum, 2017). Because indefinite treatment is not appropriate for some diseases with narrow treatment windows, such as cancer, other options have been proposed that create funds to subsidize medications or invest in the healthcare infrastructure for communities that provided research participants; however, sponsors and investigators are frequently unaware of the need to prospectively plan, disclose, and form partnerships to ensure continued access in

host countries (Ananworanich et al., 2004; Banerjee et al., 2010; Prasad et al., 2016). This is further complicated by concerns of inconsistency in investigator qualifications, improperly constituted ethics committees, corrupt practices, potential conflicts of interest due to industry funding, and infrequent and delayed reporting of study results in peer-reviewed journals for trials conducted in the developing world (Bristow et al., 2016; Glickman et al., 2009; Miller, Korn, & Ross, 2015; Morreim, 2005; Vollebregt, 2010). Therefore, trial participants from low and middle-income countries (LMICs) may be especially vulnerable to lack of access altogether or to long lags in drug approvals because of comparatively weak legal, medical, and ethical infrastructure, differences in general and health literacy, differences in access to international standards of care, and relationship dynamics with healthcare providers in their countries (Angell, 1997; Drain et al., 2014; Emanuel et al., 2004; Lurie & Wolfe, 1997; Miller et al., 2015; Mitra, 2013; van der Graaf & van Delden, 2012).

This increased reliance on data from participants in LMICs for FDA approval has created new questions of research ethics surrounding provision of expedient access to safe and effective treatments for all research participants (Angell, 1997; Emanuel et al., 2000; WHO, 2017; Wileman & Mishra, 2010). Because all research participants take risks when volunteering for clinical trials, if new drugs are not made equally available to the entire populations that bore the risks to test these new drugs, the potential for exploitation of human subjects is strengthened (Emanuel et al., 2004; Grady, 2005). While there is not a one-size-fits-all solution to this problem of ensuring expedient access to NMEs for all research participants regardless of the country in which they live, this

analysis provides insight into whether a similar level of corporate prioritization for NME approval-seeking occurs globally as it does in the United States. Analysis of covariates also identify variables associated with delays in global availability and expedient access to innovative treatments in all communities that bore the risks to test those medications first approved in the United States (Pace et al., 2006).

Purpose of the Study

The primary purpose of this quantitative study was to examine, for the years 2006-2015, whether pharmaceutical and biotechnology companies that included foreign patients in pivotal trials of NMEs sought approval in all countries providing research participants in an expedient fashion relative to FDA approval. The independent variable for the primary research question included all ex-U.S. countries contributing patients to pivotal trials for FDA approval, and the dependent variable was elapsed time to approval in all participating countries relative to FDA approval. The time to global approval was transformed and coded into four categories of expediency: expedient, that is, within 1 year of FDA approval; average, that is, between 1 and 2 years; delayed, that is, between 2-5 years of FDA approval; or severely delayed, that is, greater than 5 years since FDA approval. Research Question 2 considered the following seven covariates for impact on global approval expediency relative to FDA approval: year of U.S. approval, drug indication, orphan drug designation, FDA review type, host country income, and headquarters location and market capitalization of the sponsor companies. Independent variables were the seven covariates named above, and the dependent variable was time, transformed into the four categories of expediency relative to FDA approval. For the

years 2014 and 2015, the appropriate expediency category was applied based on the date of statistical analysis of the drug-lag time, which was April 1, 2019.

Research Questions and Hypotheses

The primary research question was answered by secondary data sets containing information on individual drug approvals from FDA, European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA), and the summary basis of approval documents provided by FDA on their public websites. Research Question 2 was designed to examine relationship(s) of covariates on the expediency of drug approvals relative to approval by the FDA. For the primary research question (RQ1), the context and time span of interest were those NME's approved by the FDA between the years 2006 and 2015. The dependent variable was elapsed time, coded into one of four categories of expediency based on elapsed time from U.S. approval of each drug to its approval in all countries that provided research participants in pivotal trials. The time-period for each expediency category was defined by me: (a) approval in all countries within 1 year of FDA approval was considered expedient, (b) approval in all countries within 1-2 years was considered average, (c) greater than 2 but under 5 years relative to FDA approval was considered delayed, and (d) approval in all countries in 5 years or greater relative to FDA approval was considered severely delayed. It was not expected that all first NME approvals between 2006 and 2015 would include foreign participants. The 66% threshold estimates for the null and alternative hypotheses for the primary research question were based on the observed average frequency between 2004 and 2013 that the FDA's approval was the first in the world (Bujar et al., 2014). I

proposed that no greater than same proportion of drugs first approved by the FDA between 2006 and 2015 would meet the expedient approval category, that is, approved in all countries providing research subjects in pivotal trials within 1 year of the FDA's approval.

For Research Question 2, I examined each covariate for association with any expediency category, expedient, average, delayed, or severely delayed in all countries, relative to FDA approval for each drug between 2006 and 2015. The null hypothesis was that covariates would not be associated with expediency categories (expedient, average, delayed, or severely delayed). Bujar et al., 2014 reported the average approval times for the FDA, EMA, and PMDA for the 2009-2013 period were 318, 480, and 363 days, respectively, with the maximum difference in mean approval time observed between 2009 and 2013 as 162 days (480-318 days). Considering the 162-day difference, if applications were filed to FDA and each participating regulatory agency within approximately 200 days of each other, there would be a low probability of change in the expediency outcome because categories span 1-year, 2-year, 2-5-year and greater than 5-year periods. It was plausible that the premium market regulatory agencies would improve their review times on an annual basis over the 2006-2015 period of the study; however, it was unknown and beyond the scope of this study whether regulatory agencies outside the United States, EU, and Japan would demonstrate similar improvements.

> RQ1: Of the NME's first approved by the FDA between 2006 and 2015 that included foreign patients in pivotal trials, what proportion of sponsoring companies achieved expedient approval in all participating countries?

$H_0$1: Fewer than 66% of drugs were expediently approved (within 1 year of FDA approval) in all host countries.

H_a1: Sixty-six percent or more of drugs were expediently approved (within 1 year of FDA approval) in all host countries.

RQ2: Are covariates of year of U.S. approval year, drug indication, FDA review type, host country characteristics, and sponsor company characteristics associated with specific approval time categories (expedient, average, delayed, or severely delayed) in all host countries?

$H_0$2: Covariate types are not associated with specific approval time categories in all host countries (expedient, average, delayed, severely delayed).

H_a2: Covariate types are associated with specific approval time categories in all host countries (expedient, average, delayed, severely delayed).

Theoretical Foundation for the Study

The overall goal of my study was to examine relationships between variables relating to the global availability of NMEs first approved in the United States between 2006 and 2015 that included foreign patient participation in trials deemed pivotal for the product's U.S. approval. This study includes only first approvals of NMEs in the United States versus generics and supplemental approvals of NMEs previously approved in the United States for different indications. I examined expediency of approval in all countries contributing research subjects relative to U.S. approval as the primary outcome, and thresholds of 1, 1-2 years, 2-5 years, and 5 years or greater were assigned categories of expedient, delayed, and severely delayed, respectively. I also examined seven covariates

thought to potentially influence expediency as a secondary research question; those covariates were year of U.S. approval, drug indication, FDA review type, orphan designation host country income, and the sponsor company headquarters location and market capitalization. The theoretical framework selected for this study was Pratt and Loff's (2014) research for health justice (RHJ) framework, which was adapted from Ruger's (2010) health capability model (HCM). A description and understanding of the HCM is valuable as a foundation for the later presentation of the RHJ framework (Pratt & Loff, 2014). The RHJ framework describes the research environment for international clinical trial subjects specifically, whereas the HCM framework describes an individual's perspective on a desire for health and their ability to pursue the necessary actions to ensure good health (Pratt & Loff, 2014; Ruger, 2010). Both the HCM and the RHJ models are also relevant to the concept of healthcare as a human right, a topic of significant debate in the United States over the past 2 decades.

Health Capability Model Description, Philosophical Foundation and Relationship to Research for Health Justice Framework

The HCM outlines factors in the environment that individuals and populations seeking good health encounter on the personal and societal levels that affect their ability to act as their own agents in pursuing good health (Ruger, 2010). There are two major components of the HCM, and each is distinguished by (a) efforts of individuals to seek a state of overall good health, and (b) recognition that the ability to successfully pursue a state of good health is influenced by both internal and external factors (Ruger, 2010). The HCM posits that the combination of the intrinsic desire to seek health and the ability to

pursue good health can be aggregated into a composite termed *health capability* (Ruger, 2010). Health capability is composed of both barriers and advantages, and each is influenced by both internal and external factors (Ruger, 2004, 2010). Self-directed factors are generally expressions of autonomy, a fundamental ethical principle of self-determination, which in the research context is the foundation for informed consent. In the health capability context, the principle of autonomy describes the individual's ability to make decisions about personal actions that are salutary, neutral, or harmful to health. Conversely, health capability is also influenced by the principle of paternalism, defined as involuntary prohibitions that assume that individuals are incapable or unlikely to make choices that are healthy or those that lower risks (Ruger, 2010). Some examples of paternalism are speed limits, laws prohibiting smoking in public, bans of trans-fat containing foods, local taxes on beverages with high sugar content, and the schedule of covered grocery items in Supplemental Nutritional Assistance Programs funded by federal and state governments (Ruger, 2010; U.S. Department of Agriculture, 2017).

Frequently, paternalistic measures have a paradoxical effect when the health consequences of a decision or of a physical state are not sufficiently rooted in the prevailing societal logic, or when such measures are in direct conflict with social constructions of autonomy (Resnik, 2010). In 2006, and 2008, respectively, New York and California prohibited restaurants from adding trans fats to foods (Brownell & Pomeranz, 2014). These state bans on trans fats are an example of an evidence-based measure intended to reduce risks of cardiovascular disease at the population level (Brownell & Pomeranz, 2014). However, the bans were controversial and initially

unpopular because many trans fat containing foods were anchored to ethnic, cultural, or religious identity (Resnik, 2010). The cardiovascular risk reductions of eliminating trans fats were ignored, largely because at the societal level, making individual food choices is regarded as a right with similar autonomous weight as freedom of speech or freedom of religion (Resnik, 2010; Ruger, 2010). Ultimately, in an effort to reduce cardiovascular risk at the U.S. population level, the FDA required content labeling, then removed trans fats from the generally regarded as safe category in 2015, and has ultimately instituted a federal ban of additive trans fats in all foods beginning in June of 2018 (U.S. FDA, 2018a). As healthier substitutes for partially hydrogenated oils were found that did not alter the taste, convenience, or ability to prepare culturally valued foods, the prior objection to paternalism waned, and today, trans fats are viewed socially as hazardous (Brownell & Pomeranz, 2014; Resnik, 2010).

Similarly, when population-based methods to address the U.S. obesity epidemic, a nonfatal condition, began to be discussed, there was resistance from additional stakeholders, those without primary interests in health capability. In response to the City of New York's "portion cap" ban on sales of sugary drink serving sizes of greater than 16 ounces, the beverage industry responded by asserting that a greater proportion of the causality for obesity was from inactivity versus from consumption of sugary beverages (Herrick, 2009; Pomeranz & Brownell, 2014). Further, common associations of lean body physical characteristics with health inspired a contradictory myth, notably promoted by Coca-Cola, which was deemed the "obesity paradox" where it was reported that extra weight, in both the overweight and obese body mass index ranges, conferred a protective

effect on mortality for patients with heart attack, stroke, heart failure, and diabetes (Banack & Kaufman, 2013). This counterintuitive claim for mortality was confusing, as the establishment of obesity as a risk factor for development of cardiovascular disease and type 2 diabetes was uncontroversial (Centers for Disease Control and Prevention [CDC], 2017). The obesity paradox spawned dozens of additional cohort analyses and statistical adjustments for selection bias among many experts. Ultimately, for patients with heart failure, the originally quoted odds ratios for death for overweight and obese persons were underestimated by 58% and 39%, respectively (Banack & Kaufman, 2013; Lavie & Ventura, 2015). While the obesity paradox remains incompletely resolved, the large portion sugary drink ban was found to be legally unconstitutional and was never implemented in New York (Pomeranz & Brownell, 2014). These examples illustrate the complexity of societal factors and influence of stakeholders in individual health capability decision making, particularly when paternalistic forces such as regulations are proposed (Ruger, 2010). In summary, for individuals, health capacity is influenced by a significant number of factors that can alter decision making. Whether those factors increase or decrease autonomy or modulate paternalistic measures, the individual's capacity for making the best health decisions is impacted. This could be in the context of seeking treatment from a qualified physician, seeing information about a clinical trial, or having the knowledge to ask about posttrial arrangements for continued treatment should the investigational drug be safe and effective.

Research for Health Justice Framework

The RHJ framework is specific to patient participation in clinical trials, and it is anchored to Aristotle's concept of the individual's right to health and ability to flourish (Papadimos, 2007; Pratt & Loff, 2014; Taylor, 1956). This flourishing includes a notion that more affluent countries have a duty to reduce the disparities between the communities that host their research, and the existing standards of care available to all in the sponsoring nation (Pratt & Loff, 2014; Pratt, Zion, & Loff, 2012). The RHJ framework is specifically built around 3 central tenets: 1) a focus on selecting appropriate host countries for participation in clinical trials, 2) the commitment to strengthening research capacity of the host community and 3) to contemplate and plan appropriately to provide post-trial benefits (Pratt & Loff, 2014). Aristotle wrote that the soul is the seat of the life force (Taylor, 1956). Additionally, it is the soul, through the body's senses, that enables consciousness to exist (Papadimos, 2007; Taylor, 1956). The human experience of the world; pleasure, pain, thoughts, imagination, and desires are captured by the body, and integrated and understood through consciousness, which is the force of the soul. The integration of these experiences gained from an individual's existence and their interaction with other bodies, nature and souls, allows growth, and flourishing (Papadimos, 2007; Taylor, 1956).

Aristotle believed that health was indispensable to both developing and maintaining this flourishing and happiness, and it is this indispensability that the health of the body must be a fundamental right to which each individual soul is entitled (Taylor, 1956). Aristotle also believed that there are influences on the soul and body at the

community level, and communicating one's desires and thoughts with other souls and bodies is essential to flourishing (Taylor, 1956). Therefore, souls are not solitary forces, rather, individual health is linked to the flourishing of one's community (Dainesi & Goldbaum, 2012; Taylor, 1956). Placing Aristotle's concept of flourishing community health into a contemporary and clinical research context; while individuals participate in research, individuals have encounters with physician-investigators, and individual data are collected, the community is impacted by the research, the observation, the introduction of a new agent, and the effects, whether positive, negative, of the observations themselves and the new drug being tested (Lavery et al., 2010).

State or national motivations for developing and maintaining a positive state of health among its citizens are to create economic and technologic growth, invest in education and infrastructure, decrease economic inequalities and health disparities, all of which can impact domestic stability and security (Dyakova & Hamelmann, 2018). State and federal governments can incentivize citizens to make salutary choices, and can impose prohibitions or limit opportunities to make harmful ones (Ruger, 2010). In all systems, healthcare and medical research lie at an intersection of physician's duties to patients, the prioritization the nation places on a healthy populace, the climate of innovation in healthcare a government wishes to create, the incentives for research sponsors, the amount of support the community and nation can offer to the sick, including research participants, and the responsibilities of the physician-investigator to both the research project and to the well-being of the participants under their care.

International medical research sponsored by foreign companies creates additional dimensions to the existing tension between the interests of the local patient, and the interests of the sponsor. Sponsors have the business or academic interest of completing the research quickly and with high fidelity, enabling rapid product approvals, often for the benefit of patients in premium priced markets, to maximize shareholder return on investment (Poitras, 2009). Developing countries, with weaker health and legal infrastructure, are at increased risk when foreign sponsored clinical trials are hosted in their communities. At its foundation, the RHJ framework contemplates this additional tension created by sponsors' business objectives and presents front-end mitigations to minimize the probability that foreign sponsors of clinical research can conduct trials with little community or national relevance, to benefit foreign versus host communities (Pratt & Loff, 2014).

Within and between societies, justice is one of the fundamental ethical values that must exist to establish an individual's and a society's sense of and belief in fairness. Aristotle included a sense of fairness and justice in his description of a flourishing soul and a flourishing society and Immanuel Kant included justice as one of the fundamentals of his moral law (Taylor, 1956). Kant, in 1785, stated that no man can justify using another man as a means to an end (Taylor, 1956). This fundamental statement in ethics will be carefully examined in the foreign sponsorship of clinical trials in developing countries context; a scenario where potential for departure from the fundamentals of Kantian justice exists, both during and after completion of the foreign sponsored international clinical research.

Because the RHJ model was designed to address the specific context of international medical research, its mission is to ensure justice across all populations participating in clinical trials, while not impeding the advancement of medical science and availability of new treatments to global patients (Pratt & Loff, 2014). The RHJ framework includes assumption of obligations which commit medical research to principles that inherently limit its capacity to exploit patients, beginning with elements that ensure research is always prioritized to reduce the gap between the most vulnerable patients and those most secure in their health (Pratt & Loff, 2014). RHJ is also grounded in a fundamental principle that countries with higher incomes and levels of development have obligations to LMICs to make the research locally relevant, and in the process reducing health disparities in the host countries, a principle that is often not aligned with shareholder value maximization (SVM) for corporations with publicly traded shares (Poitras, 2009; Pratt et al., 2012).

RHJ framework also takes a community view, versus an individual view on research participation, and considers the impact of the trial, the intervention and the physician investigator on the community further into the future than simply the in-life duration of the clinical trial (Pratt & Loff, 2014). RHJ provides proposals for long term partnerships between academic, industry and non-profit organizations from higher income research sponsor countries and the host countries. RHJ provides several suggestions for allocation of expertise, assigning roles to the most experienced in areas such as epidemiology, logistics, building infrastructure and research capacity building over time with the goal of establishing or improving the permanent protective

infrastructure through investments by entities which have performed research projects in these communities (Pratt & Loff, 2014). Post-trial commitments are of particular interest, as provision of continued access to drugs determined to be safe and effective for a fixed period of time has been the most frequent exchange for performing research in the host communities (Banerjee et al., 2010; Pace et al., 2006; Prasad et al., 2016; Pratt & Loff, 2014; WMA, 2013). As more experience has been gained, recognition that, if the first condition of RHJ framework has been met e.g.; high local need for a treatment, providing continued treatment for participants in the pivotal clinical trial does not consider incident cases, nor the prevalent cases excluded from treatment in the research protocol. Furthermore, expansion of the post-trial commitment tenet of the RHJ framework is warranted, assuming data on prioritization of approvals from this study demonstrates the potential for development or intensifying of a drug-lag between sponsoring and host countries for international clinical trials conducted between 2006 and 2015 for which the FDA was the first approving regulatory agency (Venkatakrishnan et al., 2016; Wardell, 1973; Wileman & Mishra, 2010; Yonemori et al., 2011).

In summary, the RHJ framework proposes several elements as priorities that do not conform to the conventional business objectives of intellectual property protection, revenue growth and SVM for the pharmaceutical and biotechnology companies responsible for sponsoring the development of the majority of NMEs seeking approvals by the FDA during the 2006-2015 period of this study (Poitras, 2009; Pratt & Loff, 2014). Additionally, many of the legal protections, particularly those of patents and Intellectual Property (IP) in the United States, conflict with the RHJ objectives of

increasing access to new treatments and diminishing health disparities between the developed and developing world (Pratt & Loff, 2014). Ironically, US patents and IP protection impede global distribution of new products to patients in countries, including those which contributed necessary data to the product approvals in the United States, EU and Japan (Collier, 2013). Frequently, the matter of NME approval is discussed in a business context vs a global health context, assigning responsibility for drug disparities/drug-lag to developing countries whose legal systems are not empowered or inclined to ensure patent and IP protection to a standard expected by US companies (Collier, 2013). The net result in the worst case is an unfair exchange, especially in countries contributing patients to NME development trials, of the risks of testing new drugs, with reliable access to the drugs that are found to be safe and effective by developed world regulatory agencies. If jurisdictions offering patent and IP protections along with premium pricing are the primary drivers for corporate prioritization of registration, then this study should demonstrate whether that pattern occurs during the 2006-2015 period. It is then a reasonable conclusion that significant time-lag in approvals in developing world, or LMIC countries, is associated with corporate prioritization of revenue from premium priced markets and SVM, versus reductions in health and treatment disparities between developed and developing countries, a fundamental of the RHJ framework (Pratt & Loff, 2014).

Nature of the Study

The nature of this quantitative methods study was to use publicly available secondary data sources to determine the frequency and the time-lag in which new

molecular entities first approved by FDA in the decade of 2006-2015 were made available in all countries which hosted clinical trials deemed pivotal to FDA approval. International guidelines from CIOMS, EMA, WMA and the RHJ framework state that sponsoring companies have a duty to both close gaps in health disparities between host and sponsoring countries, and to facilitate sustainable, post-trial access to successful interventions in host communities (NBAC, 2001b; Pratt & Loff, 2014; WMA, 2013). However, the frequency, durability and ubiquity with which post-trial access to medications found to be safe and effective occurs in participating countries, particularly those outside the US, EU and Japan was unknown (Pratt & Loff, 2014; UNAIDS, 2012; WMA, 2013). The ensuing knowledge from these analyses of annual US drug approvals and availability to all host countries provides clarification to the fundamental Kantian question of whether some research participants have served as a means-to-an-end and if so, for what duration (Papadimos, 2007; Walker, 1999). Meeting the threshold for the means-to-an-end question is whether patient data benefits more fortunate patients in the higher income countries of the United States, EU, and Japan before benefitting all participants in all host countries for a period of 2 years or more (van der Graaf & van Delden, 2012). Analysis of relationships between covariates and the time lag of treatment availability provides insight on points for education and planning for sponsors, host country governments, and regulators to prospectively minimize gaps in access and to facilitate global availability of all NMEs, especially those which represent breakthroughs, and treat diseases with high unmet needs. Determinants of time and approval gaps relative to U.S. approval can potentially be addressed by regulators, sponsoring

companies, international non-profit organizations, host countries, ethics committees, professional societies or a combination of all will be clarified allowing resolution of any identified disparities as suggested in the RHJ framework (Pratt & Loff, 2014).

This primary research question of this quantitative study examined, for the years 2006-2015, whether pharmaceutical and biotechnology companies that included foreign patients in pivotal trials, sought local approval in all countries providing research participants in an expedient fashion relative to U.S. FDA approval. The independent variable for the primary research question included all ex-US countries contributing patients to pivotal trials for FDA approval, and the dependent variable was elapsed time to approval in all participating countries, relative to U.S. FDA approval. The time to global approval was coded into 4 categories of expediency: Expedient, e.g.; within 1-year of FDA approval, Average e.g.; between 1-2 years since FDA approval, Delayed, e.g.; between 2-5 years since FDA approval, or Severely Delayed, e.g.; greater than 5 years since FDA approval.

Table 1

Descriptions of Primary Outcome Variables

Expediency category	Definition
Expedient	Approval in all participating countries within 1 year of FDA approval
Average	Approval in all participating countries between 1-2 years of FDA approval
Delayed	Approval in all participating countries between 2-5 years of FDA approval
Severely delayed	Approval in all participating countries in greater than 5-years from FDA approval

The second research question considered the following seven covariates for impact on global approval expediency relative to U.S. FDA approval: Year of U.S. approval, drug indication, FDA review type, Orphan designation, Host country income and Sponsor company characteristics of market capitalization and headquarters location. Independent variables were the seven named covariates, and the dependent variable is time, which, as with the primary research question, was coded into the 4 categories of expediency relative to US FDA approval. For the years 2014 and 2015, the appropriate expediency category was applied as of the date of this analysis as of April 1, 2019.

Table 2

Expanded Descriptions of Covariates for Research Question 2

Covariate	Description
Year of U.S. approval	Calendar year of FDA approval between 2006 and 2015 will be assessed for impact on expediency of drug approval in all participating countries.
Drug indication	The specific approved indication, and indication type, e.g. oncology, cardiovascular, anti-infective, rare disease will be assessed for impact on expediency of drug approval in all participating countries.
FDA review type	The FDA review classification; Standard Review (10 months), Priority Review (6 months).
Orphan designation	Orphan designation (under 200,000 patients in United States)
Host country characteristics	Host Country World Bank Income Category; Low, Lower-Middle, Upper-Middle, High (World-Bank, 2017)
Sponsor company characteristics	Country of Headquarters, Publicly Traded or Private, Market Capitalization (if available)

The primary outcome data were collected from three secondary sources, two within the US FDA and one from the Centre for Innovation in Regulatory Science (CIRS); a neutral, independent, U.K. based subsidiary company of Thomson Reuters.

Data from these 3 sources were aggregated into a master Microsoft Excel spreadsheet organized serially by year and individual drug. Variables supporting the primary analysis, e.g.; drug name, sponsor, date of FDA approval, countries involved in pivotal trials and approval dates in each country were included, as were all details for covariates noted in Table 1. The first FDA source was the annual NME approvals listing home page, hosted on the FDA's public website located at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm. Annual approval reports for all drug and biologics NMEs approved between 1999 and 2018 are available on this public site. The reports include the drug name (generic and trademark), the approved indication, approval date, sponsor name and the classification of the review (priority or standard). The U.S. FDA is the regulatory agency, headquartered in Silver Spring, Maryland, responsible for licensure of all new drugs, biologics and medical devices in the United States. Their assessment of new drugs and biologics requires that applicants demonstrate that their drug or biologic meets clinical standards of efficacy, safety and standards of purity, through best practices in chemistry, manufacturing and controls. The second FDA source (2014) is the public website housing the detailed review information and conclusions arranged by section approval for each individual approved drug. An example Drug Approval Package home page for the drug Farxiga™ approved in 2014 is available here: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/202293Orig1s000TOC.cfm. The section detail reports linked to each Drug Approval Package home page provide

additional details on pivotal trials, their locations, review type and approval type. The most relevant sections containing details for this study are the approval letter(s), the summary review, medical review and statistical reviews. If necessary, additional details for pivotal trials were obtained from a search of the National Institutes of Health (NIH) clinical trials database (2019) www.clinicaltrials.gov, where additional trial specific details are located (Zarin, Tse, Williams, Califf, & Ide, 2011).

CIRS reports on new drug approvals in the United States, EU, and Japan are issued annually and list the approvals each year in the United States, EU, and Japan as well as compare the previous 10 years of regulatory agency performance and present trends analyses. CIRS data are collected from the FDA reports referenced previously, and from similar reports provided by the EMA and the Japanese Regulatory Authority, the PMDA. Links to examples of EMA and PMDA reports are included:

- EMA: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/01/WC500242079.pdf
- PMDA: https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html

Data files from CIRS were requested, however they are not publicly available. The authors of the CIRS R&D briefing reports did provide PDF versions of their reports which covered the 10-year period of interest for this study. Relevant data were entered from CIRS reports into the master excel spreadsheet for analysis by SPSS™ statistical analysis software. Specific country drug approval dates outside the EU and Japan not

available via internet searches e.g. via Google, individual sponsors were contacted by email or telephone to determine the dates of approval in each country and those were entered into the master excel spreadsheet.

Literature Review Literature Search Strategy

The literature search strategy was built upon several key areas of literature necessary to cover the foundational topics providing context to this study of global availability of new drugs approved between 2006 and 2015 in each country that hosted trials deemed pivotal for the FDA's approval. Those key areas are; Principles of current and historical roots of ethics in human subject research, a brief history of human subject research, the difference in obligations between the typical physician-patient relationship and physician-investigator-to-patient relationship, FDA history, description of the FDA's drug development process and current regulations for drug approvals, and the concepts of drug-lag and FDA review performance since the first PDUFA modernization act in 1992. Several literature and agency databases were searched to obtain full articles and agency reports in PDF format for review. The databases were selected based on greatest relevance to medical and ethical journal articles and/or regulatory and economic report content. The most cited journals include *British Medial Journal* and affiliated journals, *Journal of the American Medical Association* and affiliated journals*, Lancet, Nature, the New England Journal of Medicine*, *American Journal of Bioethics, Bioethics and Journal of Medical Ethics.* The PubMed search engine for articles within the National Library of Medicine and the Library of Congress databases were the primary tools for obtaining peer reviewed journal articles and book citations. Google scholar was used as a search

engine to access various government, regulatory and non-profit organization reports and international guidelines, such as those from the World Bank, International Conference on Harmonization (ICH), World Health Organization (WHO), the World Medical Association (WMA), and the Council for International Organizations of Medical Sciences (CIOMS) and the Organization for Economic Cooperation and Development (OECD). Government organization and regulatory guidelines, reports, histories and regulations are primarily from FDA, the U.S. Department of Health and Human Services (DHHS), the EMA, and Japan's PMDA.

Broad search terms included: globalization of clinical trials, clinical trials in developing countries, philosophy of ethics, bioethics, history of medical ethics, post-trial access, drug-lag, US and global prescription drug prices, pharmaceutical and biotechnology revenue growth, FDA history, drug development process, and the PDUFA.

Journal articles, with the exceptions of those original publications providing examples of historically important departures from contemporary medical ethics, range in publication date from 1966-2018 and all were published in English. Selected reports summarizing regulatory agency approval activities and history include data from 1990-2018. Textbook references range from 1958-2017. The literature review was organized by the following broad topics; ethical principles and philosophy, ethics and the physician-patient relationship in modern medical research, examples of departures from ethics in lineal research, FDA regulatory history and policy in the 20th and 21st centuries, FDA process of drug development and approval, globalization of clinical research, post-trial access, revenue growth in prescription drug markets, and globalization of clinical

research since the introduction of the PDUFA in 1992. Additional sections include important bioethics cases in human subject research in the 20th and 21st centuries, and the generation of contemporary ethical guidance through application of fundamental principles in human ethics. Following a review of the roots of modern medical ethics in moral philosophy, I briefly reviewed modern clinical research and some notable cases of ethical transgressions. I also reviewed drug development and regulatory principles. I summarize literature relating to my problem statement below, which includes primarily regulatory agency reports and industry non-profit summaries which clarify the gaps in the literature relating to medical history, medical ethics and the drug development process.

Human Subject Research: Physician Versus Physician Investigator

Human subject research, defined broadly, is any scientific investigation involving the participation of human subjects that is intended to observe and evaluate the effects of some variable on the human condition with the objectives of contributing to generalizable knowledge on the disease, or an intervention's impact on the patient and the disease (Hellman & Hellman, 1991; Sheldon, 1999). Research on humans lies at the intersection of medical practice and scientific investigation, and its pursuit of generalizable knowledge creates a complex situation for the physician investigator when the clinical encounter includes the addition of obligations to research (Freedman, 1987; Hellman & Hellman, 1991). The physician-investigator must balance their primary responsibility for the best interests of the patient, *primum non nocere;* first, do no harm, with the requirements of the research protocol and the potentially broad applications of those research findings to populations suffering from medical conditions (Emanuel et al., 2000;

Freedman, 1987; Hellman & Hellman, 1991; Lázaro-Muñoz, 2014). Herein lies the challenge of balancing the physician's contract with the individual patient, and the physician-investigator's desire to conduct credible research, the results of which could potentially impact populations positively (Lemmens & Miller, 2002; Lázaro-Muñoz, 2014; Morreim, 2005). Much legal and philosophical debate has occurred over whether a legal framework can be applied to first, the physician-patient relationship, and second, to the physician-investigator-patient relationship and how those two frameworks may differ (Morreim, 2005). The physician-patient relationship is codified by many medical societies, the majority of which have substantive grounding in both ancient and modern principles of ethics. This context of this study is developed around the American Medical Association's (AMA) rubric for the physician-patient relationship as well as the guidelines for conduct of physician-investigators, referenced in CIOMS, FDA, International Council for Harmonization and WMA (AMA, 2016; WMA, 2013). The physician and the patient form their relationship most often when the patient seeks the consultation of the physician for diagnosis or treatment (AMA, 2016). At the foundation of the physician's code of ethics is a moral obligation for the physician to assist the patient and address their suffering, even above the physician's own self-interest (AMA, 2016; Papadimos, 2007). The partnership that the physician and patient form is based on trust, and this trust binds the physician to use their best judgment to advocate for the patient and their best health interests (AMA, 2016). Legally, this physician-patient relationship has been described as fiduciary, with the physician being professionally bound to act as an agent for the patient and their best interest, because the patient is both

in weakened state of health, and because their medical knowledge and expertise about the causes and treatment of their medical condition is less than their physician's (Morreim, 2005). Therefore, from a legal perspective, there is general agreement that the physician is the patient's fiduciary agent based on the trust formed in the clinical encounter and the moral obligation that the physician accepts when treating the patient (Lemmens & Miller, 2002; Lázaro-Muñoz, 2014). The physician-investigator relationship however has been a topic that has been significantly debated within the legal and scientific communities, particularly as clinical trials have globalized over the past 25 years (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016; Emanuel, 2013; Lemmens & Miller, 2002; Miller & Weijer, 2006; Morreim, 2005). As the number of potentially therapeutic products under study, and the requirements of regulatory agencies increased over the 20th century, the needs for physician-scientists has expended significantly, however codification of physician-scientist responsibilities has not occurred (Beecher, 1966; Schafer, 2010). This ambiguity has been at the foundation of the discussion of ethical transgressions by physician-investigators throughout the history of scientific inquiry into whether interventions intended to treat or curing human diseases are safe and effective (Beecher, 1966). At its core is the question of whether the physician-investigator trades off portions of their obligation to the patient as a physician, in exchange for the scientific objectives of the overall clinical investigation (Lemmens & Miller, 2002). To that end, significant debate among physician-investigators, physicians and legal experts exists over whether the nature of the physician-investigator to patient relationship is fiduciary in a similar way as the physician-patient relationship has been

agreed to be (Lemmens & Miller, 2002; Miller & Weijer, 2006). Stated differently, there continues to be debate over where the primary responsibilities of the physician-investigator lie. On one hand, the physician-investigator must be loyal to the best interests and medical well-being of the patient as required by both their professional code as physicians, and because the clinical protocol requirement medical stability. On the other hand, the physician-investigator must ensure compliance with the clinical protocol to ensure the generalizability of the research conditions and the data collected and therefore this conceivably conflicts with the prioritization of a patient's best interest (Emanuel et al., 2004; Morreim, 2005; Orth & Schicktanz, 2017). Finally, in the context of conducting clinical research in developing countries, questions exist over whether it is the role of the physician-investigator to ensure that the sponsor of the research complies with regulations and guidance regarding sustainable treatment, or the role of local government to ensure that sponsors comply with international guidelines in the absence of local laws (Emanuel et al., 2004; Orth & Schicktanz, 2017; Pace et al., 2006).

Brief History of Clinical Research in the Western World

References to scientific inquiry of factors influencing risk and benefits to human wellness are recorded across societies through antiquity (Bothwell & Podolsky, 2016). Beginning in the 18th century however, in parallel with the enlightenment, the scientific literature began to contain discussions of methods and reports of observational and interventional experiments in humans, such as those conducted in 1747 on the HMS Salisbury by James Lind, which demonstrated the comparative efficacy of citrus fruits in eliminating scurvy (Bothwell & Podolsky, 2016). Lind chose 12 sailors with scurvy and

assigned 6 pairs to a range of treatments from a quart of cider daily, to a quart of sea water daily, to daily consumption of lime or orange juice or a period of one week (Bothwell & Podolsky, 2016). Within a week, Lind reported that the sailors assigned to citrus consumption were so improved that they were assisting those assigned to the other remedy groups (Bothwell & Podolsky, 2016).

More urgent than the prevention of scurvy in the 18th century however, was action to protect the population from epidemics of smallpox surging throughout Europe (CDC, 2016). Smallpox, now eradicated, was an infection with approximately a 50% case-fatality rate that ultimately killed and disfigured hundreds of millions since at least the time of ancient Egypt, (CDC, 2016; Riedel, 2005). Observations that smallpox infection survivors became immune to infection during subsequent epidemics led to study and acceptance of the practice of variolation (Riedel, 2005; Weiss & Esparza, 2015). Variolation was introduction of material from the scabs or pustules of infected individuals to uninfected persons, with the intention of inducing a mild infection in the recipient, and thus preventing a full infection on future exposures to smallpox (Riedel, 2005).

Variolation had been practiced throughout Asia for centuries was introduced to Britain after a diplomat's wife observed the practice in Constantinople in 1717 and advocated for its consideration during a 1721 epidemic (Riedel, 2005; Weiss & Esparza, 2015). Before widespread practice was permitted, two human experiments on the efficacy of variolation were conducted in Britain in 1721; one in Newgate prison, where prisoners were variolated and then re-exposed to live smallpox, and a second in St James Parish

orphanage in London, where a similar experiment was conducted in children (Weiss & Esparza, 2015). It is both unclear and unlikely that physicians explained all the risks of variolation and sought and obtained informed consent of prisoners and children at this time, however it is noted that the prisoners, all sentenced to death, were offered amnesty if they survived (Weiss & Esparza, 2015). All the variolated prisoners and children survived their subsequent exposures to live smallpox (Weiss & Esparza, 2015). Based on the evidence provided from these experiments, the practice of variolation became widespread in Britain, their colonies, and in many parts of Europe (CDC, 2016; Weiss & Esparza, 2015).

In this context, in 1796, Edward Jenner summarized observational data, and designed a demonstration that exposure to cowpox virus by dairy-maids conferred a protective effect against contraction of smallpox infections (Riedel, 2005; Weiss & Esparza, 2015). Jenner's experiment was to "vaccinate" (latin root: *vaca* = *cow*) an eight year old boy, Joseph Phipps, with material obtained from a cowpox pustule from a dairy-maid's hand (CDC, 2016; Riedel, 2005). Jenner then "vaccinated" others before submitting his observations and experimental results to the Royal Academy in London (Riedel, 2005). At the time, the enlightenment of scientific inquiry was well established, however the connection between physician conduct and moral philosophy had not been established. The 1721 Newgate prison variolation experiment demonstrates some fundamental consideration regarding an exchange of a risk of smallpox infection and death for a pardon, it is unclear whether consideration was given to the thought that the prisoners were in a vulnerable position compared to the physician-investigators (Riedel,

2005). The variolation experiment on children at St. James orphanage in that same year demonstrates a likely conclusion that the experiment could be conducted more practically in that group, and that orphaned children had some diminished social value compared to children with living parents (Riedel, 2005). No exchange of risk-reward was noted in the St. James orphanage experiment other than the possibility of conferring immunity to future smallpox infections to the children.

The 19th and early 20th centuries brought significant further interest in generating objective scientific evidence demonstrating an understanding of health and disease and the efficacy of preventives and treatments to medicine. Generation of Pasteur's germ theory of disease followed the observational work of Semmelweis, Snow and Lister on communicability of certain diseases (Best & Neuhauser, 2004; Gawande, 2004). Commercial research, development, regulation and licensure of pharmaceutical and biotechnology agents has experienced enormous growth in the past 120 years, and has been a major contributor to the increases in global life expectancy observed in the 20th century (Lichtenberg, 2017). Development of preventions and treatments for communicable diseases such as smallpox, diphtheria, pertussis, tetanus, rabies, tuberculosis, malaria, measles, polio, syphilis and other sexually transmitted diseases were the primary objectives of pharmaceutical research and development for the first half of the 20th century. The middle decades of the 20th century saw significant expansions of both the number of clinical trials as well as the introduction of the first randomized-controlled trials (Kinch et al., 2014). The requirement for human studies demonstrating safety and efficacy prior to drug approval contributed to the rapid expansion of products

in commercial development in the 20th century (U.S. FDA, 2014b). After several tragic incidents killed and disfigured many patients in the early-mid 1900s; from contaminated serum, to contaminated sulfa elixir, to the teratogenic effects of thalidomide, regulation of new drugs became progressively more stringent throughout the 20th century (Kinch et al., 2014). From the 1960s to the present, with the exceptions of HIV and hepatitis, clinical research has primarily focused on the development of treatments for non-communicable diseases such as heart disease, cancer, diabetes and psychiatric disorders (Kinch et al., 2014). U.S. licensure, production and administration of antitoxins and vaccine began in the last decade of the 19th century has continued even into the 2000s (Kinch et al., 2014). Sulfa and penicillin anti-infectives were developed in the 1930's and 40's, as were the first chemotherapies for the treatment of cancer (DeVita & Chu, 2008). Biologics such as human insulin and growth hormone produced from recombinant DNA technology began to be approved in the 1980s, and the first approvals of therapeutic monoclonal antibodies began in the late 1980s (Kinch et al., 2014; Liu, 2014). Finally, most recently, the first immunotherapies and cell therapies began to be approved in the 2000s, with now those giving way to the first approved human gene therapy in 2017 (Smalley, 2017). Therefore, while the 20th century has seen both monumental scientific advances in therapies, it also witnessed some of the most severe ethical transgressions in by physician-investigators that have occurred since human subject research began. During World War II, and in the two decades thereafter some of the most well-known ethical transgressions occurred, despite the development of the Nuremberg code following the Nazi Doctors Trial in 1946-47 (Ferdowsian, 2011; OHRP, 2016). Several

additional seminal documents providing ethical guidance have followed for sponsors of human subject research and physician-investigators, including the Declaration of Helsinki, the Belmont Report and the International Conference on Harmonization's Guidelines for Good Clinical Practice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016; International Council for Harmonization, 2016; Wileman & Mishra, 2010; WMA, 2013). However, as the number, study designs and scale of research projects have grown to their current global scale and complexity, the ethics and the probability to inadvertently transgress has increased. Each decade of the 20th and 21st centuries has provided often more than one example that the ethical landscape changes in parallel with the growth of clinical research (Emanuel et al., 2004). Contrasting forces remain the academic and commercial desire for generalizable medical scientific information to gain approval and initiate sales, and the rights of each of the human subjects who agrees to participate in a clinical trial, whether they believe, or are told that the experiment is not designed to benefit them directly (Appelbaum, Anatchkova, Albert, Dunn, & Lidz, 2012). Beecher, 1966, observed the growth of the pharmaceutical industry in the first half of the 20th century and correctly anticipated that the advances in scientific and medical technology would increasingly be funded by industry. Therefore, a greater need for responsible practitioners of human subject research would be required to decrease the risks of an unfavorable exchange between the interests of the patient, and the interests of advancing medical science, the interests of industry sponsors of research, and the interests of academic advancement for investigators (Beecher, 1966). Beecher's concern over the growth of the pharmaceutical

and medical device industries and their impact on physicians and patients is similar to President Dwight Eisenhower's warning in his farewell address in January of 1961 of the expanding influence of the military-industrial complex, and the distortions of power and influence that accompany such expansion (Beecher, 1966; Eisenhower, 1961). The timeline in figure 2 below illustrates with the parallel growth of human subject research, some egregious examples of unethical research conduct by US investigators can occur despite ethical guidance documents being developed for physician-investigators, regulators and sponsors.

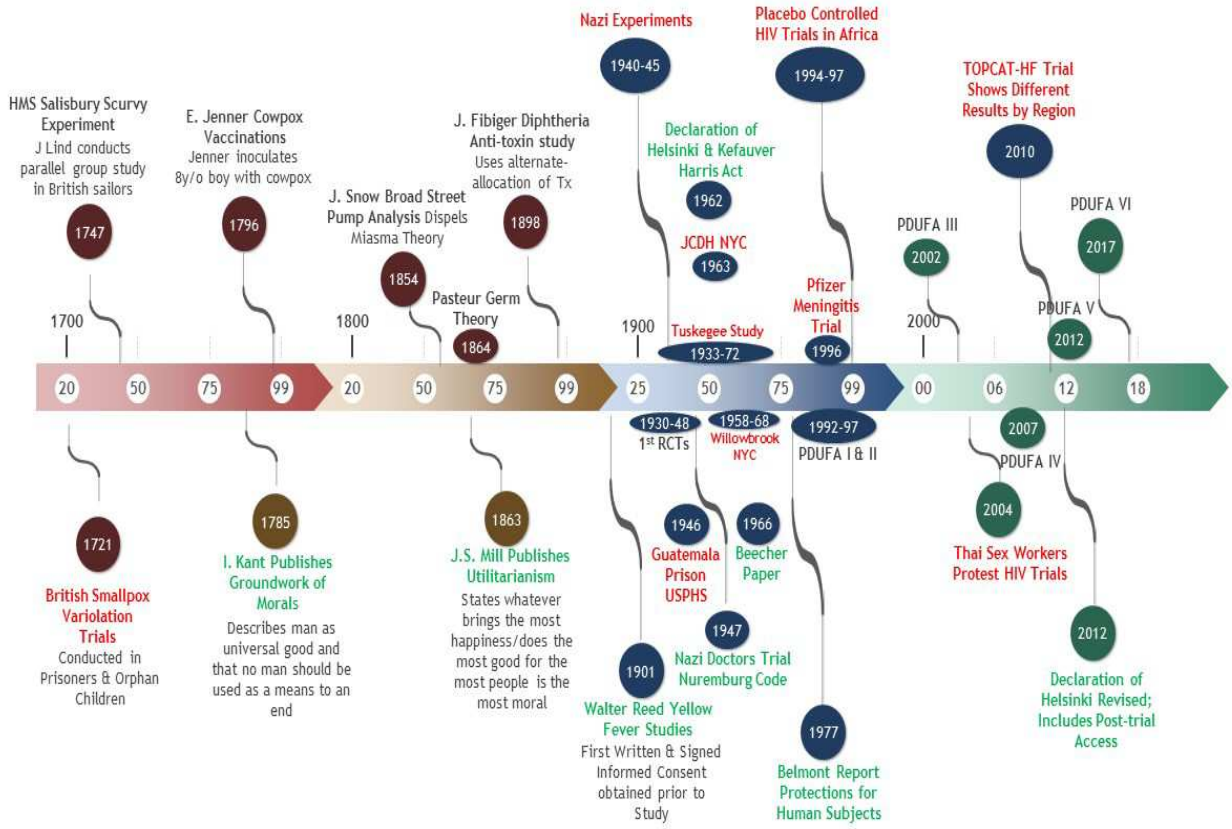

Figure 2: Important historical moments in clinical trials and medical ethics.

Foundations of Medical Ethics in Philosophy

What philosophical grounding and mechanisms exist to ensure that appropriate balance exist when priorities of the physician compete with the priorities of the physician-investigator and the sponsor of the research? The physician-investigator's duties to patient and to research are bound by ethical principles contained in the moral philosophies of universalism and utilitarianism, respectively. Universalism as a broad principle begins with Aristotle in the 4th century B.C. and was elaborated by Immanuel Kant in 1785. The general premise of universalism is that humans are composed of

elements of both body and soul, with soul being the life-force, or what has come to be known as consciousness, and the body and the senses being the interfaces with our environment (Walker, 1999). That consciousness is the essence of humanity and the within that essence is a right to flourish and be healthy, and that right to flourish forms a portion of the essence of the duties of a physician to care for their patients (Papadimos, 2007; Taylor, 1956). In Kant's 1785 Groundwork of the Metaphysics of Morals, he outlines his construction of the moral duties of humans and how a sense of these duties influences the actions one takes in an environment where man has free will (Kant, 2009). Kant proposes that each man has inherent value, which it is every man's duty to respect, and that no man should take actions that use another man as the means to achievement of a desired outcome/end (Kant, 2009).

Applying Aristotle's and Kant's principles to the sponsors of and physician-investigators participating in human subject research in the present context, the appearance of a moral dilemma appears if all research subjects are not treated equally not simply during, but after the completion of the clinical trial (Emanuel et al., 2004; Grady, 2005; Papadimos, 2007). Furthermore, both the research sponsor and the physician-investigator are faced with a tension between: a) upholding the duty to respect each patient's inherent value, b) the moral principle of not using another man as a means to achieve a desired outcome, with c) ensuring the scientific integrity of the experiment, and d) the advancement of science to improve and preserve human health at the population level (Mandal, Ponnambath, & Parija, 2016; Schafer, 2010). As such, the physician practitioner is not impacted by this tension, as his/her duty lies in assuring the best

interests of the individual patient versus consideration of the integrity of a scientific investigation and persons with whom he/she is not directly engaged in a physician-patient relationship.

John Stuart Mill's utilitarian philosophy serves a partial counter-weight to the dilemma faced by the physician-scientist's duty to preserve of the individual's rights in the context of a clinical trial. Utilitarian philosophy states that the approach which provides the greatest amount of benefit for the greatest number of individuals, is the most moral approach (Mill & Gray, 2008). Taking the utilitarian approach, the investigator facet of the physician-investigator role, accepts a moral imperative to pursue a course leading to the greatest benefit to the greatest number of individuals, even if the majority of those individuals are not under his/her clinical care. The sponsor of the research has a utilitarian interest in finding the investigational product which provides the greatest benefit to the greatest number of patients, and to advance those treatments to approval. Conversely, if the sponsor of the research is a corporation, this moral obligation is conflicted by the corporate pursuit of approval to generate revenue from the treatment, fulfilling the fiduciary responsibility that sponsor executives have to the corporate shareholders. Priorities of the patient and the research has been largely mitigated by the requirement of informed consent and the review and approval of the research protocol by an independent ethics committee (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016; International Council for Harmonization, 2016).

Contemporary Medical Research Ethics and Notable Cases of Transgression

In 1974, following the exposure of the ethical problems in the U.S. Public Health Service's Natural History of Syphilis study in Tuskegee Alabama, the National Research Act was passed into law by the US Congress (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016). The law created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was given the mandate to identify the basic ethical principles and framework within which all biomedical and behavioral human subject research was to be conducted (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016). In 1978 the committee produced a document titled; "The Ethical Principles and Guidelines for the Protection of Human Subjects of Research" which is also termed the Belmont Report, after the Maryland conference center where it was completed (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016). The Belmont Report was codified into the Code of Federal Regulations in 1979 and has also been referred to as the Common Rule which has become the gold-standard by which human subject research is conducted (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016).

The Belmont Report outlined three fundamental principles which must be in place for research to be considered ethical; Respect for Persons, Beneficence and Justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016). A fourth principle, non-maleficence is added to clarify

minimization of risk and access to care if harmed while participating in research (Farisco, Ferrigno, Petrini, & Rosmini, 2014). Each principle forms the foundation of several elements necessary for the conduct of clinical trials today.

Table 3

Principles in Belmont Report and Application to Clinical Research

Principle	Application
Respect for persons	Autonomy must be respected, Participation is Voluntary, Informed Consent must be obtained, and Researchers may not deceive participants
Beneficence	A standard of no harm, maximization of benefits and minimizing risks to each participant
Nonmaleficence	Assurance that intentional harm is prohibited, and that medical care is available if participants are harmed during the research
Justice	Assurance of fairness in administration of study qualification, and all study procedures, and assurance that all risks and benefits are distributed fairly among all participants

Note. Adapted from National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2016)

Kant's moral code forms the basis that requires the physician-investigator to respect the research participant's autonomy/free will by ensuring them that participation in research is voluntary and refusing to participate does not impact the physician's duty to the patient or the quality of healthcare they provide (Kant, 2009). Furthermore, the principle of justice ensures that risks and potential benefits of the research are distributed fairly and equally amongst the participants. Thus, if there is a significant gap between the number of countries where a new drug is approved and available, and the total number of countries which provided research participants, the benefits of the research will not have been distributed fairly and the principle of justice will have been violated. In the United States, the FDA is not responsible for regulating drug prices for the drugs it approves, the

drug manufacturers set their prices, which are then negotiated with various payers (such as Medicare, Medicaid, Insurance Companies, HMOs and retail pharmacies). In other regulatory jurisdictions, such as the EU, many member states have single-payer systems, and therefore drug pricing is often part of the regulatory approval process. Since globalization in clinical trials began its expansion into the developing world, examples of questionably ethical practices, such as sponsor's discontinuation of patients from beneficial investigational treatment, and inappropriate placebo-controlled trials, several international organizations have produced statements prospective planning for post-trial access to treatment. It should be noted that none of these organizations are regulatory agencies or national health authorities and therefore sponsors and physician-investigators are not legally obligated to follow recommendations for providing a post-trial access plan for investigational products deemed to be beneficial to all participants (MRCT, 2016). It is also notable that in cases where investigational drugs are found to be safe and effective in pivotal trials, removing patients from treatment may impose a risk of harm, especially in cases where alternative treatments do not exist or are not available to the research participant for other reasons e.g.; cost. In such cases, the forced discontinuation of treatment would create a moral dilemma with the principle of non-maleficence and potentially respect for persons if the participant had not been informed at trial initiation of the possibility of benefit and removal of the benefit at the discretion of the study sponsor (Grady, 2005).

Table 4

Guidelines with Posttrial Access Statements

Organization/Document	Brief Statement
Declaration of Helsinki (2013)	Sponsors, Researchers and Host-Country Governments should make provisions for all participants who still need the intervention if it is determined to be beneficial in the trial
CIOMS/WHO (2002)	Sponsors should continue to provide access to beneficial interventions pending regulatory approval
United Nations (2005)	Host Countries and other stakeholders should provide new diagnostic and therapeutic modalities or products stemming from research and support for health services
UN AIDS (2012)	Stakeholders should ensure that participants who are infected during a prevention trial are provided access to treatment regimens from among those internationally recognized as optimal. Agreement to do so should be sought in advance of the trial
Nuffield Council (2005)	Researchers should endeavor, before trial initiation to secure post-trial access to effective interventions for participants in the trial and that the lack of such arrangements should have to be justified with the ethics committee

Note. Adapted from MRCT (2015)

Historically, the adoption of newly codified ethics practices in human subject research indicates that caution is recommended as expansion in the number of investigators, subjects, research protocols and participating countries in human subject research occurs (Angell, 1997; Emanuel et al., 2000; Farisco et al., 2014; N. Kass, 2014; Lurie & Wolfe, 1997). The Nuremburg Code, a foundation for the modern requirements of informed consent and institutional ethical review of human medical research was issued in August 1947, and took decades to become fully adopted, even among respected institutions and clinical researchers in the United States (Mulford, 1967; OHRP, 2016). Excursions from the code occurred after 1947, in some cases for decades, by academic researchers, the US Public Health Service (USPHS), the NIH, the CDC, and others

(Angell, 1997; Lurie & Wolfe, 1997; Msamanga & Fawzi, 1997; Reverby, 2001). These ethical transgressions were sometimes egregious, as Beecher, Lurie & Wolfe, Reverby and Walter emphasize in their reviews of published human studies (Beecher, 1966; Lurie & Wolfe, 1997; Reverby, 2014; Walter, 2012).

Table 5

Notable Ethical Transgressions in Clinical Research

Event (Date)	Primary Principle Violated
U.K. - Nuffield Prison/St James Orphanage (1721)	Respect for persons, Autonomy, Nonmaleficence
U.S. - Natural History of Syphilis (1934-72)	Respect for persons, Beneficence, Nonmaleficence, Justice
Germany- Nazi doctors (1940-45)	Respect for persons, Beneficence, Nonmaleficence
U.S. Statesville Prison malaria experiments (1942)	Respect for persons
U.S./Guatemala – USPHS STD experiments (1946)	Respect for persons, Beneficence, Nonmaleficence
U.S. Ohio State Prison, Sloan Kettering, and Jewish Chronic Disease Hospital (1960-64)	Respect for persons, Beneficence, Nonmaleficence
U.S. Willowbrook School (1956-70)	Respect for persons, Nonmaleficence
Uganda/U.S. vertical transmission antiretroviral trials (1994-96)	Nonmaleficence, Beneficence, Justice

Brief Summary of the U.S. Food and Drug Administration History

The FDA has a broad purview to regulate food, drugs, and medical devices. The division regulating new drug approvals for pharmaceutical products is the Center for Drug Evaluation and Research (CDER) and is comprised of 14 special divisions corresponding to the areas of medical specialty for the majority of new drug indications. In parallel, the FDA has the Center for Biologics Evaluation and Research (CBER), arranged in similar therapeutic divisions. Finally, the Center for Devices and Radiologic Health (CDRH) is responsible for the review and approval of all medical devices and radiation emitting products (Van Norman, 2016b). The FDA has, since its departure as a section of the U.S. patent office in the mid-19th century, has had the purview to evaluate whether drugs were working in the manner they were advertised (U.S. FDA, 2018b). In 1938, the year following the contamination of a sulfanilamide elixir with ethylene glycol, which resulted in the deaths of more than 100 patients, the Federal Food, Drug and Cosmetics act was passed, which gave the FDA broader powers to ensure the safety as well as the claimed efficacy of drugs (Van Norman, 2016b). In 1962, the FDA was given additional powers with the passage of the Kefauver-Harris Act (KHA) (Greene & Podolsky, 2012). The KHA gave the FDA a mandate to assess the efficacy, monitor the accuracy of pharmaceutical advertising claims, and established the tradition of requiring adequate, well-controlled e.g.; randomized, placebo-controlled trials, prior to the drug's approval for marketing (Greene & Podolsky, 2012). The 3-phase approach to clinical drug development initiated with the KHA in 1962 remains the gold standard today, as

does the standard for demonstration of efficacy and safety, the randomized-controlled trial (Bothwell & Podolsky, 2016; Van Norman, 2016b).

Though the KHA was viewed as a barrier by the pharmaceutical industry and the American Medical Association, it had significant public support following the tragic, disfiguring and disabling teratogenic effects which occurred after expectant mothers had taken the drug thalidomide, an anti-emetic, administered during pregnancy (U.S. FDA, 2014b; Greene & Podolsky, 2012). Thalidomide had not yet been approved for use in the United States, however, approximately 10,000 children in 46 countries were affected and both public and regulatory consciousness was raised about possible teratogenic effects of prescription drugs (U.S. FDA, 2014b). The KHA granted the FDA both prospective, for drugs in development, and mandated a retrospective review and approval for drugs already approved between 1938 and 1962 (Greene & Podolsky, 2012; Van Norman, 2016b). A result of the KHA mandated retrospective reviews was the removal of more than 600 drugs from the market for objective lack of efficacy (Greene & Podolsky, 2012). By granting the FDA the power to prospectively and retrospectively demand proof of safety and efficacy, the agency became backlogged, and by the mid 1970's, the U.K. pharmaceutical market began to observe a difference between both the speed of new drug approvals, and the subsequent differences in their national formularies versus the approved US formulary; the time difference associated with the difference in formularies was termed "drug-lag" (Wardell, 1973; Wileman & Mishra, 2010).

The FDA initially denied the existence of a significant drug-lag, but ultimately the shorter review and approval times and the increasing number of new drugs available on

the United Kingdom formulary versus the United States, became clear to regulators and clinicians (Van Norman, 2016b; Wardell, 1973). The observed drug-lag inspired significant discussion in clinicians' professional circles in the 1980s, particularly in infectious diseases, due to the magnitude and severity of AIDS epidemic and the complete lack of treatment options (Klein, 2017). Highly visible advocacy for AIDS treatment, and convincing arguments allowing acceptance of surrogate endpoints; e.g.; reductions in viral load ultimately led to the approval of Zivoduvine (AZT) in 1987, 7-years after from the first publication of HIV/AIDS case studies (Greene & Podolsky, 2012; Kinch et al., 2014). Significant drug-lag was also noted in psychiatry and cardiology in the United Kingdom versus the United States during the 1980s, as practitioners called for reduction in review times and to increase the number of drugs available for treatment of chronic non-communicable conditions as well (Vinar, Klein, Potter, & Gause, 1991). It is important to note that in the 1980s and early 1990s, academics and practitioners were more concerned with the therapeutic gap that drug-lag created, whereas the pharmaceutical industry was more concerned over protracted review times and uncertainty of review outcomes (Greene & Podolsky, 2012). At the time, neither were concerned about the lag-time for international clinical trial participants to receive access to new drugs, as the globalization of industry-sponsored clinical trials had not yet begun its ascent to today's prevalence (Tufts Center for the Study of Drug Development, 2009).

These discussions ultimately led the groundswell which inspired the FDA modernization act, also known as PDUFA I, passed into law in 1992. PDUFA has been

renewed 5 times, most recently in 2017 (U.S. FDA, 2012). The Prescription Drug User Fee Act has been a significant overhaul to the FDA which requires the applicants for new drug approvals to cost-share with the FDA by paying a filing fee as well as additional fees during the drug review process (DHHS, 2017a). In fiscal year 2018, the PDUFA fees are expected to generate approximately $900 million of the FDA's $1.12 Bn budget, or 85% (DHHS, 2017a). Application fees for 2018 are $2.4 million for a full FDA review of a new drug application (NDA) or biologic license application (BLA) that includes clinical data (DHHS, 2017a). Such cost sharing by industry has allowed the FDA to modernize technology, make additional hires and to engineer more efficient processes within and between divisions and other regulatory agencies to allow data sharing and review optimization (DHHS, 2017a). The FDA's commitment under PDUFA was to reliably complete standard and priority reviews on schedules of 10 and 6 months respectively, and to eliminate drug-lag, particularly between the US, EU and Japan (U.S. FDA, 2012).

The funding from the user fees and review optimizations has allowed the FDA to commit to increasing capacity and speed and to provide transparency on performance. Since PDUFA I in 1992, the average standard NDA/BLA review time has been reduced from more than 20 months to approximately 10 months, in 2016 (U.S. FDA, 2017d). Likewise, priority reviews have been reduced from an average of 16 months in 1993, to 8 months is 2016 (U.S. FDA, 2017d). Increased and structured communications between the FDA and sponsors was also a part of PDUFA I-V modernization, particularly relating to the development of orphan and products for the treatment of rare diseases and diseases with high unmet medical need . PDUFA I-V introduced more flexible trial and U.S. FDA

review options for sponsors, as well as issuance of priority review vouncers as a reward for developing drugs for rare diseases in pediatrics (U.S. FDA, 2014a). The drug lag observed in the 1970s-early 1990s has also been addressed since initiation of PDUFA 1-V, with 60% of the FDA approvals from 2016 being the first in the world, versus approximately 10% first in world in 1993 (U.S. FDA, 2017d).

Phases and Objectives of Drug Development and U.S. Food and Drug Administration Review

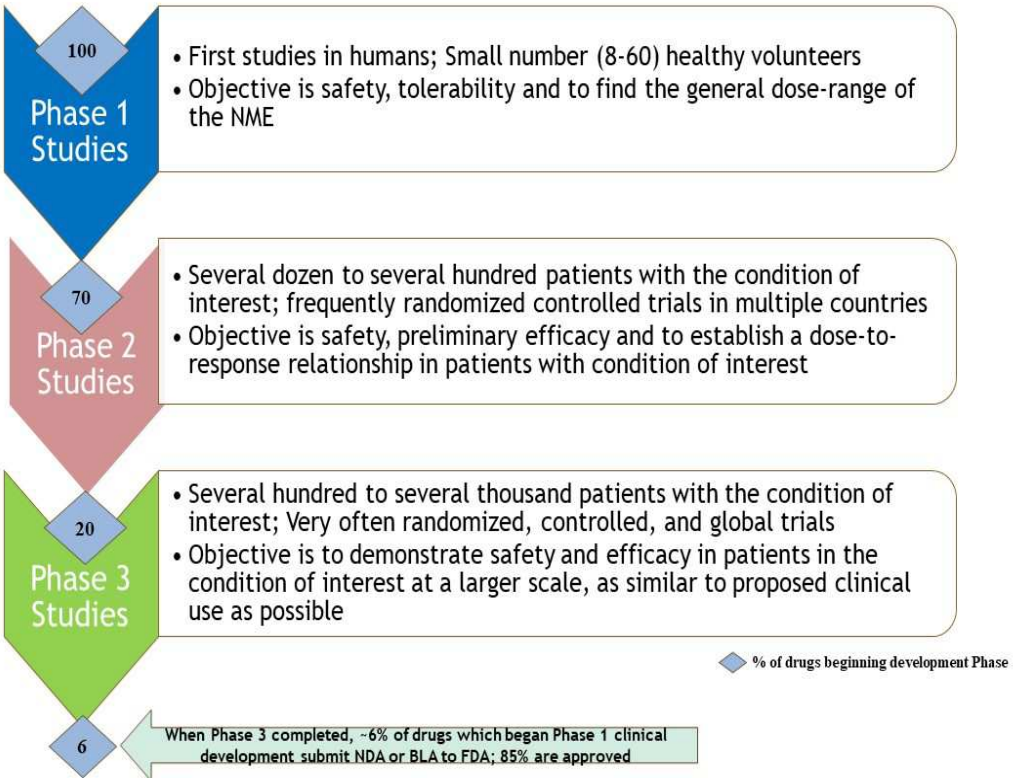

Figure 3. Drug development phases. Adapted from Van Norman (2016).

Figure 3 illustrates the process and objectives for each phase of clinical development, which are similar globally (Van Norman, 2016b). Beginning with Phase 1,

first in human trials, are most frequently in normal volunteers, and have the main objective of safety, tolerability and to identify a general dose-range (Van Norman, 2016b). There are some exceptions, such as oncology and rare disease drugs which may begin with patients, however the majority of Phase 1 trials are conducted in normal volunteers (Van Norman, 2016b). Oncology, Orphan drug and rare diseases are special cases Phase 1 and their development can be complicated by therapeutic misconceptions by patients, especially those who have no treatment options except participation in a clinical trial (Appelbaum et al., 2012). Phase 2 studies are the first trials in the patient population of interest and are generally randomized, controlled trials conducted on one to several countries and focused on establishing and understanding the safety and a dose-response relationship between the drug and the parameter of interest e.g.; LDL cholesterol for a lipid lowering drug or Hemoglobin A1c for a type 2 diabetes agent (U.S. FDA, 2017a; Van Norman, 2016b). Phase 3 trials have the objective of studying the new drug in the broadest population with the disease of interest and measuring it's safety and efficacy in a population most similar to the one in which the drug would be marketed (Van Norman, 2016b). Phase 3 trials are usually large, randomized, controlled and global, depending on the disease of interest (Van Norman, 2016b).

Many estimates and narratives exist about the development costs and probability of approval of a new drug, once it enters clinical development and completes each phase of development. Because development costs and success rates are considered trade secrets, each must be interpreted with care based on the author's affiliations. One group has conducted a series of annual anonymized surveys of pharmaceutical companies in an

attempt to estimate costs and probabilities of success in a consistent manner (DiMasi, Grabowski, & Hansen, 2016). DiMasi, et al. estimated in 2016 that the cost to develop a new drug are approximately $1.3Bn, with probabilities of approval, when completing each phase of clinical development as follows: 31% of drugs entering Phase 1 will not enter Phase 2, 70% of drugs entering Phase 2 will not enter Phase 3, and 70% of drugs entering Phase 3 will not go on to file a new drug application (DiMasi et al., 2016). If a drug files an NDA or BLA with the FDA however, the probability of approval in 2016 was approximately 85% (U.S. FDA, 2017c). Stated differently, roughly 90-95% of drugs entering Phase 1 trials will not go on to be approved by the FDA as is illustrated with the blue diamonds in figure 3 above (DiMasi et al., 2016).

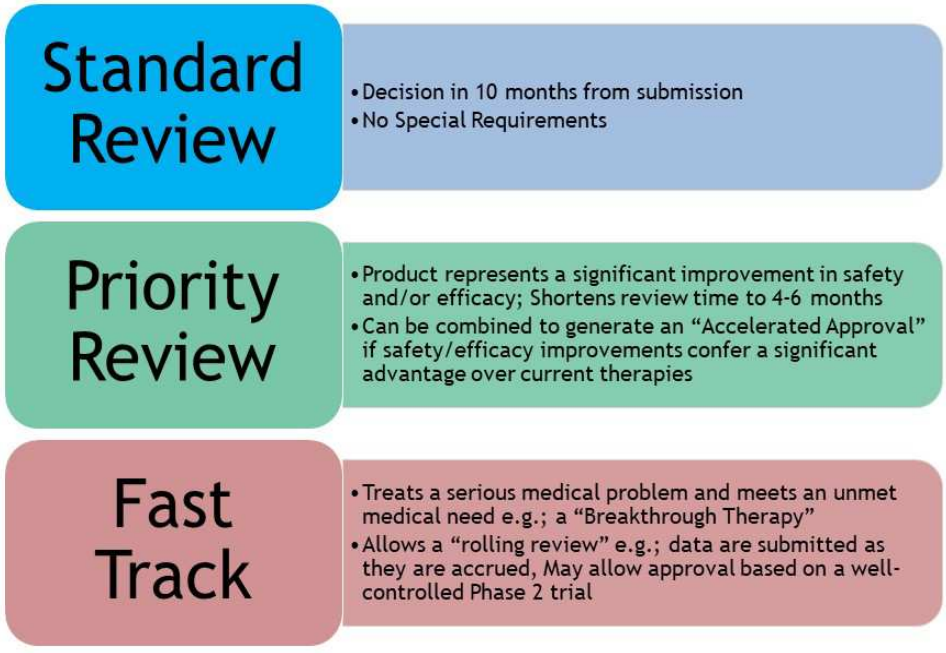

Figure 4: General FDA review and approval types.

Figure 4 illustrates the 3 general review categories that an application will be reviewed under (U.S. FDA, 2014a). Since PDUFA I was enacted, the standard review time is mandated to be 10 months from the date of the application, assuming the content if the application is found to be acceptable (U.S. FDA, 2017d; Somerville & Kloda, 2015). Priority review and Fast Track designations are categories of prioritization where the FDA deems the product as a significant improvement over the current therapies and/or provides a treatment option where a significant unmet medical need exists (Somerville & Kloda, 2015; Van Norman, 2016b). Priority and Fast track reviews are intended to give the FDA review teams the internal mandate to deliver action within 4-6 months, and/or in a more expedient manner than the standard review (U.S. FDA, 2012; Somerville & Kloda, 2015; Van Norman, 2016b). In 2015 and 2016, the FDA granted 17 and 20 priority reviews, respectively and completed all of them according to the expedited timeline of 4-6 months (Kinch et al., 2014).

Prescription Drug User Fee Act Modernization Impact and Comparison to European Union Process

FDA's PDUFA 1-V have made a significant impact on the pharmaceutical and biotechnology industries, catalyzing signficant growth in the US prescription drug market since 1992 (Hartman et al., 2018). The greater organization, increased transparency and legal mandates for completion reviews according to specific time-frames by the FDA with PDUFA I-V have reduced the risks for new product development and catalyzed an interest in filing NDAs and BLAs with the FDA first (DiMasi et al., 2016). While the EU adopted similar efforts to both streamline and centralize the approval process for all

member states in 1995, there remain four options for drug approvals in the EU: (a) Centralized procedure, where each member state has representation and approval for all EU member states is issued, (b) National Process, which is a specific state-by-state process, (c) Mutual recognition, which ocurs when an EU member state has approved a drug through their national process and applies for approval in another EU member state, and (d) Decentrlaized procedure, a process allowing application for simultaneous approval in more than one but not all EU member states (Van Norman, 2016a). In 2016, Centralized procedure EU approval times were approximately 45 days longer than the FDA's on average.

Gaps in the Literature

My literature review identified four gaps relevant to this study. Those gaps include: (1) few references to any association between the FDA's modernization act, beginning with PDUFA I in 1992, and the genesis of broad and rapid expansion of global participation in clinical trials, (2) the paucity of clear roles and division of responsibilities for physician-investigators, sponsors, regulators and ministries of health to all patients and communities which participated in global pivotal trials, (3) a lack of quantitative metrics for sponsors to ensure timely and sustained access to all host countries for NCEs determined to be safe and effective by the FDA, and (4) an analysis of the time-lag between development of new, and/or refinement of established ethical principles in human subject research and their adoption by global practitioners, as evidenced by continued ethical transgressions following seminal ethical guidance documents such as the Nuremburg Code, the Declaration of Helsinki and the Belmont Report. Gap 1 relates

to a probable stimulus for the rapid growth in international clinical research by U.S> companies, Gap 2 relates to ambiguity in the role and scope of responsibilities for physician-investigators, sponsors and regulators, and the lack of guidance and regulations assigning responsibilities, Gap 3 describes the subsequent need for development and reporting of metrics for global access to new drugs by sponsoring companies, and the introduction of industry-wide best practices, and Gap 4 is related to the observed time lag for adoption of newly established ethical practices by physician-investigators, sponsors and regulators as evidenced by examples of transgressions in modern clinical research occurring sometimes decades after clear guidance such as the Nuremberg Code, the Belmont Report and the Declaration of Helsinki were published. Addressing gap 3 is the primary objective of this study, which is to propose a time-based framework to evaluate sponsor performance in making newly FDA approved NMEs available in all countries which provided research subjects to pivotal trials.

Addressing the Literature Gap on Timely Global Availability and Access

The findings from this study, either alone or in combination other parameters of sponsor compliance, such as timely peer-reviewed publication of study results will inform the construction of an objective ethical compliance scorecard by which companies can be evaluated by sponsors themselves, patients and advocates, physician-investigators, ethics committees, host country ministries of health, policy-makers, other companies considering international trials, regulatory agencies, and international health and advocacy organizations (Miller et al., 2015). It is hoped that the results of both the primary and secondary analyses will provide a picture of whether sponsoring companies

are prioritizing access to all trial participants and their communities with the same or similar levels of expediency. Any patterns of regional differences in access or expediency by sponsor location, drug indication, host country demographics, or other covariates which emerge will be valuable to host countries with respect to assurances they can demand of present and future clinical trial sponsors. The results may permit international health, professional and advocacy organizations such as the WHO, the WMA and the United Nations to assess the performance of sponsors and to ensure that correctable barriers do not exist in any host countries which demonstrate inequalities in access and/or protracted times to local approval relative to FDA approvals. Other sponsoring pharmaceutical and biotechnology corporations with corporate responsibility statements that include patient access as a priority, such as the Danish biopharmaceutical company, Novo-Nordisk, for example, may have significant interest in their performance on an annual and drug-by-drug basis, and how their performance compares to other companies both competing in the same markets as well as those conducting research in host countries in different indications (Novo-Nordisk, 2018).

Definition of Terms

Important terms I have used in this study are defined as follows:

Accelerated approval: A type of FDA approval granted if a drug treats a serious condition and shows early evidence of substantial improvement over existing therapies through direct or surrogate endpoints (Somerville & Kloda, 2015). Accelerated approvals are conditional and allow the drug to be marketed while trials confirming efficacy are completed in the post-marketing setting (Somerville & Kloda, 2015).

Approval: The affirmative outcome of a regulatory agency's review (such as the FDA's) of a new drug application to grant a license to market a new product due to demonstration of safety and efficacy in adequately controlled clinical trials (U.S. FDA, 2016).

Autonomy: The ability of competent subjects to make their own decisions be recognized and respected, while also protecting the autonomy of the vulnerable by preventing the imposition of unwanted decisions (Beauchamp & Childress, 2013; Owonikoko, 2013; Varelius, 2006)

Average approval duration: An elapsed time between 366-730 days between FDA approval and approval of the drug in all countries which participated in pivotal trials.

Beneficence: The philosophy of do no harm while maximizing benefits for the research project and minimizing risks to the research subjects (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016).

Breakthrough therapy: Breakthrough therapy is defined as a drug, used alone or in combination with another drug, intended to treat a serious or life-threatening condition, demonstrates a substantial improvement in one or more clinical endpoints based on early clinical information (U.S. FDA, 2014a; Somerville & Kloda, 2015).

Clinical trial: A research study in which one or more human participants are prospectively assigned to one or more interventions; which may include placebo or other control; to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (NIH, 2017b).

Corporate fiduciary responsibility: duties in a corporate setting require directors to apply their best business judgment, to act in good faith, and to promote the best interests of the corporation (Poitras, 2009).

Delayed approval time: An approval duration of greater than 731 days but less than 1826 days since FDA approval of a particular NME.

Drug-lag: Any delay in making a drug available in a particular market relative to approval in a reference market, such as FDA approval in the United States. (Wileman & Mishra, 2010)

Equipoise (clinical): The existence of a legitimate scientific question as to whether the standard treatment or an investigational treatment is superior (Freedman, 1987).

Expedient approval time: A duration of 1-365 elapsed days between FDA approval of an NME, and approval in all countries contributing patients in pivotal clinical trials.

Fast-track review: A type of FDA review that allows applications to be made in a piecemeal fashion; reserved for drugs intended to treat serious conditions with a high unmet medical need (U.S. FDA, 2014a; Somerville & Kloda, 2015).

Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial; in FDA regulations, an investigational new drug is any substance (such as a drug, vaccine, or biological product) for which FDA approval is being sought (ICH, 2016).

Justice: Ensuring reasonable, non-exploitative, and well-considered procedures are administered fairly; the fair distribution of costs and benefits to potential research participants (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016)

New molecular entity (NME): A drug that contains an active moiety that has never been approved by the FDA or marketed in the United States (U.S. FDA, 2014a)

Nonmaleficence: To do no harm; e.g.; Physician-investigators must refrain from providing ineffective treatments or acting with malice toward patients (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016)

Orphan indication: Diseases which affect fewer than 200,000 persons in the United States or, if more than 200,000 persons, indications for which there is not a reasonable expectation that U.S. sales will recuperate the development costs of the drug (U.S. FDA, 2013)

PDUFA I-VI: The Prescription Drug User Fee Act, the first version of which was passed into law in 1992, with the objectives of modernizing the FDA's technology, speeding its review process, increasing its capacity and improving transparency for review and approval of new drugs (U.S. FDA, 2012).

Physician: A skilled professional trained and licensed to practice medicine; specifically, an individual possessing a doctor of allopathic or osteopathic medicine.

Physician-investigator: An individual who actually conducts a clinical investigation and under whose immediate direction an investigational agent (drug) is administered to a patient (U.S. FDA, 2017b; Schafer, 2010).

Physician-patient fiduciary relationship: A responsibility established between physicians and patients, implicitly or explicitly, in which both agree to allocate to clinicians discretion, the ability to act on patients' behalf with respect to their health (Lázaro-Muñoz, 2014).

Priority review: A type of FDA review that is 6 months in duration, and requires that the drug has potential to treat a serious condition and represents a significant improvement in current treatment, if any (U.S. FDA, 2013).

Respect for persons: Protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent. Researchers must be truthful and conduct no deception (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2016).

Severely Delayed approval time: A duration of 1826 or greater elapsed days between FDA approval and drug approval in all countries participating in pivotal trials for a particular NME.

Standard FDA review: Ten months in duration, with no requirements for rare or serious diseases or unmet medical need (U.S. FDA, 2013).

Therapeutic misconception: The belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge (Appelbaum et al., 2012).

Assumptions

The main assumptions I made for the data collection and the conduct of this study were that the data available from the secondary sources, primarily from the various FDA, EMA, PMDA and clincialtrials.gov websites and reports were accurate. Additionally, in the case of the CIRS source of secondary data, where aggregated reports on comparative drug approvals resides, the same assumption of accuracy was made. Finally, in cases where necessary data were not available on public regulatory or non-profit websites; e.g.; if a sponsor was contacted directly to determine approval date of a product in a specific country, reporting of their responses assumed the sponsors' report to a consumer's inquiry are accurate.

Scope and Delimitation

The intent of this study was to generate a categorical method for assessing the lag-time between approval of NMEs in the United States, and all countries contributing pivotal human clinical trial data to new drug applications upon which FDA approvals were based between 2006-2015. I also provide an analysis of several covariates and an assessment of their impact on expediency of drug approvals in all countries which hosted pivotal clinical trials. The primary analysis, and analyses of covariates serve as surrogates for understanding whether the potential for exploitation of patients by foreign sponsoring companies conducting global clinical trials exists in certain circumstances. Secondary data from public websites of the FDA and other regulatory agencies, the NIH, non-profit organizations and a free trial of a subscription-based data aggregating service were used to calculate the magnitude of drug-lag, in months. Delimitation of the study is that the

approval date in a particular country does not fully indicate whether a product is available to the patients who need it, e.g.; it is possible that the drug is approved but not yet reimbursed by the health system, that it is not and may never be reimbursed and therefore both not affordable and unavailable to patients, or that other considerations exist which make the approved drug unavailable in all countries which participated in development. It is possible that myriad factors influence the time to approval on a region-by-region or country-by-country basis which are not generalizable across borders; and an in-depth analysis of those factors is beyond the scope of this study. The time-based nature of the primary and secondary research questions gives credibility to the generalizability of the results, however, the single perspective, e.g.; the approval date by the FDA relative to all other countries is a known limitation.

Significance

Post-trial access to safe and effective medications tested in host countries is a fundamental of global bioethics codified in the WHO, UNAIDS, Council for International Organizations of Medical Sciences, guidelines as well as the Declaration of Helsinki (Pace et al., 2006; WMA, 2013). However, legal or jurisdictional requirements to register all drugs found to be safe and effective in countries providing research subjects are uncommon and if post-trial access is provided to subjects, it is sporadic and short-term (Chieffi et al., 2017; Dainesi & Goldbaum, 2012). Furthermore, trial sponsors are under no legal requirement to offer expanded access to patients in all countries who participated in their clinical trials, nor is there an academic, regulatory or industry framework for contemplating the success scenario of drug approval in the United States,

EU or Japan, and how to prioritize drug access for all countries providing research participants (Darrow et al., 2015). Because no legal requirement exists, the frequency and speed of this short and long-term access post-FDA approval is un-reported by sponsors (Grady, 2005; Sofaer et al., 2009).

This investigation is unique in its examination of the time-lag from FDA drug approval to complete availability of the new drug in all countries which provided research subjects to pivotal trials. The purpose of this study was to assess, for the first time, the frequency and timing of access to U.S. approved NMEs in all countries contributing research participants to pivotal trials supporting U.S. FDA approvals between 2006 and 2015. The primary assessment determined, relative to U.S. approval, whether sponsoring companies sought and received marketing approval in all other countries contributing patients to pivotal trials according to a four-category scale of expediency (Expedient, Average, Delayed, Severely Delayed). Having data on the expediency of by-country approvals for individual drugs relative to FDA approvals provides a metric of transparency and justice to research subjects in all countries, ministries of health, physician-investigators, regulatory agencies, policy makers and current and future sponsors and contract research organizations which does not currently exist. The research also considered FDA-specific covariates such as orphan indication, and the type of FDA review such as standard or priority review and their impact on global approval and availability of NMEs. Other covariates such as the drug indication, headquarters location, maturity and capitalization of sponsor companies, and host country incomes were examined for effects on timing to availability of the treatment in all

countries which provided research subjects for NMEs approved in the United States between 2006 and 2015.

Summary and Conclusion

Results from this study provide an objective measurement of sponsor performance for ensuring access to all research participants, their communities, and host countries that did not previously exist. The results of this study add to the transparency with which sponsors of clinical research conduct themselves, similar to the 2007 FDA mandate for sponsors to register all trials and to publish trial results on clinicaltrials.gov (NIH, 2017a). The significance or ubiquity with which the results of this study may be considered meaningful and result in action across various stakeholders is unclear without a mandate from a powerful health authority such as the FDA, EMA or PMDA.

Currently, there exists a role and responsibility ambiguity between sponsors, physician-investigators, ministries of health, ethics committees and other stakeholders for prioritizing assurance of access to drugs for communities and individuals who bore the risks to test them before the new drug was confirmed to be safe and effective. International committees and non-profit organizations such as CIOMS, UNAIDS, the WMA, the U.S. National Bioethics Advisory Committee, and the Nuffield Council on Bioethics all clearly endorse prospective planning and disclosure of plans for post-trial access prior to initiation of a clinical trial (NBAC, 2001a; UNAIDS, 2012; WMA, 2013).

Ambiguities lie in the parties holding primary responsibility for assessing and maintaining compliance with the pre-trial plan, particularly in resource constrained LMICs. Further ambiguities regarding duration of access, and to whom the drug access is

to be provided, e.g.; to research participants only, or to community members in need who supported the researchers and participants also exist and must be resolved fairly. Additionally, the recommendations for post-trial planning have been interpreted in a short-term context, versus a permanent one. Ensuring that the sponsor seeks local approval for the new treatment, at a locally indexed affordable price, as soon as possible following the FDA's approval of the NME is the most just and sustainable approach. Alternative approaches such as drug access funds, support of local healthcare infrastructure and other solutions may be acceptable, however a trusted, unbiased and systematic mechanism for evaluation and administration is necessary.

Seeking local approval places a specific burden on the sponsor, and there may be myriad business, logistic or other reasons why sponsors may choose to prioritize seeking approval in some countries versus others. Conceivably, those reasons could be related to prediction of low to no revenue from the host country, or the host country's economic position, the amount of intellectual property (IP) risk the sponsor perceives in the host country, the sponsor's perception of logistics in making the drug available in a non-research setting, among many other considerations.

In conclusion, if adoption of approval expediency performance metrics was done by sponsoring companies, or by the first approving regulatory agencies, which could encourage sponsors to prioritize expedient and equal access to all host countries in the most affordable manner plausible, that would be a significant positive global social change. Establishment of additional transparency into sponsor company practices and justice for all who have both directly participated in and hosted clinical research in their

communities would be beneficial to the former group, and both beneficial to and welcomed by the latter. Introduction of practices that unite global communities and sponsoring companies in a mutual belief in improving global health and advancing global justice simultaneously are plausible with prioritization and cooperation. Once roles and priorities are established, advancing both global justice and health will likely be both self-fulfilling and self-sustaining.

Section 2: Research Design and Data Collection

Introduction

Global participation in clinical trials has increased since the 1990s, with 69% of patients included in the FDA's new drug approvals for 2015 recruited outside the United States (U.S. FDA, 2017a; Kinch et al., 2014; Tufts Center for the Study of Drug Development, 2009). This increased participation includes patients from the developing world, whose countries have variability in the establishment, function, and oversight of the components necessary to ensure proper ethical conduct of research with human subjects (Angell, 1997; Emanuel et al., 2004). This rapid growth in globalization of clinical trials has led to ambiguity in allocation of responsibilities for assurance of posttrial access to effective medications. These ambiguities exist between the roles of sponsors themselves, physician-investigators, ministries of health, ethics committees, and agencies responsible for new drug approvals, and there is little data on how research sponsors prioritize the continued treatment of participants whose trial data established the safety and efficacy of NMEs (Angell, 1997; Annas, 2009; Miller et al., 2017). Little data exist summarizing proportions of patients continuing treatment through extension trials, or via sponsor investment in healthcare infrastructure of host countries or though sponsor investment in drug access funds or through sponsors seeking approval in all countries that contributed patients with equal priority as they do in the United States, EU, and Japan (Banerjee et al., 2010; Prasad et al., 2016; Pratt et al., 2012).

The purpose of this study was to evaluate, based on publicly available information, the priority with which sponsors gained approval in all countries that hosted

clinical trials deemed pivotal for FDA approval between the years 2006 and 2015. The data from this study complement existing data sets and their assessment of clinical trial transparency through measurement of frequency and timing of clinical trial publications (Miller et al., 2017). Utilization of the primary outcome data provides an indicator of corporate prioritization of global health based on the expediency with which companies pursue approval in all countries that hosted pivotal clinical trials. Knowledge generated from this analysis may guide sponsors and key stakeholders in host counties such as physician-investigators, ethics committees, and ministries of health in planning for the posttrial period and engaging the best methods to ensure that all host populations benefit from NMEs found to be beneficial in all communities that took the risks to test them. Also, knowledge generated from this study contributes to a heretofore nonexistent component of an ethical scorecard for pharmaceutical companies, as proposed by Miller et al. (2017). Further, I completed analysis of covariates such as year of approval, drug indication, orphan designation, sponsor characteristics, type of review, and host country income that may influence the expediency of drug approvals in all countries hosting pivotal clinical trials. Knowledge generated from the analysis of covariates provides insight into how sponsor companies, physician investigators, ethics committees, ministries of health, regulatory agencies, and policy makers can minimize gaps in availability of new drugs to research participants.

The primary research question was addressed through a review of FDA NME approvals for the years 2006-2015. The population of interest was identified from the NME approvals between the years 2006 and 2015 in which the FDA's approval was the

first in the world. These data are available on the FDA's annual drug approvals website for NMEs. For the subset of NMEs for which the FDA is first in world approval and those that included international patients in pivotal clinical trials, I calculated the time-lag in months from the date of the U.S. approval to the date of approval in the last host country. Any time-lag was coded into one of four elapsed time-based categories; expedient, average, delayed, or severely delayed. I assessed covariates with regard to whether they impacted the category of any observed time-lags.

In this section, I describe the study design, rationale, and methods. I identify the study population and present the strategies for any sampling and filtering. I also describe the process of data collection, coding, and management as well as the data analysis plan. This section includes summaries of the quantitative descriptive and inferential statistical methods used to test hypotheses for the primary research question and analyses of the relevant covariates for the secondary research question. This section includes ethical procedures and addresses both internal and external threats to validity. I used data from the FDA's Annual NME approvals database, as well as FDA summary bases of approvals to provide the population for the primary analysis. I identified those therapeutic NMEs approved by the FDA between 2006 and 2015 that included data from ex-U.S. subjects and collected information for the drug approval in each participating country from sources including but not limited to, the EMA website, the PMDA website, websites of other local ministries of health for participating countries, sponsors themselves, and a free subscription to a pharmaceutical data aggregator hosted by Springer Publications for approval dates for each drug of interest in each country of interest. I utilized public

databases such as Clinicaltrials.gov for confirmation of details, such as enrollment-by-country and start and completion dates of various clinical trials that were not available in regulatory databases.

Research Design and Rationale

This study was a quantitative study investigating first prevalence and second magnitude of differences between the independent variables and the dependent variable. This was an analysis of secondary data retrieved from the annual NME approval reports from the FDA between 2006 and 2015. For the primary research question, independent variables were regulatory approvals in each country providing patients to pivotal trials for drugs receiving FDA approval between 2006 and 2015. The dependent variable for the primary research question was time, more specifically, time-lag in months between those drugs that received first-in-world approval by the FDA. Following the primary analysis in research question 1, an inferential analysis of the dependent variable, drug-lag, was performed which compared the drug-lag across regions to each other and tested any differences for significance. In research question 2, I analyzed additional independent variables including year of FDA approval, drug indication, orphan designation, FDA review type, sponsor company location and market capitalization, and host country income to test for any association between independent variables to the coded gradations in the time lag between U.S. and each host country's drug approval.

Collection and analysis of quantitative data was the appropriate methodology to answer the primary research question, which was to calculate prevalence and time differences between first NME approvals in the United States and their subsequent

approvals in all countries that hosted pivotal clinical trials between 2006 and 2015. Collection of quantitative data from the annual NME approval reports from the FDA, EMA, PMDA, and ministries of health from participating countries was efficient, simple, and required limited resources to collect and transform data types. I determined quantitative data and quantitative methods for analysis to be most appropriate to investigate these research questions because they are clear, precise, numeric, and objective (Creswell, 2014). Some quantitative data were further transformed into semiquantitative, ordinal levels of measurement consistently, and these further transformations conferred greater meaning to and interpretation of the outcomes through both descriptive and inferential statistical analyses (Creswell, 2014; Frankfort-Nachmias & Nachmias, 2008). Frequency distributions, magnitudes of differences, hypothesis testing, and exploration of associations between independent variables and the dependent variable, time, for the secondary research questions were all possible because these data were quantitative.

Related research regarding company transparency in publications of clinical trials, such as studies by Miller et al. (2017) and Viergever & Li (2015), used quantitative data and descriptive statistics to summarize the frequencies and times to compliance by pharmaceutical companies with trial registration regulations and publication guidelines established both by the NIH and the International Council of Medical Journal Editors (ICMJE), respectively (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2017b; ICMJE, 2018; Miller et al., 2017; Viergever & Li, 2015). Miller and colleagues (2017) attempted to construct a compliance

and transparency scorecard based on adherence to FDA regulations for registration and updating the clinicaltrials.gov trial registry and adherence to the publication guidance offered by ICMJE as a surrogate for transparency. This research applied a similar approach through quantitative analysis of whether sponsoring companies were honoring statements in guidance documents issued by WMA, CIOMS, UNAIDS, NBAC, and the NCOB pertaining to posttrial availability of newly approved drugs to all participants in all countries.

The research questions and their associated hypotheses were as follows:

RQ1: Of the NME's first approved by the FDA between 2006 and 2015 that included foreign patients in pivotal trials, what proportion of sponsoring companies achieved expedient approval in all participating countries?

$H_0$1: Fewer than 66% of drugs were expediently approved (within 1 year of FDA approval) in all host countries.

H_a1: 66% or more of drugs were expediently approved (within 1 year of FDA approval) in all host countries.

RQ1a (Inferential analysis): Are the observed regional drug-lags of U.S.-EU, U.S.-last country, EU-last country and a simulated 24-month U.S.-last country matched pairs different from each other?

H_o1b: No difference exists in drug-lag between matched pairs U.S.-EU, US-LC, EU-LC and U.S.-24

H_a1b: A difference exists in drug-lag between matched pairs U.S.-EU, US-LC, EU-LC and U.S-24

RQ2**:** Are covariates of year of U.S. approval year, drug indication, orphan designation, FDA review type, host country characteristics and sponsor company characteristics associated with specific approval time categories (expedient, average, delayed, or severely delayed) in all host countries?

$H_0$2: Covariate types are not associated with specific approval time categories in all host countries (expedient, average, delayed, severely delayed).

H_a2: Covariate types are associated with specific approval time categories in all host countries (expedient, average, delayed, severely delayed).

Each of the seven covariates was tested for association with an elapsed time range from FDA approval, which has been coded into the four expediency categories, yielding a binary outcome of: (a) associated or (b) not associated. The threshold for assigning association to the outcome was frequency of co-occurrence of independent and dependent variable in 50% or greater of cases (Hinkle, Wiersma, & Jurs, 2003). Strong positive associations are considered present if the frequency of co-occurrence of independent and dependent variables occurs in 70% or more of cases and strong negative associations are considered if dependent and independent variables co-occur in 30% or fewer cases (Hinkle et al., 2003). Associated outcomes, whether positive or negative, are reported as such.

Methodology

Population, Sampling Procedures, and Data Collection Methods

Population. The overall target population was the total number of NME approvals completed by the U.S. Food and Drug Administration for calendar years 2006

through 2015 inclusive. Excluded from the data set of annual FDA approvals during that period were generic drugs, biosimilars and medical devices, none of which qualify as NMEs. Approvals of a simultaneous or second indications for already approved NMEs in the same year are excluded from the data set, as were those NMEs for which the FDA's approval is not the first in the world. The choice of the time frame (2006-2015 inclusive) was made because it provided a decade of approvals data during a period of expansion both in the number of countries participating in clinical trials, but also in the proportion of ex-US versus U.S. patients included in each application for FDA approval (U.S. FDA, 2017a; Tufts Center for the Study of Drug Development, 2009). The choice of both the U.S. FDA as the regulatory agency, and of an NME's first approval in the United States allowed discrete and quantitative benchmarking of US approval dates versus the approval dates in each country providing patients to pivotal trials.

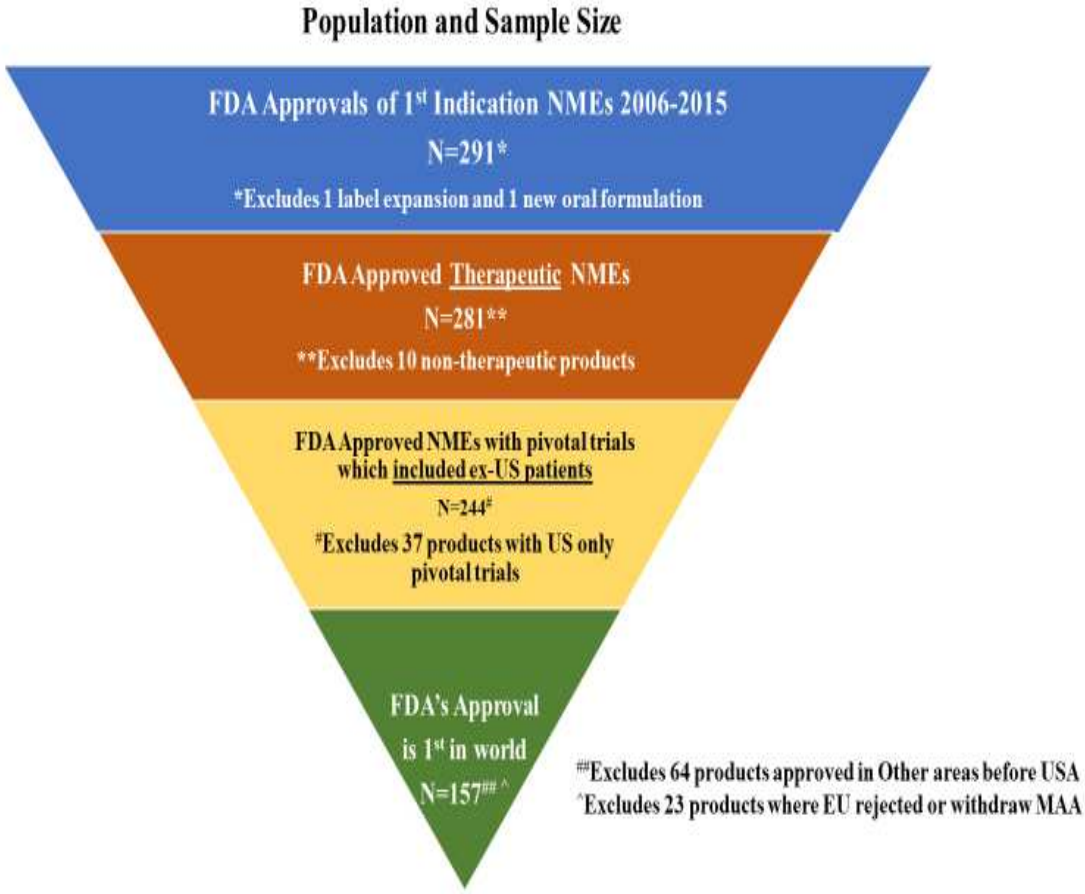

Figure 5. Population sample from FDA approvals 2006-2015.

Sampling frame. All data collection and analysis in this study were sampled from secondary data sets on drug approvals housed primarily on the U.S. FDA's public websites. Figure 5 describes the filtering of the overall FDA approval data set, to the primary data set of interest for this study, e.g.; drugs first approved by the FDA between 2006-2015. Access to annual reports of all drug approvals in a PDF format are housed on the public website of the FDA. Further details of the entire FDA review of each approved drug are housed, also in a PDF format, in the summary basis of approval section of the

FDA's public website. The inclusion criteria for the sample data were the following: a) the FDA approval must have occurred between the dates of January 1, 2006 and December 31, 2015, b) the FDA approved molecule must meet the definition of an NME, c) only one NME indication approval is counted if more than one indication is approved either simultaneously or in the same year, e.g.; simultaneous approvals for different types of non-Hodgkin lymphoma, and d) only those NME's approved, where the pivotal trials included any ex-US patients, and the FDA's is the first in the world approval of the NME.

While not present in each FDA annual approval report, data on the FDA's first in world approvals was compiled by a combination of public resources including FDA division director status reports and annual reports on regulatory agency performance compiled by the Centre for Innovation in Regulatory Science (CIRS), a United Kingdom based non-profit organization which tracks comparative performance of drug regulatory agencies. The former FDA Division Director, Dr. John Jenkins, was contacted via email and provided on-line links to 2015 and 2016 updates, and no special permission was necessary (J. Jenkins, personal communication, May 13, 2018). CIRS annual reports are available on-line or via request. CIRS reports capturing the 2006-2015 period were requested, and on-line links were provided by Dr. Magdalena Bujar of CIRS. If necessary, for collection of necessary data for the primary research question, each sponsoring company were contacted for the exact dates of approval for each drug in each participating country if the approval dates are not provided on local health authority public websites such as the EMA for EU countries, PMDA for Japan and/or other

participating countries. Additional data, relating to the independent variables in the secondary research questions were obtained from sources noted in Table 6.

Table 6

Independent Variable Details Research Question 2

Variable/Level of measurement	Data source
Year of U.S. approval/ Ordinal	Calendar year of FDA approval is provided in each FDA NME Annual Approval Summary Report available on the FDA's public website.
Drug indication/ Nominal	The specific approved indication is included in each FDA NME Annual Approval Summary Report available on the FDA's public website.
FDA review type Nominal	The FDA review classification; Standard Review (10 months), Priority Review (6 months) and are included in each FDA NME Annual Approval Summary Report available on the FDA's public website.
Orphan designation Nominal	Orphan designation (under 200,000 patients in United States) available on the FDA's public website housing the summary approval data for each individual NME.
Host country characteristics/ Ordinal	World Bank Income Category; Low, Lower-Middle, Upper-Middle, High is available, for each country, on the World Bank's public website.
Sponsor company characteristics/ Nominal	Country of Headquarters, Publicly Traded or Private, Market Capitalization at time of United States Approval (if available), available on each company's corporate website and via NYSE or NASDAQ public records.

Each of the independent variables included in research question 2 is relevant to the overall project because each conceivably influences the time to FDA approval for any specific NME. For those variables not determined by the FDA itself, e.g.; host country characteristics and sponsor company characteristics, each can exert influence over the time taken to complete FDA review. Host country characteristics can, for example, influence the time to completion of the FDA's review if the reviewing division has no

experience with patient data from that country and clinical sites have not been previously inspected by FDA inspectors. Sponsoring company characteristics such as experience and capitalization can influence both the time taken for FDA review, as well as the prioritization, preparation and execution of approval filings in all participating countries.

Data access. The source for the primary data was the US Food and Drug Administration's annual NME approval reports are housed on the FDA's public website and are available for download in PDF format. These reports contain no confidential information of the patient participants in clinical trials included for each NME, nor do they contain any proprietary information of the approved drug's sponsor or disclose identities of drug structure and formulation or participating physician-investigators. The content of each annual NME report includes the following elements: Application Number, Proprietary drug name, Generic drug name, Applicant/Sponsor name, Classification/type of review, Approval date and Approved indication for the NME. Data for the Proprietary drug name, Applicant/Sponsor name, Classification of review type, Approved indication and Approval date were entered into a master excel spreadsheet containing all NMEs approved between calendar years 2006 and 2015 inclusive. The completeness of the master spreadsheet was cross-checked against each year's summary report on the FDA, EMA and each participating country's drug formulary websites, as available. Individual tabs in the master excel spreadsheet were created to capture all data elements required for each covariate summarized in Table 6 and manually entered.

Other sources for data relating to the covariates included in the secondary research question were collected from two additional sources available on the FDA's

public website. Details of countries with sites included in the pivotal clinical trials were collected from the Summary Approval section of the FDA's public website for each individual approved NME. Details on pivotal trials and any post-approval requirements were manually entered into the appropriate tab in the master excel spreadsheet. Drug approval dates for each individual country were obtained through public websites for each country's ministry of health, or, for countries which do not maintain these data on public websites, the sponsoring company was contacted and their reported approval date in each country was entered into the appropriate covariate tab in the data spreadsheet. In cases where approval status and approval dates were not available, a free subscription to a pharmaceutical data aggregating subscription, ADIS Insight, hosted by Springer Publications was consulted and the data recorded in the master spreadsheet.

Sample size. The primary research question and the testing of the null and alternative hypotheses were descriptive in nature and therefore a sample size calculation was not necessary. Figure 4 illustrates the filtering of cases from the original number of 293 NME approvals to the analysis data set, which yielded an analysis data set of 157 therapeutic drugs first approved in the United States between 2006 and 2015. Because the population for the primary and secondary research populations is therapeutic NMEs first approved in the United States, an inferential analysis of the primary research question was conducted using the European Union approval date of each NME, as a reference point by calculating the numeric difference in months for each drug first approved in the United States versus the approval date in the EU. The difference in approval date between the first approval (United States), the intermediate approval (EU) and last host

country approval (LC), measured in months, constitutes a measurement of "drug lag", which was inferentially analyzed for statistical significance via nonparametric rank tests for paired samples from both the U.S. and EU approval date benchmarks.

The secondary research question examined associations between covariates and approval dates in all countries included in pivotal trials. The chi-square test was chosen for inferential analysis of nominal covariates. The sample size for this inferential analysis was calculated based on an effect size of 0.5. An absolute value of 0.5 is the midpoint of the r values (|0.3-0.7|) for which a correlation is considered moderate, be it positive or negative (Glantz, 2012). At a power of 90% and statistical significance at the 0.05 level, a minimum sample size of 43 was required to test the hypothesis for the secondary research question which explored the associations between each covariate and any approval lag between the United States and the last approval in the countries participating in each drug's pivotal trial (QFAB, 2018).

Data Collection Method

The broad study population sampled includes all NMEs approved by the U.S Food and Drug Administration between January 1, 2006 and December 31, 2015. Figure 4 illustrates how the population sample was refined by selecting those NMEs, where the FDA's approval represented the first in world approval of that molecule for its first approved indication. For example, if an NME was approved by the FDA for two different indications in the same calendar year, the indication and date of the first approval was selected and the second indication approval date was excluded, because, by definition, the molecule no longer meets the definition of NME. The FDA annual NME approval

reports for the years 2006-2015, available on the FDA's public website contain the entirety of drugs included in the sample for this study. Similarly, the drug approval dates for those approved by the EMA were accessed from the EMA's public website which aggregates the same approval date and indication data.

Data Analysis Plan

SPSS was used for data analysis of the primary and all secondary research questions. Hypotheses for primary and secondary research questions were tested with descriptive versus inferential statistical methods. All descriptive statistics, including measures of central tendency, frequencies, percentages and cross-tabulations were performed by SPSS. All descriptive data outputs, including summaries, tables and graphs were generated by SPSS and included as appropriate in the Results section with interpretations.

With reference to the primary research question and to allow inferential analysis, each drug's approval date in the European Union was used as a reference. A Wilcoxon's Signed-Ranks test was conducted, comparing the drug-lag between the United States-EU, the drug lag between EU approval and the last participating host country's approval, an adjusted United States-last host country approval and a simulated United States-24-month drug lag population. Median lags between the United States-EU, the EU-last host country approval, the U.S.-last host country and the simulated U.S.-24-month population were assessed for statistical significance. Further inferential analysis of covariates included in the secondary research question included a chi-square analysis for independence of covariates to the observed categorical value for drug-lag between the U.S. approval and

last participating country's (LC) approval. All descriptive and an inferential analysis were performed with SPSS.

Preparation of the data for analysis included a manual review and assessment of completeness of values necessary to the primary research question. These elements included the date of FDA approval and the dates of approval for the all countries included in pivotal trials considered by the FDA to have been pivotal to their first approval of the NME, between January 01, 2006 and December 31, 2015. The same manual missing data review and assessment was performed for each covariate and the entire data set was examined for patterns of missing data. No recognizable patters existed, and the SPSS missing data, duplicate data and identification of unusual data functions were used to programmatically interrogate the complete data set and report frequencies of missing data, duplicate data and outliers were completed. An assumption that overall frequency of missing data in the primary research question data set of less than 5%, was assumed to be by chance. For the primary analysis, missing values were planned to be replaced with the mean value for the lag-time variable in the data set, i.e. if the average lag-time between U.S. and last country's drug approval = 40.5 months, 40.5 will be entered for each missing time value. Missing values for each covariate in each portion of the secondary research question, because they are nominal, were planned to be replaced with the most frequently occurring value in that data set if missing. For drugs approved by the FDA in years 2014 and 2015, the status of approval in the last participating country was assessed by a cutoff date of April 1, 2019.

Descriptive analyses. Both the primary and secondary research questions are addressed through application of descriptive statistical methods, because the null and alternative hypotheses for both research questions are based on frequencies of time-based categorical outcomes for the dependent variable. Descriptive statistical analysis was conducted with SPSS, allowing frequencies, minimum-maximum range, with mean, median and mode as measures of central tendency, and standard deviations. Descriptive analysis also provided insight into whether the data are normally distributed, any patterns and outliers present in the data set, visible as large dispersions or potentially through other patterns. Large ranges, interquartile ranges and standard deviations can lead to false precision for the measures of central tendency, especially in cases where smaller samples are used to represent larger populations (Leicester, 2017). The 10 year time period for US drug approvals between 2006-2015 used as a sample provides an adequate sample size to conclude that any associations found between independent variables and the dependent variable are not likely to be due to chance (Glantz, 2012).

Inferential analysis. The hypothesis in research question 1, which was answered descriptively, is whether fewer than 66% of drugs first approved in the United States are approved in all countries which hosted the pivotal clinical trials within 12 months of the FDA's approval. Following the descriptive analysis, and before coding the numeric outcomes of the primary analysis to the four categories of expediency previously referenced, inferential statistical methods were used to further investigate both the magnitude of the time delay for drug approvals in the last host country between 2006 and 2015. Because this study's sample considers only the NMEs first approved in the United

States, the median approval delay, or drug lag, for the United States will be 0 months. To account for this, the EU approval date for each NME during the 2006-2015 period was added to the analysis as a reference population. A Wilcoxon Signed-Rank test was performed to assess whether the approval delays in the last participating host country versus the United States, and versus the EU as a reference population, are statistically significantly different from each other. The Wilcoxon Signed-Rank test is a test used for paired data and is used to assess the significance of the differences between the 2 groups being tested, with the null hypothesis being that the medians of the 2 groups being tested are the same (Glantz, 2012). This inferential analysis of the primary research question sets up further investigation of which and to what extent the 7 covariates evaluated in the secondary research question contribute to any observed delays in drug approval in EU host countries, as well as the host country with the last chronologic approval.

Two proposed adjustments to correct for the median drug lag value of zero for the United States were planned. First, adding the EU as reference population, because it differs in approval date from the US FDA and will thus has a value greater than zero as the calculated drug lag. Including the EU as a reference population also provides additional information regarding the significance of the drug-lag for host countries both inside and outside the premium priced United States and EU markets. Second, a simulated median value of 12 months was proposed to be imputed for the U.S. drug lag, and that value was to be tested for statistical significance against the median drug lag for the last approved country which participated in each pivotal clinical trial for each U.S. approved NME. The choice of 12 months for the imputed U.S. drug lag value in the final

comparison corresponds to the expedient approval outcome category of the primary research question, upon which the hypothesis is based. The results section includes an adjustment to the simulated value from 12 months to 24 months, based on the observed drug-lag values.

Table 7

Data Pairs for Testing in the Wilcoxon signed-rank test

Pairs for comparison	Description
U.S. approval lag; approval in last host country	Median U.S. lag = 0 months; compared to median months elapsed between U.S. approval and approval in last host country
U.S. approval lag; approval in European Union	Median U.S. lag = 0 months; compared to median months elapsed between U.S. approval and approval in European Union
EU approval lag; approval in last host country	Median EU lag from U.S. approval in months; compared to median host country lag from U.S. approval in months
U.S. approval lag + 24 months; approval in last host country	Simulated median value of 24 months applied to U.S. approval lag; compared to median months elapsed between U.S. approval and last Host country approval

Table 7 shows the four paired Wilcoxon signed-rank tests to be performed to assess the significance of the differences in approval times for the United States versus the last host country approvals, the United States versus the EU approvals, the EU versus last host country approvals, and the adjusted U.S. approval lag, versus the last host country approval.

The magnitude or strength of associations between the 7 covariates included in the secondary research question were assessed through inferential statistics. Each covariate could exert either positive or negative influence over the dependent variable,

time or approval expediency category between U.S. and last host country's drug approval, through logical or practical means. Using orphan indication status as an example, granting of an orphan indication, i.e.; fewer than 200,000 cases in the United States, can positively influence the FDA's prioritization of the drug's approval due to high unmet medical need, which can influence other countries' ministries of health in a similar way to expedite approval in all countries which participated in the pivotal trials. Conversely, orphan status of may cause companies to prioritize approvals in the higher premium markets such as the United States, EU and Japan and not pursue approval in countries with a small number of patients with the disease and less favorable drug pricing, despite their having participated in pivotal clinical trials. This association was examined using cross-tabulation of each covariate and the approval expediency category calculated for each drug, e.g.; Expedient, Average, Delayed and Severely Delayed. A chi-square inferential analysis was conducted to assess each covariate's positive or negative level of association with any particular approval expediency category. Level of association is determined by a minimum absolute value of |0.5-1|, as these considered a moderate to strong linear association (Glantz, 2012). Chi-square values meeting an absolute value criterion of 0.5 to 1 indicate that covariate as positive for influencing the dependent variable in a directional nature, either positively, or negatively. The direction of the association between covariates and the approval time category, positive or negative, is reported.

Validity

Validity in research, stated broadly, is the ability of the investigator, through the methods and instruments they employ, to demonstrate that what is being measured is what was intended to be measured, that the methods support an accurate analysis of the observations and measurements made, to an extent that they can be generalized to a broader population (Frankfort-Nachmias & Nachmias, 2008). The investigator must demonstrate that they considered and addressed significant areas where potential errors with the data, issues with their analysis of the data, and other elements have been minimized. Identification of areas where errors may encroach upon the validity of this quantitative study are important because several independent variables are being assessed for influence on the single dependent variable. Two ways in which the validity of this study's assessments can be questioned are: (1) to fail to consider, include and analyze an important extraneous variable which may have a simultaneous and similar influence on the dependent variable, as the independent variables of interest and (2) to fail to identify, recognize and address a confounding variable, which is a variable influencing both the independent and dependent variable, which can lead to false associations between independent and dependent variable as well as false conclusions (Frankfort-Nachmias & Nachmias, 2008; Glantz, 2012). Broadly, there are two types of threats to the validity of a study; threats to internal validity and threats to external validity, each type is defined and addressed in the forthcoming sections.

Threats to Internal Validity

The definition of internal validity hinges on the requirement that the investigator has considered, through the investigational design, mitigations or elimination of the influence of factors on the dependent variable which are not included in the study (Frankfort-Nachmias & Nachmias, 2008). Not doing so can cause false or inaccurate inferences to be made, or to lead to inaccurate interpretations of the magnitude of relationship or influence of independent variables on the dependent variable. Myriad threats to internal validity in studies of secondary data sets exist, including the primary concern that the methods used to collect the data were not prospectively designed to address the specific research questions that the investigator conducting the secondary analyses wishes to address (Cheng & Phillips, 2014). Related to this primary concern is an inability to influence or improve the methods of the original study to contemporary standards or to account for changes in terminology, definitions, or other differences (Cheng & Phillips, 2014). If the methods of collection, definitions and measurements of the primary data are not clearly documented, subsequent analyses by investigators unaffiliated with the original data collection may introduce assumptions which can be confounding (Cheng & Phillips, 2014). Because this investigation relies of data emanating from public health authorities and relies on more absolute data points, such as dates, specific drug names, specific countries, and standardized definitions, such as World Bank income categories, the risks of nuance, changes or other impacts on the data used for the primary and secondary analyses are minimal. The largest threat to internal validity for this investigation lies in cases where primary data, such as drug approval

dates in countries outside the United States or EU, are not present on public websites, and thus reliance on individual inquiries to the sponsoring companies was required. These data may be less reliable than data collected from publicly hosted government supported websites, impacting the validity of the primary analyses conducted in this investigation. Furthermore, because this investigation considered the time period of 2006-2015, covariates such as country income categories and sponsoring company characteristics may have changed over time, which is the primary reason for including calendar approval year as a covariate in this investigation.

Threats to External Validity

External validity refers to the ability to extend, or generalize the results of the investigation to the population level, or levels beyond the limits of the sample studied (Frankfort-Nachmias & Nachmias, 2008). The data sets included, which provide the data for the analyses of the primary and secondary research questions are nearly exclusively aggregated and reported by neutral third parties, such as the U.S. Food and Drug Administration, the EMA, the NIH, the Center for Innovation in Regulatory Sciences, the World Bank and NASDAQ, and are therefore unlikely to contain systematic errors or other types of bias which places limits on their validity or ability to be extrapolated. The targeted secondary data, as they are hosted in each respective organizational database, are deemed to be appropriate to answer the primary and secondary research questions proposed for this study. The level of completeness of the data for samples drawn from each hosted data set were evaluated for completeness, for a high proportion of outliers

and internal logic through data cleaning methods described in the data analysis section for this study.

Caution should be taken in generalizing the results of this study to countries which did not participate in international pivotal trials for new molecular entities approved by the FDA during the 2006-2015 period, as those are the limits of this sample. Furthermore, differences found between regions in simultaneous or expedient approval in all host countries through this analysis, it will be necessary to collect additional information, within the scope of an additional study, to determine whether any corporate or practical rationale influenced these observed outcomes.

Ethical Procedures

The sources for the data in this study, the U.S. FDA, the EMA, the CIRS data reports, Clinicaltrials.gov, ADIS Insight and other ministry of health websites do not contain personally identifiable, private or sensitive medical information, and are available on the public websites previously listed. The data are available for public use and do not require licenses from the agencies which publicly host the data. All individual data contained within the FDA's new drug applications (NDAs) and the EU's product marketing applications (PMAs) in order to be considered an acceptable submission to these regulatory agencies, is completely de-identified, (ICH, 2016). The data for research question 1 includes calendar dates, and the data for research question 2 relate to covariates in the public domain which do not involve individuals and do not require access of private, sensitive, protected or personally identifiable data, nor are any data of these types necessary to complete the outlined analyses. Because the source raw data are

de-identified, any resulting data sets are generated after application of rigorous submission standards by regulatory agencies and provided to the public only after a thorough application of both data protection standards and data quality standards. Thus these data sets have a very low risk of containing sensitive or identifiable information considered to put individuals or groups of individuals at risk of being identified (Tripathy, 2013).

The Walden University Institutional Review Board (IRB) granted approval prior to completion of any analyses on these data. Data entry and quality standards were applied to the data prior to its statistical analysis and application of data cleaning methods for missing data, outliers and potentially spurious raw data were completed through SPSS and manual data cleaning methods. Sharing of the results and study outcomes will be done with Walden University IRB if required and with representatives of the FDA, the EMA, and members from the Centers for Innovation in Regulatory Sciences, all of which contributed raw data to this study. Publication of the results would occur with permission of those agencies contributing raw data if required and, also if necessary, from the Walden University IRB.

Summary

Section 2 includes a statement of the primary and secondary research questions, the dependent and independent variables, the hypotheses tested and the descriptive and inferential statistical methods. The secondary data sources and criteria for selection of cases which ultimately comprised the sample for the research are also described. Methods for data management, cleaning, manual data entry into Microsoft Excel™ tabbed

spreadsheets, from the secondary data sources and addressing missing data were described. To be eligible for inclusion in the sample, the period of analysis was FDA NME approvals over a calendar-decade, beginning on 01 January, 2006 through 31 December 2015. This choice of a 10-year period was prospectively made, versus defining the sampling duration and resulting sample size based on a formal, pre-determined sample size calculation. A description of any threats to internal and external validity are presented, as are potential mitigations and strategies for minimization. A summary of the ethical approval procedures followed both prior to data analysis and prior to publication, if necessary, are described. The results of the descriptive and inferential statistical analyses will be presented in Section 3.

Section 3: Presentation of the Results and Findings

The primary purpose of this study was to evaluate, over a 10-year period, the time to availability, or drug lag of newly FDA-approved drugs in all countries that hosted clinical trials considered by the FDA as pivotal to the NME's approval. Independent variable covariates such as the year of approval, the drug's primary indication, host country income, sponsor company location and market capitalization, the priority assigned by the FDA to the drug's review, and whether the drug was granted orphan designation were explored for an association with the magnitude of any observed drug lag, the dependent variable. Review of the all NMEs approved by FDA between January 1, 2006, and December 31, 2015, demonstrated that the majority relied on clinical data generated in multinational clinical trials. The FDA's annual drug approvals (ADAs) and each individual drug's drug approval package (DAP) were the secondary data sources to which the foundation of this research was benchmarked; both are available in PDF format on the FDA's website under drug approvals.

I calculated drug lag by sampling a subset of all approved NMEs during the 2006-2015 period obtained from the FDA's ADAs for NMEs. The inclusion and exclusion criteria limited the sample to include the following cases: FDA's approval was the first in the world for the product, the approved product was a therapeutic versus a diagnostic agent, and ex-U.S. patients were included in trials deemed by the FDA as pivotal to the product's approval. The designation of a trial as pivotal was determined via a review of the statistical review section in the FDA's DAP documents for the NMEs approved between January 1, 2006 and Dec 31, 2015.

The increment in months between the FDA's approval of a specific product and the approval of that product in all countries that hosted pivotal trials is the individual product's drug-lag, and this was the primary outcome for the main research question. The magnitude of drug-lag was measured in months and categorized into four time-based categories, expedient approval, average approval, delayed approval and severely delayed approval. The drug-lag periods in months assigned to each category were 0-12, 13-24, 25-60, and greater than 60 months, respectively.

Drug-lag can be calculated on several bases, and for the primary analysis I used the most inclusive method, which was the time to known approval of the product in all countries hosting pivotal clinical trials. In this study I calculated drug-lag in months on the bases of (a) individual product drug-lag, that is, time from U.S. approval to approval in last participating country; and (b) regional authority drug-lag, that is, time from FDA approval to EU approval, or time from FDA and EU approvals to last-country approval, for the purposes of comparison. Drug-lag data for the EU and all host countries were collected from government ministry of health websites, public press releases, sponsor company inquiries and other free, internet-based sources from which specific country drug approval dates could be verified. For this study I also considered as secondary research questions the following covariates for association with the dependent variable, drug-lag: year of approval, approved indication, sponsor company characteristics of market cap and world headquarters, the World Bank economic category of host countries, the orphan-drug status granted by FDA, and whether priority or standard review was

granted by the FDA. The research questions and their associated hypotheses are as follows:

RQ1: Of the NME's first approved by the FDA between 2006 and 2015 that included ex-U.S. patients in pivotal trials, what proportion of drugs achieved expedient approval/drug-lag of 0-12 months in all participating countries?

The dependent variable for the primary research question was the percentage of individual products with an expedient individual product drug-lag category (i.e., 12 months or less), and the independent variable of time measured in months.

$H_0$1: Fewer than 66% of drugs were expediently approved (within 12 months of FDA approval) in all host countries.

H_a1: 66% or more of drugs were expediently approved (within 12 months of FDA approval) in all host countries.

I then performed an inferential analysis of RQ1 to assess whether a difference exists in the drug-lag between the U.S.-EU, U.S.-LC, and the EU-LC pairs. A fourth, simulated group called U.S.-24 was added for comparison to the U.S.-LC group to simulate a case, for example where the EU approved a product first and the U.S. approval lagged by 24 months. For all Wilcoxon signed rank comparisons the null and alternative hypotheses were the following:

$H_0$1a: No difference exists in drug-lag between matched-pairs US-EU, US-LC, EU-LC and US-24.

H_a1b: A difference exists in drug-lag between matched-pairs US-EU, US-LC, EU-LC and US-24.

RQ2**:** Are the covariates of year of U.S. approval, drug indication, orphan designation, FDA review type, host country World Bank income category, sponsor company market capitalization and country/region of company headquarters associated with specific approval time/drug-lag categories (expedient, average, delayed, or severely delayed) for individual products?

The dependent variable was the specific approval time/drug-lag category, and the independent variable for each evaluation was one of the named covariates above. The hypotheses for the year of U.S. approval (independent variable) and the approval time/drug lag category (dependent variable) were:

$H_0$2a: Year of U.S. approval is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2a: Year of U.S. approval is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

The null and alternative hypotheses for the covariate drug indication (independent variable) and approval time/drug lag category (dependent variable) were:

$H_0$2b: Drug indication is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2b: Drug indication is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

The null and alternative hypotheses for the covariate orphan designation (independent variable) and approval time/drug lag category (dependent variable) were:

$H_0$2c: Orphan designation is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2c: Orphan designation is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

The null and alternative hypotheses for the covariate FDA review type (independent variable) and approval time/drug lag category (dependent variable) were:

$H_0$2d: FDA review type is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2d: FDA review type is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

The null and alternative hypotheses for the covariate host country World Bank income classification (independent variable) and the approval time/drug lag category (dependent variable) were:

$H_0$2e: Host country World Bank income classification is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2e: Host country World Bank income classification is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

The null and alternative hypotheses for the covariate sponsor company market capitalization (independent variable) and the approval time/drug lag category (dependent variable) were:

$H_0$2f: Sponsor company market capitalization is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2f: Sponsor company market capitalization is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

The null and alternative hypotheses for the covariate sponsor company headquarters location (independent variable) and the approval time/drug lag category (dependent variable) were:

$H_0$2g: Sponsor company headquarters location is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

H_a2g: Sponsor company headquarters location is associated with specific approval time/drug lag categories in all host countries (expedient, average, delayed, severely delayed).

Description of the sample population, including case inclusion and exclusion criteria, the process and procedures for data collection, the time span of concentrated data access, entry and cleaning, and the imputation method or assumptions for any missing data is included in Section 3. A summary of the descriptive and inferential statistical methods is included. I report descriptive statistics, the counts, the frequencies, ranges (min-max), standard deviation, measures of central tendency (mean, median), and percentages. I also report results from inferential statistical analyses.

Data Collection

U.S. Food and Drug Administration, European Medicines Agency, Clinical Trials and National Ministry of Health Drug Approval Data

The FDA, EMA and many of the countries participating in international pivotal trials post either a PDF, MS Excel spreadsheet or interactive database allowing queries about local drug approval and date of the drug's first approval on their public websites. No sources accessed included any personally identifiable, confidential or otherwise protected information. The FDA's ADA reports are specific to year and include; drug generic and brand name, date of approval, indication, sponsor name, whether orphan designation was granted, and whether a priority or standard review was performed. The ADAs are available in PDF format and required manual entry of the above variables into a Microsoft Excel spreadsheet. Statistical and clinical sections from the FDA's individual DAPs, also in PDF format, were reviewed to ascertain details about each specific product approved between 2006 and 2015. Statistical sections of DAPs included the statistical reviewers' determination of the specific clinical trials the FDA considered to be pivotal to

the product's approval. In some cases, the DAP included which specific countries pivotal trials were performed in, but in approximately 80% of cases, the publicly available databases Clinicaltrials.gov and the EudraCT on-line repository of clinical trials at Eudract.europa.eu were searched for specific pivotal clinical trial site information. In approximately 10% of cases, trial site data were not visible in these US or EU clinical trial repositories, which required a medical literature search, completed through google scholar. Ultimately, host country information was obtained for all pivotal trials completed in the ten-year period.

Approval dates, generic and brand names and indications for all drugs in EU countries were available from a comprehensive Microsoft excel spreadsheet downloaded from the EMA website at https://www.ema.europa.eu/en/medicines. Searching for drug approvals, indications and approval dates on ex-US country websites and databases was done first on brand-name, and secondly on generic-name if the brand-name was not recognized. The brand name of medications outside of the United States frequently differs, but the generic name does not. Google-translate was used for all foreign language websites except for Spanish, as the researcher is proficient in Spanish and English languages. On-line Cyrillic and Turkish character translators were used for queries into the ministry of health websites of Russia and Turkey.

Because the objective of this research is to describe global availability of drugs approved by the FDA and to quantify and categorize any time-lag, relative to U.S. and EU approvals, the gold-standard sources of approval and approval date data were national

ministry of health websites or answers to direct queries from the researcher to the product manufacturer.

Because there were gaps in availability of approvals and precise approval dates in the countries referenced above, two additional approaches not specifically outlined in Section 2 were taken to ascertain reliable drug approval and approval date data when sponsor companies did not respond to queries, or their responses were not adequately specific. The first approach was to complete internet searches of retail pharmacies for the branded or generic name of the drug in countries without approval information posted on ministry of health websites. The second approach was to request a free and time limited subscription to the Springer Publications product ADIS-Insight product, which aggregates data from approximately 200 different public websites to create profiles on approved drug products. The latter approach permitted confirmation of approval, or not, in each host country. Similar to Ministry of Health and all other internet-based sources of data, the ADIS Insight product contained no confidential or protected health information. Other sources of information for collection of covariate information were the World Bank 2014 spreadsheet for country incomes, which categorizes countries into 4 income categories, corporate and/or product websites to ascertain the sponsor company's corporate headquarters location, and the databases of the New York Stock Exchange and NASDAQ for historical market capitalization information. The two sources mentioned above withstanding, all information from these data sources provided adequate and complete information and is consistent with the prior data analysis plan proposed in Section 2.

Sampling and Time Frame

Permission to analyze the study data was granted by the Walden University IRB on January 8, 2018, number 0534307. Following IRB approval, I downloaded the FDA from 2006 to 2015, inclusive, and began manual entry into a master Microsoft excel spreadsheet for all product approvals during the specified 2006-2015 time period on January 21, 2019. Both generic and branded drug names were entered, as well as approval date, indication, orphan status, review type and sponsor name from the FDA reports. Following completion of manual entry of the above data, I downloaded the EMA's master approvals spreadsheet from 31 December, 2018. I searched the EMA's master spreadsheet by brand and generic names as well as indication and entered the approval dates into the master spreadsheet. For those U.S. approved drugs not appearing on the EMA's approval list, I did an on-line search to determine whether any of the missing drugs utilized a de-centralized review process in Europe versus the centralized process represented in the EMA approval spreadsheet, approximately 15 examples of de-centralized approval were found and those approval dates were entered into the master spreadsheet as well.

I then reviewed the FDA's DAP for each individual drug to determine whether the product was truly an NME or a re-formulation or new combination of previously approved products. I also noted whether the product was a therapeutic vs as imaging or diagnostic agent. Finally, the statistical and clinical sections of each DAP were reviewed to determine which trials were considered pivotal to approval. Protocol numbers and the numbers of study participants were entered to assist in the next phase of the research,

which was to consult the on-line databases clinicaltrials.gov and the EudraCT on-line trial repository for host country information. All country information per-trial was entered into the master Microsoft excel spreadsheet. I then entered data on covariates not present in the FDA's or EMA's data sets. Each country's World Bank income status was manually entered from the World Bank's 2014 global income spreadsheet, and the market capitalization information on the date of the U.S. FDA's approval was entered for each company from NASDAQ or NYSE archival databases. Data entry was completed on 13 April 2019, and consisted of approximately 9,000 manually entered fields.

Data Preparation

The data collected consisted largely of categorical data, with the exception of dates of approval for each product in the United States, EU and the Last Country (LC) approval date in which pivotal trials were conducted. Individual product approval dates in the US, EU and LC are compared, and a difference between them calculated in months, yielding the individual product drug-lag. Calendar approval dates from FDA (US), EMA (EU) and individual country sources were entered into the master spreadsheet in a dd/mm/yyyy format. Date differences in months were calculated in Microsoft Excel and labeled as variables US-LC_lag(Mo); US-EU_lag(Mo) and EU-LC_lag(Mo), respectively. In product cases where more than one host country had not approved a product yet, i.e.; more than one country with the approval date of 4/1/2019, the host country with the lowest World Bank income category was recorded in the WB income category data field of the master spreadsheet to capture any potential associations between drug lag and lower income countries.

Values for drug-lag in months can be transformed into the four time-based categories specified in section 2, but also can be grouped to create binary values corresponding to US-LC, US-EU and EU-LC drug-lag ranges of 0-24 months and 24 months or greater, thus permitting the possibility of further post hoc inferential analyses such as logistic regression.

Two of the covariates in research question 2, Orphan Status and FDA Review Type also have binary values, i.e.; orphan vs. non-orphan, and priority vs. standard reviews, respectively. The additional 5 covariates assessed for association with drug-lag in research question 2, all have greater than 2 possible values. US Approval Year has ten possible values corresponding to each of the ten years from 2006 through 2015. Broad Drug Indication has 16 values; Sponsor Market Cap has 5 values; Host Country World Bank Income has 4 possible values, and Company HQ has 4 values. Further detail on potential groupings of covariates for research question 2 are included in the Data Grouping section.

In the course of colleting the variables chosen for analysis and hypothesis testing, I collected several additional relevant variables which are not part of hypothesis testing. These variables are: overall number of countries participating in pivotal trials for the sample, number of countries per-product in which pivotal trials were conducted and the number of countries in which the product was not approved in greater than 1 country. Those variables are reported descriptively in Table 9.

Missing Data

Efforts were made to minimize missing data. The most significant challenge encountered was the determination of drug approval dates for countries not posting national formularies with drug approvals and approval dates on-line. Of the 82 countries included in this sample which participated in pivotal clinical trials, the majority provide public access to national formularies of approved drugs. Notable exceptions which do not post formularies and approval dates on-line were; South Africa, Ukraine, China, Thailand, Belarus, Mexico and the Philippines. The number of products each hosted pivotal trials for are, in order or presentation above; 46, 33, 24, 25, 8, 51 and 17, totaling 204 or 8.1% missing cases of approval data for the pivotal trials leading to product approvals between 2006 and 2015. The majority of pivotal trials each of the above country participated in were large multi-national trials in which several of the above countries were participants simultaneously. No cases existed where individual product approval data and dates were unavailable for less than 70% of participating countries in any specific product's pivotal trials. However, given the proportion of missing data and the fact that the missing data are not missing at random, i.e.; they were missing consistently from specific participating countries, and the dependence of the calculation of individual product drug-lag on the date of approval in the last host-country, further efforts were made to determine approval status and date for all host countries (Little, Jorgensen, Lang, & Moore, 2014). During the search efforts to fill in this specific gap, I frequently encountered partial reports on the products of interest produced by the

subscription-based product, ADIS-insight from Springer publications. The full reports available only via subscription.

I contacted Springer publications on 04 April 2019 and described my objectives. Springer personnel requested that I attend an on-line demonstration of their product to determine whether it would be suitable for the research objectives, and the session occurred on April 8, 2019. The demonstration clarified that the product would be useful for providing missing approval and approval date information for products in the above referenced countries. I was granted a free account for 2 weeks, which was the final data collection effort made in this study. A profile within ADIS-insight was available for each product I identified as having missing country approval and approval date data. Within each product profile, a listing of all clinical trials, whether considered by FDA to be pivotal or not, the participating countries of each, whether the product is approved, and the date of approval for every country in which the product is licensed. Access to ADIS-insight allowed all 204 cases of missing data for each country to be found. These data were entered between April 9 and 13, 2019. The ADIS-insight database was not originally specified as a secondary source in Section 2, as it was my belief that approval and approval date information would be provided by national ministry of health websites or other secondary and publicly-available sources.

Variables and Data Groupings

Table 8 below includes variable descriptions, types and field title for each variable in the master data analysis spreadsheet. Research question 1 assesses the proportion of products approved within 12 months or less of the FDA's approval, when

the FDA's approval is the first approval in the world. Stated differently, research question 1 evaluates the proportion of products with a drug-lag of 12 months or less, relative to US approval for products where the US approval was first in the world. 2 different approval dates are used as benchmarks for calculation of the drug-lag. The first is the is the Last Country (LC) approval date, which represents the most contemporary approval date for the product in the country or countries where pivotal trials were conducted. The second approval date upon which drug-lag is benchmarked is the EU approval date, which represents centralized and decentralized approvals for each product in the 28 countries of the European Union.

For all analyses, drug-lag in months is calculated by taking the difference of the U.S. approval date and the most contemporary approval for that product in the LC; abbreviated US-LC lag. Similarly, the US-EU drug-lag in months was calculated and used as a reference population. An approval date of 4/1/2019 was entered for any country in which the product was not yet approved at the time of this analysis. 12 cases exist where all ex-US countries hosting pivotal trials were in the EU. In those cases, the LC approval date is the same date as the EU approval date, making the US-LC drug-lag the same as the US-EU drug-lag. Finally, for the EU-LC comparison, the drug lag would be 0 months for those 12 products, since the LC and EU approval dates are the same.

In section 2, I further specify the drug-lag into 3 additional time-based categories beyond the 0-12 month (Expedient) category used in research question 1. The additional 3 drug-lag categories are; 13-24 months (Average), 25-60 months (Delayed) and greater than 60 months (Severely Delayed). To enable additional post hoc inferential statistical

analyses, drug-lag may be converted to a binary variable where 0 = a US-LC drug-lag value of 24 months or less, and 1 = a US-LC drug lag value of 25 months or greater.

Research question 2 evaluates 7 covariates for association with the observed drug-lag category US-LC lag. 2 of the covariates analyzed in research question 2; Orphan Status and FDA Review Type are nominal and binary, and the additional 5 covariates included in research question 2 have 3 or greater categories within each. 2 of the remaining 5 covariates are ordinal variables which can be ranked from low to high, i.e.; Host Country World Bank Income Category, and Sponsor Market Capitalization. and may be combined to allow valid statistical comparisons of categorical data based on low observed frequencies in some categories with greater specificity. For example, the covariate Broad Indication has 16 different categories within it. Grouping categories within Broad Indication to a smaller number i.e.; Oncology, Anti-Infective and "Other" may concentrate some less frequently approved product indications and permit inclusion of Broad Indication in further post hoc inferential analyses. Therefore, while combining categories sacrifices some descriptive specificity, it may permit further post hoc inferential analyses to be performed.

Table 8

Independent and Dependent Variables with Field Names

Variable Description	Field Title	Variable
Approval year (2006-2015)	Approval_Yr	Independent
Drug indication	Broad_Indication	Independent
Orphan indication	Orphan_Status	Independent
FDA review type	Review_Type	Independent
Last host country World Bank income category	LC_WB_Cat	Independent
Sponsor headquarters country	Sponsor_HQ	Independent
Sponsor market capitalization at U.S. approval	Sponsor_Mkt_Cap	Independent
Drug-lag: U.S. approval-EU approval (Mo)	US-EU_lag(Mo)	Index
Drug-lag: EU approval-LC (Mo) for Wilcoxon Test	EU-LC_lag(Mo)	Index
Drug-lag: Adjusted US-LC for Wilcoxon test	US-LC_24	Simulation
Drugs approved in all countries within 12 mo.	US-LC_lag_Cat	RQ 1 Dependent
Drug-lag: U.S. approval-last host country (months)	US-LC_lag(Mo)	RQ 2 Dependent

Analysis of Results for the Study Sample

Sample Selection

I used IBM SPSS Version 25 statistical analysis package to conduct descriptive statistical analyses of all demographic characteristics for all independent and dependent variables. Counts, frequencies and percentages for each variable were calculated using SPSS. Measures of central tendency and variability were calculated for each independent and dependent variable as appropriate and those descriptive results are presented in Tables 11 and 12.

The sample selection details included in Figure 4 and Table 8 were hand-tabulated. The counts of censored cases by reason from the total sample are included in Figure 4 and Table 8 and I have included the narrative justification for censoring each type of case in this section. Because the primary purpose of this study is to investigate the global availability of products in countries which participated in pivotal clinical trials, and to measure the time to that availability, the primary filter on the total NME approvals between 2006 and 2015 is removing cases where the U.S. FDA's approval was not the first in the world. Concentrating on products with the distinction of FDA's first in world approval allows an objective benchmark with which to measure drug-lag, due to the transparency and detail of records that the FDA makes publicly available.

The total count of NMEs approved by the FDA between Jan 1, 2006 and December 31, was 293. 64 cases (22%) of the total approvals were removed due to FDA's approval not being first in world, which represents the largest category of censored cases. The second most frequent reason for censoring cases was that pivotal

trials did not include ex-US patients. 37 products (13%) did not include ex-US patients in their pivotal trials. Even if such cases were first in world approvals, the exclusivity of US patients in pivotal trials changes the ethical landscape, as the risks and burdens of clinical research were borne by the U.S. population exclusively, versus shared between the US and other countries. Another ethical consideration in cases where pivotal trials were conducted in US patients exclusively is that, so long as the effective drug is available to those populations who were research subjects, the principle of justice is upheld.

The third most frequent reason for censoring cases was if the marketing application was withdrawn in the EU and/or all ex-US markets, which occurred 23 times (7%) of cases. Censoring these cases is justified, as including them would raise the possibility that the drug-lag value would be falsely inflated due to the sponsor's abandonment of plans to market in all countries where the product performed pivotal trials. It is assumed that by rejection or withdrawal of ex-US marketing applications, sponsors will never seek approval in these ex-US countries, thereby theoretically inflating the drug-lag value. Fourth, NME products which were not therapeutic, n=10 (3%) were censored from the sample, as there is an assumed diminished drive to market in non-premium paying countries and the ethical force driving access to a non-therapeutic agent vs a new therapeutic agent is assumed to be weaker. Finally, 2 cases were found (1%) where the products which appeared in the FDA's annual NME approval report which were new formulations of already approved drugs or a new combination which did not contain any new agent. The final total sample for this study of the NMEs approved between 2006 and 2015, considering all adjustments is 157, or 54% of the 293 (291)

NME products approved by the FDA in that ten-year period. My 54% ratio of selected cases to total NMEs approved within the 2006-2015 period is similar to the ratio of US first in world approvals reported by Larochelle, et al in their review of FDA NME approvals between 2000-2010 for a different objective. Their sample had 61% (172 of 282) of the total FDA NME approvals between 2001 and 2010 were U.S. first in world approvals, a difference of less than 10% from my 2006-2015 sample` (Larochelle, Downing, Ross, & David, 2017).

Table 9

Final Sample Selection Details

Variable	Frequency	Percent
Total FDA Approvals of New Molecular Entities (2006-2015)	N=293	N=100
Adjustments		
Not first approval for that NME	2	1
Not a therapeutic agent	10	3
Pivotal trials did not include Ex-U.S. patients	37	13
FDA approval was not first in world for product	64	22
Marketing application withdrawn or rejected	23	7
Total	157	54

Note. n=157.

Additional demographic data not included in hypothesis testing, but relevant for understanding the overall context of the sample are included below in Table 10. Importantly, 71 of the 157, or 45% of the products in the sample remain unapproved as of

April 1, 2019 in more than one country which hosted pivotal trials between 2006 and 2015. 82 unique countries in the sample hosted at least one pivotal trial, and the development of the 157 products included in the sample were sponsored by, coincidentally, 82 unique companies. 26 of the 82 sponsor companies were acquired by or merged with another company at the time of U.S. marketing application filing or prior to FDA product approval. Because the sponsor company market capitalization covariate was measured on the date of the U.S. product approval, mergers and acquisitions may affect the interpretation of the market capitalization covariate, as post-merger/acquisition market capitalizations reflect those of the acquiring company, i.e.; a larger market capitalization than the acquired company. The descriptive statistics of host countries per-product demonstrate globalization in drug development between 2006-2015 with minimum-maximum values of 1-39 ex-US countries hosting pivotal trials, with a mean number of 16 host-countries per product.

Table 10

Relevant Additional Data

Variable	N	Min	Max	Mean	Std. deviation
Unique sponsor companies in sample	82				
Sponsor company merger/acquisition	26				
Unique host countries in sample	82				
Product remains unapproved in 1 > country	71				
Host countries per product in sample	157	1	39	16	9.71

Descriptive Statistics of Variables Used in Hypothesis Testing

Drug-lag is the dependent variable of interest for research questions 1 and 2, and therefore descriptive statistics will first be reported for the 3 regional assessments of drug-lag; US-EU lag, US-Last Country (LC) lag, and EU-Last Country (LC) lag. Descriptive Statistics and measures of central tendency are reported in Table 11. The number of valid cases for each regional drug-lag calculation is 157. The largest mean and median values for drug-lag occur in the U.S.-Last Country assessment at 66 and 63 months, respectively. The EU-Last country assessment has mean and median values of 53.1 and 50 months, respectively, followed by the shorter mean and median drug-lag observed in the U.S.-EU assessment of 12.6 and 7 months, respectively. U.S.-EU and EU-LC assessments both include minimum values of zero, as in the former case, products in the sample were approved by the FDA and the EMA within 30 days of each other. In the case of the EU-LC assessment, the minimum zero value corresponds to products/cases where host countries outside the European Union did not participate in pivotal trials, therefore making the drug-lag zero months for those cases.

Table 11

Descriptive Statistics and Measures of Central Tendency Drug Lag in Months

Variable (valid)	N	Percent (*N* = 100)	Minimum	Maximum	Mean	Median	Std. deviation
US-EU Lag (Mo)	157	100	0	136	12.6	7	17.98
US-LC Lag (Mo)	157	100	1	158	66.0	63	42.02
EU-LC Lag (Mo)	157	100	0	144	53.1	50	40.99

Note. (*n* = 157).

Descriptive statistics of the additional 7 independent variables included in research question 2 are included in Table 11. I report valid cases, frequencies and percent for categorical variables in Table 12. For the variable Year of FDA Approval, years 6-10 (2011-2015) have nearly two-thirds, or 63.7% of the FDA approvals for this sample in the decade studied. The single year with the largest number of approvals in this sample was 2015, with 24 approvals. The variable Broad Indication, the largest indication approved during the decade in this sample was Oncology with 54 products approved, or 33.1% of the total products approved. Anti-Infective products, with 29 approvals, constitutes 18.5% of the approvals in the period and was the only other indication with greater than 10% of the approvals in this sample in the period. The Last Host Country World Bank Income Category had High Income Countries as the most frequent, at 65 or 41.4%. Upper Middle Income and Lower Middle-Income Countries were similar with 29.9% and 28.7% of approvals, respectively. While two World Bank Low Income Countries participated in the pivotal trials included in the sample, neither Tanzania nor Uganda were a Last-Country, and therefore the Low-Income category appears as zero in this analysis.

The Product Sponsor Market Capitalization variable has 5 categories, and is dominated by large cap companies, with 107, or 68.2% of the approvals in the sample being achieved by large cap companies. Large-cap companies were defined previously as having a market capitalization of over $10 billion dollars. Also as previously mentioned, due to corporate acquisitions during the sample period, of the 157 product approvals in the sample, 82 individual companies were represented. Proportionally, Mid-Cap, Small-

Cap, Micro-Cap and Private companies have similar numbers of approvals in the sample. Similarly, the majority of pivotal trial sponsors were companies with headquarters in the United States, 61.8% and the EU 33.1%. Japanese and one Canadian company received product approvals in the sample period, respectively. For FDA Review Type, Priority Reviews (FDA action within 6 months) were more frequently granted at 53.7% than Standard Reviews (FDA action within 10 months), which were granted 42.7% of the time. Finally, Orphan designation, i.e. the product's target indication is relatively rare, afflicting 200,000 or fewer patients in the United States, was granted in 37.6% of the product approvals in this sample, versus non-Orphan designation, which is standard for non-rare diseases and occurred in 62.4% of the products approved in this sample.

Table 12

Descriptive Statistics for Categorical Variables

Variable (Valid)	Frequency (N = 157)	Percent (N = 100)
Year of FDA Approval		
2006	14	8.9
2007	11	7
2008	9	5.7
2009	12	7.6
2010	11	7
2011	15	9.6
2012	22	14
2013	16	10.2
2014	23	14.6
2015	24	15.3
Total	157	100
Broad Drug Indication		
Anti-Infective	29	18.5
Allergy/Immunology	6	3.8
Anesthesia/Analgesia	1	0.6
Cardiovascular	9	5.7
Dermatology	1	0.6
Endocrinology	13	8.3
Genito-Urinary	2	1.3
Hematology	5	3.2
Musculoskeletal	1	0.6
Neurology	8	5.1
Oncology	52	33.1
Ophthalmology	4	2.5
Psychiatry	7	4.5
Pulmonary	2	1.3
Rare Diseases	10	6.4
Total	157	100
Last Host Country Income Category		
World Bank High Income (HI)	65	41.4
World Bank Upper Middle Income (UMI)	47	29.9
World Bank Lower Middle Income (LMI)	45	28.7
World Bank Low Income (LI)	0	0
Total	157	100
Product Sponsor Company Market Capitalization		
Large Cap	107	68.2
Medium (Mid) Cap	11	7
Small Cap	14	8.9
Micro Cap	14	8.9
Private Company	11	7
Total	157	100
Trial Sponsor World HQ Location		
United States	97	61.8
EU	52	33.1
Canada	1	0.6
Japan	7	4.5
Total	157	100
FDA Review Type		
Priority Review	90	57.3
Standard Review	67	42.7
Total	157	100
Orphan Designation		
Orphan	59	37.6
Non-Orphan	98	62.4
Total	157	100

Note. (N = 157).

Evaluation of Statistical Assumptions

The hypothesis testing for Research question 1 relies upon arithmetic proportions and therefore requires no additional preparation or testing for normality or linearity as would be necessary when choosing parametric or non-parametric inferential analyses. The second level of testing for research question 1 is a statistical analysis of the paired observations in the sample using the Wilcoxon Signed Rank Test of Paired Samples to determine whether observed differences between the U.S.-EU, the U.S.-LC and the EU-LC values for drug-lag have more than a zero difference from each other. In section 2, a fourth, simulated sample was proposed, which included a mean and median value of 12 months for drug-lag. This sample was intended to simulate a mean US drug-lag value of 12 months, for comparison to the U.S.-EU, U.S.-LC, EU-LC drug lag values. In Table 10, however, the descriptive results of the US-EU drug-lag show a mean drug lag of 12.6 months, and therefore, the prospectively defined simulation sample of 12 months was abandoned, and the simulated sample was changed to a simulated sample with a mean drug-lag value of 24 months. The simulated sample US-24 was compared to U.S.-EU, U.S.-LC and EU-LC samples with the Wilcoxon test and the results are included in Table 15.

Determination of normality, i.e.; whether the data from my sample are normally distributed, determines which inferential tests are appropriate for analysis. Assumption of normality can be achieved by generation of a histogram to see, roughly, whether the shape of the histogram approximates a normal bell-curve, and if so, the data are likely to be normally distributed (Glantz, 2012). Visualizing the histograms of the U.S.-EU, U.S.-

LC, EU-LC, and US-24 data, none appear to be normally distributed. More specific than a visual approximation, are the tests of normal distribution present within SPSS version 25. I chose the Kolmogorov-Smirnov (K-S) and the Shapiro-Wilk's tests to assess the normality of each of the independent and dependent variables in my sample. If the results conflicted between the 2 tests for normality, the Shapiro-Wilk's result was used. The results of the normality tests are presented in Table 13. If the results of the tests for normality are statistically significant at the level of $p < .05$, then this causes a rejection of the null hypothesis which states that the data are normally distributed (Glantz, 2012). Therefore, because all Shapiro-Wilk's test results are statistically significant, the assumption is that all 4 groups tested are not normally distributed.

Table 13

Tests for Normality of Data

Variable	K-S Result	Shapiro-Wilk's result
US-EU Lag (Mo)	.000*	.000*
US-LC Lag (Mo)	.076	.000*
EU-LC Lag (Mo)	.001*	.000*
US-24 Lag (Mo)	.000*	.000*

Note. * $p < .05$

Research question 2 is an assessment of a series of associations between ordinal, time-based categories of drug-lag and other nominal variables obtained from the FDA, the EU, the World Bank, NASDAQ and NYSE and other sources potentially associated with the time to approval of products in countries which performed pivotal trials. No specific preparation of the nominal variables analyzed via chi-square analyses is necessary to determine whether these variables are associated with time-based categories

of drug-lag. For nominal variables with significant numbers of categories within them, such as Broad Indication, grouping of less frequent indications together will allow, on a post hoc basis consolidation of cases into a smaller number of cells in the contingency table. Such groupings, while decreasing specificity of results, may yield identification of significant positive or negative associations of independent variables with the dependent variable. Similarly, a post hoc consolidation of the four categories of the dependent variable into two categories; Average (0-24 month lag) and Delayed (25 months or greater) may yield associations with covariates that the n=157 sample size did not permit with the more specific original drug lag categories of the dependent variable.

Inferential Analysis

Research Question 1: Proportions Analysis and Wilcoxon Signed Rank Tests

RQ1a: Of the NME's first approved by the US FDA between 2006 and 2015 which included ex-US patients in pivotal trials, what proportion of drugs achieved expedient approval/drug-lag of 0-12 months in all participating countries?

$H_0$1a: Fewer than 66% of all NMEs approved by the FDA will be approved in all host countries within 12 months.

H_a1a: 66% or greater of all NMEs approved by the FDA will be approved in all host countries within 12 months.

Of the 157 FDA approvals granted in the sample period, i.e.; between January 1, 2006 and December 31, 2015, a total of 15, or 9.6% of products were approved in the last participating country within 12 months of the US FDA's approval. This proportion is less than the 66% stipulated in the null hypothesis, and therefore, for research question 1, the

null hypothesis is accepted. Table 14 presents more detail on the drug-lag for the 157 product approvals in the U.S.-Last Country sample, which is the primary population for Research Question 1. Table 14 also presents the proportional drug-lag data from the US-EU sample and the EU-Last Country sample for comparison. Testing the same hypothesis with the US-EU and the EU-LC samples leads to different results than observed with the U.S.-LC sample. At 12 months post FDA approval, 72% of the drugs approved in the US are also approved in the EU. This observation would cause a rejection of null hypothesis for the US-EU sample, as the 12-month threshold is 66%. Conversely, for the EU-LC sample, while a greater proportion, 22.9% of products were approved within 12 months, the null hypothesis would not be rejected for this sample, as the threshold for rejection is 66%. The null hypothesis of the Wilcoxon Signed Rank Test analyzes paired related samples, and assumes that the samples have a difference of zero. Therefore, a comparison of each drug-lag sample paired against another, i.e.; U.S.-EU_lag versus U.S.-LC_lag will assess if there is a difference in drug-lag between the paired samples.

Table 14

Drug-Lag for the US-Last Country; US-EU and EU-Last Country Samples in Months

Sample/Drug-lag category	Number of approvals	Percent
U.S.-last country sample		
0-12 Months (expedient)	15	9.6
13-24 Months (average)	18	11.5
25-60 Months (delayed)	45	28.7
Greater than 60 months (severely delayed)	79	50.3
Total	157	100
U.S.-EU sample		
0-12 Months (expedient)	113	72
13-24 Months (average)	26	16.8
25-60 Months (delayed)	13	8.3
Greater than 60 Months (severely delayed)	5	3.2
Total	157	100
EU-last country sample		
0-12 Months (expedient)	36	22.9
13-24 Months (average)	11	7
25-60 Months (delayed)	46	29.3
Greater than 60 months (severely delayed)	64	40.8
Total	157	100

Note. ($N = 157$).

Wilcoxon Signed Rank Test of Paired Samples.

The three drug-lag samples; US-EU-Lag, US-LC-Lag, EU-LC-Lag and a simulated sample, US-24_Sim were tested and assessed for differences from each other by the Wilcoxon Signed Rank Test. The results are reported in Table 15 below. All samples have *p*-values less than 0.01 and thus, the null hypothesis of the drug-lag in months being the same for each paired sample is rejected, both for the 3 pairs tested with the observed real data, and the 3 pairs tested in the US-24 simulation.

Table 15

Wilcoxon Signed Rank Test of Observed and Simulated Paired Samples

Paired Samples *N* = 157	*Z* Statistic	*P* Value
US-EU and US-LC	-10.353	< .001*
US-EU and EU-LC	-8.526	< .001*
US-LC and EU-LC	-10.769	< .001*
US-EU and US-24 simulation	-8.529	< .001*
US-LC and US-24 simulation	-9.371	< .001*
EU-LC and US-24 simulation	-7.399	< .001*

Note. *$p < .05$

Research Question 2: Chi-Square Analyses

Seven covariates, approval year, broad drug indication, last host country World Bank income category, product sponsor market capitalization, sponsor headquarters location, FDA review type, and orphan designation were assessed for association with the dependent variable, drug-lag between the U.S. approval and drug approval in the last country. If a drug remained unapproved in a pivotal trial country as of 01 April 2019, that date was entered as the cutoff. 71 products were identified where the drug remained unapproved in more than one pivotal trial country at the 01 April 2019 cutoff date. In

those cases, the World Bank Income Category for the lowest unapproved country was recorded. Prospectively, magnitude of drug-lag from FDA approval was defined into four categories: expedient (0-12 months of lag), average (13-24 months of lag), delayed (25-60 months of lag), and severely delayed (greater than 60 months of lag). Chi-square inferential analysis was performed to identify association and its effect size, if any, of the identified relationship.

For covariate 1 in RQ2, FDA approval year, the null hypothesis was the following:

$H_0$2a: Year of FDA approval is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Detailed chi-square results for each independent variable comparison are presented in Table 15. Results of the prospective chi-square analysis of association of FDA approval year to US-LC drug-lag was statistically significant, $p < .001$ with a moderate to large Cramer's V effect size of .461 (Pallant, 2005). This indicates a rejection of the null hypothesis of no association between FDA approval year and US-LC drug lag, and acceptance of the alternative hypothesis that there is an association between FDA approval year and US-LC drug-lag. This result was tested further in a post hoc analysis.

For covariate 2 in RQ2, broad drug indication, the null hypothesis was the following:

$H_0$2b: Broad drug indication is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Results of the prospective chi-square analysis for association between broad drug indication and US-LC drug-lag were not significant, $p = .510$, leading to the acceptance of the null hypothesis that broad drug indication is not associated with US-LC drug lag.

For covariate 3 in RQ2, orphan status, the null hypothesis was the following:

$H_0$2c: Orphan status is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Results of the prospective chi-square analysis for association between orphan status and US-LC drug-lag were not significant, $p = .144$, leading to the acceptance of the null hypothesis that orphan status is not associated with US-LC drug lag.

For covariate 4 in RQ2, FDA review type, the null hypothesis was the following:

$H_0$2d: FDA review type is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Results of the prospective chi-square analysis for association between FDA review type and US-LC drug-lag were not significant, $p = .119$, leading to the acceptance of the null hypothesis that FDA review type is not associated with US-LC drug lag.

For covariate 5 in RQ2, last host country World Bank income category, the null hypothesis was the following:

$H_0$2e: Last host country World Bank income category is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Results of the prospective chi-square analysis for association between last host country World Bank income category and US-LC drug lag were significant at the $p < .001$ level

and a moderate to large Cramer's V effect size of .427, which is moderate to large (Pallant, 2005). This level of association between last host country World Bank income category and US-LC drug lag, causes a rejection of the null hypothesis stating no association between the 2 variables, and an acceptance of the alternative hypothesis stating that an association exists.

For covariate 6 in RQ2, sponsor company market capitalization, the null hypothesis was the following:

> $H_0$2f: Sponsor company market capitalization is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Results of the prospective chi-square analysis for association between sponsor company market capitalization and US-LC drug-lag were not significant, $p = .690$, leading to the acceptance of the null hypothesis that sponsor company market capitalization is not associated with US-LC drug lag.

For covariate 7 in RQ2, sponsor company headquarters location, the null hypothesis is the following:

> $H_0$2g: Sponsor company headquarters location is not associated with specific approval time/drug lag categories in all countries (expedient, average, delayed, severely delayed).

Results of the prospective chi-square analysis for association between sponsor company headquarters location and US-LC drug-lag were not significant, $p = .872$, leading to the

acceptance of the null hypothesis that sponsor company headquarters location is not associated with US-LC drug lag.

Table 16

Chi-Square Results of Independent Variables for Research Question 2

Independent variable	*N*	Chi Square	*df*	*p* value	Cramer's V (effect size)
FDA approval year	157	100.07	27	< .001*	.461 (Mod-Lg)
Broad drug indication	157	43.02	45	.510	NA
Orphan status	157	5.41	3	.144	NA
FDA review type	157	5.84	3	.119	NA
Last host country World Bank income	157	57.23	6	< .001*	.427 (Mod-Lg)
Sponsor company market cap	157	8.34	12	.690	NA
Sponsor company HQ location	157	3.55	9	.872	NA

Note. $*p < .05$

Post Hoc Analyses

I conducted several post hoc chi square tests to confirm the findings of association between the 2 independent variables found to have associations, and the dependent variable of drug-lag time category. The Year of FDA Approval was tested again, in two ways, to account for the fact that the approval cutoff date of 01 April 2019 can truncate the outer boundary of the drug lag for the years 2014 and 2015. Specifically, the April 1, 2019 cutoff date, the maximum values of drug-lag for 2014 and 2015 are 40 months and 56 months, respectively, which causes a truncation that may affect categorization into US-LC drug lag categories 3 (26-50 Months) or 4 (50 months or greater). Furthermore, if the 10-year FDA Approval Years are divided into 2, 5-year periods, i.e.; 2006-2010 and 2011-2015, the number of samples in each period is nearly twice the number in the latter, 2011-2015 period than the 2006-2010 with 100 approvals, and 57 approvals, respectively.

The 2 different post hoc analyses completed to confirm an association between year of FDA approval and US-LC drug lag were: 1) a 4x2table with transformation of the year of FDA approval into 2, 5-year categories corresponding to 2006-2010 and 2011-2015 as the independent variable with no change to the existing 4 categories of US-LC drug lag and 2) a transformation of the dependent variable into 2 categories; one being 0-12 month drug-lag and the other being greater than 12 months of drug lag, which creates a 2x2 table for cross-tabulation and chi square testing. Results of post hoc analysis 1 demonstrate no change in the significance of the association, with a p value < .001, however the Cramer's V effect size was decreased slightly .367, indicating a moderate effect size (Pallant, 2005). Results of post hoc analysis 2 for FDA Approval Year demonstrate a change in the level of significance for association to non-significant, with a p value = .801, indicating an acceptance of the null hypothesis, stating no relationship between FDA Approval Year and US-LC drug lag.

I performed a similar post hoc confirmation of association between Last Host Country Income level and US-LC drug lag via 2 comparisons, similar to those post hoc analyses completed for the FDA Approval Year. I first divided the Last Country World Bank income levels into 2 categories; high, and low. High consists of the high income and upper-middle income countries, and low consists of the lower-middle income countries, recalling that there were no World Bank low-income countries included in the sample. The second post hoc analysis was completed by making the same change to the 4 U.S.-LC drug lag categories, reducing them to 2 and generating a 2x2 table with 0-12 months as one category, and 13 months and greater, the other. Results of both chi square

comparisons demonstrate *p* values < .05, which further confirms an association and with Cramer's V and Phi effect sizes of .339 and .206, respectively. The former corresponds to a moderate effect size, with the latter corresponding to a small-medium effect size (Pallant, 2005). Detailed results of all chi square post hoc analyses are included in Table 17.

Table 17

Post Hoc Confirmation Analyses of FDA Approval Year and World Bank Income Category

Independent variable	*N*	Chi Square	*df*	*p* value	Cramer's V /Phi (effect size)
FDA approval year 2x4 table	157	22.14	3	< .001*	.367 Moderate
FDA approval year 2x2 table	157	.063	1	.801	NA
Last host country World Bank income 2x4 table	157	18.00	3	< .001*	.339 Moderate
Last host country World Bank income 2x2 Table	157	6.66	1	< .05*	.20 Small

Note. * $p < .05$

Summary of Analyses of Research Questions and Transition

The main objective of this study was to quantitatively measure the time lag between U.S. FDA approval and the approval of new drugs in all countries that participated in trials deemed by the FDA to have been pivotal to each drug's approval. Measurement of drug-lag was the main objective of this study, and was completed by using secondary data from the U.S. FDA, the EMA, publicly available national formulary data from participating countries ministry of health websites, and by one subscription-based information product, the ADIS insight report, provided free of charge from Springer publications. By selecting those new drugs approved between Jan 1, 2006 and December 31, 2015, where FDA's was the first approval in the world, and measuring the

time-lag in months between FDA's approval and approval in the last host country for each product, I was able to complete the calculation of drug-lag between the United States and the last country in which approval was granted, if approval was granted for the product. In the case that an approval was not granted, the cutoff date of April, 1 2019 was imputed. Because of its similar role as a centralized regulatory agency, the European Medicine's Agency's approval date for each drug was recorded, and U.S.-EU drug-lag was calculated and used as a reference population from which additional comparisons could be drawn.

In this 10-year sample, I counted the proportion of drugs approved within 12 months of the FDA's approval, in the last host country for each product's pivotal trial. The null hypothesis was that fewer than 66% of FDA approved drugs would be approved in the last country within 12 months of FDA approval. The results demonstrate that 9.6% of FDA's first in world approvals between 2006 and 2015 were approved in all host countries within 12 months. This observation caused an acceptance of the null hypothesis. Further descriptive observations of the U.S.-last country drug-lag demonstrated that slightly fewer than 50% of products were approved in all host countries within 60 months of the U.S. approval and slightly greater than 50% of drugs took greater than 60 months to be approved, if they were approved in all host countries, with a mean drug-lag of 66 months. The U.S.-EU drug lag was calculated and the mean drug lag was 12.6 months. Finally, the EU-Last country drug lag was calculated and the mean drug lag was 53.1 months. Wilcoxon Summed Rank Tests were then performed on each paired sample; the U.S.-last country drug lag versus U.S.-EU drug-lag, U.S.-LC

drug lag versus EU-Last country drug lag and EU drug-lag versus EU-LC drug-lag. Each pair of samples were found to be different from each other at the $p < .001$ level. Each pair was then tested against a simulated drug lag value of 24 months with the same Wilcoxon test. Each pair in the simulated comparison was also found to be statistically significantly different from each other at the $p < .001$ level.

Research question 2 assessed the association between 7 independent covariates and the dependent variable of US-LC drug-lag, divided into four, time-based categories; 0-12 months, 13-24 months, 25-60 months and greater than 60 months. The null hypothesis for all independent covariates was that there was no association between the covariates and the dependent variable, U.S.-LC drug lag. The 7 independent covariates; FDA approval year, drug indication, orphan status, FDA review type, World Bank income category, sponsor market capitalization and sponsor headquarters were all tested with chi square analysis for association with U.S.-LC drug-lag. Two independent covariates; FDA approval year and last country World Bank income category demonstrated associations with the dependent variable, both at the $p < .001$ level, with moderate to large Cramer's V effect sizes of .461 and .427, respectively. Therefore, a rejection of the null hypothesis of no association, and acceptance of the alternative hypothesis of an association between the 2 covariates and U.S.-LC drug-lag was made.

Post hoc confirmation testing of both covariates was done by combining categories and reducing the numbers of cells in the chi square cross tabulations for both independent and dependent variables, first to 4x2 tables and then further to 2x2 tables. FDA approval year remained associated when the 10-year period was reduced to 2 5-year

periods, $p < .001$, with a moderate Cramer's V effect size of .367. When the dependent variable was reduced to 2 categories, 0-12 month and 13-months and greater US-LC drug lag, the 2x2 cross tabulation and chi square testing demonstrated a non-significant result, $p = .800$. Similar post hoc confirmatory testing of the last country World Bank income category resulted in the following stages; reduction of the LC World Bank income categories to 2, High and Low, while maintaining the 4 U.S.-LC drug lag categories, producing a 4x2 cross tabulation table for chi square analysis. The results were significant for an association $p < .001$ with a moderate Cramer's V effect size of .337. Further reducing the U.S.-LC drug lag categories, to 2, as with FDA approval year and producing a 2x2 table for cross tabulation and chi square analysis gave results of $p < .05$ for association and a low phi effect size of .200.

Section 4 includes the interpretation of the results summarized in this section. I also compare the study results and interpretations to regulatory and human rights policy, as well as to the literature base. Limitations of the study, which portions of the findings are most generalizable and which may require additional investigation are presented. Finally, implications for positive social change are presented in conclusion.

Section 4: Applications to Professional Practice and Implications for Social Change

In parallel with the globalization of clinical trials since the 1990s, questions of equal and timely access to new drugs for all research participants and their communities remain unanswered (U.S. FDA, 2017a; Kass et al., 2014). Sponsoring companies are not universally required to make products available, nor to report when their products become available in all countries that hosted their pivotal trials, though efforts have been made to construct an objective ethical scorecard for companies' performance (Miller et al., 2017). Calculation and examination of the lag-time to availability, or drug lag, in the last host country is an important potential measure of corporate social responsibility has not been completed on an annual or decade-to-decade basis in parallel with the increased globalization of clinical trials, and thus, there is a significant gap in the literature on the time to global availability of new products (U.S. FDA, 2017a; Tufts Center for the Study of Drug Development, 2009).

The primary purpose of this study was to measure, quantitatively, the lag-time between NMEs approved first in the United States between 2006-2015, and their approvals in the last country that participated in clinical trials considered as pivotal to each drug's FDA approval. The secondary objective was to identify factors associated with the magnitude of the lag time between U.S. and last host country approval of products. The secondary research question in my study examined seven independent covariates for a possible association with the duration of drug-lag during the 10-year period that I examined in my study.

The primary data for analysis were collected from the websites of the FDA, the EMA, host country ministries of health, Clinicaltrials.gov, the EU Clinical Trials Registry, the World Bank, and NASDAQ and New York Stock Exchange databases, which are publicly available on-line sources. At the conclusion of data collection from publicly available sources, I noted that several countries consistently had gaps in access to their approval and date of approval data. To address the missing data, I contacted Springer publications, the producer of ADIS insight, a product that provides reports on every U.S. approved drug and data on each product's approval globally. I requested a free trial of access to this product, which was granted, and I was able to complete the collection of missing data from countries not posting approved drug formularies on-line and in English.

I explored two research questions. RQ1 was the primary objective of the study and assessed what proportion of drugs approved in the United States between 2006 and 2015 for which the FDA approval was the first in the world were approved in all countries that hosted pivotal clinical trials within 12 months of the FDA's approval. Specifically, the null hypothesis for RQ1 was that fewer than 66% of products first approved by the FDA between 2006-2015 would be approved in all countries that hosted pivotal trials within 12 months of FDA approval. The U.S.-last country drug lag value in months was the value that tested the hypotheses in RQ1. Further descriptive categorization of the U.S.-last country drug lag was done based on the length or magnitude of the drug lag and placed into four categories: expedient (0-12 months),

average (13-24 months), delayed (25-60 months), and extremely delayed (60 months or greater).

Following the hypothesis testing and drug lag categorization in RQ1, I calculated specific drug-lag was calculated between the United States and EU to provide a reference population, as well as to assess and compare the magnitude of the EU-last country drug lag to the U.S.-last country values. Each pair was then tested by a Wilcoxon summed rank test for paired data to determine whether drug lag values were significantly different from each other. A U.S. drug lag of 24 months was also added to the Wilcoxon summed rank test to simulate a value for the 64 cases not included in this analysis, because the FDA approval was not the first in the world. The 24-month lag simulation was done to provide a further benchmark by which to assess the magnitude of the last country drug lag across a spectrum of possibilities beyond those where the FDA provides the first in world approval for a product.

Of the 293 NMEs approved by the FDA between 2006 and 2015, 157 (54%) of NMEs met the main criteria for inclusion in my sample, which were: that the NME was therapeutic versus a diagnostic agent, that the FDA approval was the first in the world, and that the NME's development included countries outside the United States. The results of the analysis of RQ1 demonstrate that the median drug lag between the U.S. approval and the last host country approval was 63 months. Specifically, 15 of 157 (9.6%) of products were approved in all host countries within 12 months of FDA approval. This proportion was below the 66% approval threshold prospectively identified in the null hypothesis of research RQ1, and thus, the null hypothesis was accepted.

Further, the proportions of drug approvals in the last host countries within 13-24 months, 25-60 months, and greater than 60 months were 11.5%, 28.7% and 50.3%, respectively.

By comparison, the drug lag between the United States and EU demonstrates that median U.S.-EU drug lag was 7 months. A similar examination of the U.S.-EU drug lag categories demonstrates that 113 of 157 (72%) of products were approved in the EU within 12 months of U.S. approval. Further, 16.8% were approved between 13-24 months, 8.3% were approved between 25-60 months, and 3.2% in 60 months or greater. Wilcoxon summed rank testing of the U.S.-EU drug lag compared to the U.S.-last country drug lag was found to be significantly different, $p < .001$. Similarly, while the EU-last country median drug lag at 50 months was shorter than U.S.-LC lag, when tested by the Wilcoxon summed ranks test against the U.S.-EU lag, and the U.S.-LC lags, the differences were both significant at the $p < .001$ level. I tested a simulated median U.S. drug-lag of 24 months against the U.S.-EU lag, the U.S.-LC lag and the EU-LC lag and all were found to be statistically significantly different at the $p < .001$ level as well. Finally, I also noted that of the 157 drugs in the sample, 71 products (45%) remain unapproved as of the April 1, 2019, cutoff date in at least one country that hosted pivotal clinical trials between 2006 and 2015.

With RQ2 I evaluated through chi-square testing whether any association existed between the covariates of year of FDA approval, drug indication, orphan status, FDA review type, World Bank income category of last host country, and the sponsor characteristics of market capitalization and country of sponsor headquarters. These independent variables were each tested against the dependent variable, drug lag, for

association. The null hypothesis for all comparisons in RQ2 were that no association exists between the independent and dependent variables. Associations were found for two of the seven covariates, FDA approval year and last host country World Bank income category. FDA approval year was associated with U.S.-last country drug lag time category, $p < .001$, with a moderate-to-large Cramer's V effect size of .461. Similarly, last host country World Bank income category was associated with US-Last country drug lag time category, $p < .001$, with a moderate-to-large Cramer's V effect size of .427.

I completed two additional levels of post hoc testing for confirmation of association between the independent and dependent variables by consolidating categories, resulting in 4x2 and 2x2 comparisons for FDA approval year and last host country income level. Consolidation at the 4x2 level confirmed association of for both FDA approval year, $p < .001$ and last host country income category, $p < .001$, with moderate Cramer's V effect sizes of .367 and .339, respectively. Further consolidation of each independent and dependent variable into 2x2 tables reveals that association of FDA approval year and U.S.-last country drug lag is not significant, $p = .801$, whereas consolidation of last host country income category and drug lag into a 2x2 table maintains an association $p < .05$ with a small-to-moderate Phi effect size of .20.

Interpretation of the Findings

Both descriptive and inferential analyses of the data collected were enlightening beyond what is present in the research literature on global availability of new drugs developed in the relatively recent, new era of globalized clinical trials. When the term drug-lag was coined by Wardell in a 1973 paper, the observation was the opposite of

what has been observed in this study, namely, the United States was the country where approvals of new drugs lagged behind those of the United Kingdom and the EU (Wardell, 1973). Several legislative steps in the 1980s and 1990s, including the FDA modernization act, the institution of user fees, and legislated, transparent timelines for action dates for new drug applications have had a positive effect on availability of NMEs in the United States (U.S. FDA, 2017d; Somerville & Kloda, 2015; Wileman & Mishra, 2010).

These prior evaluations of drug lag in the literature have, however, focused on the economic and regulatory components of drug-lag versus examining how the magnitude of drug lag is directly related to the ethical principle of justice for research participants and host communities. All patients participating in global clinical trials share the unknown risks of side effects and lack of efficacy inherent in new drug development. Yet, for those new drugs found to be effective, for research participants and those in their host countries to remain without access to those approved safe and effective NMEs they shared the risks of testing while others have access represents an injustice (Hyder, Pratt, Ali, Kass, & Sewankambo, 2014; Pratt & Loff, 2014). The magnitude of this injustice to access has not been methodically measured on a time scale from an ethical perspective in the literature.

The primary research question for this study was descriptive and was to quantify the magnitude of drug lag, in months, between U.S. approval and the approval in the last host country of pivotal trials for new drugs first approved in the United States between 2006 and 2015. The results of that U.S.-last country analysis and a comparison to the U.S.-EU drug lag are presented in Figure 6.

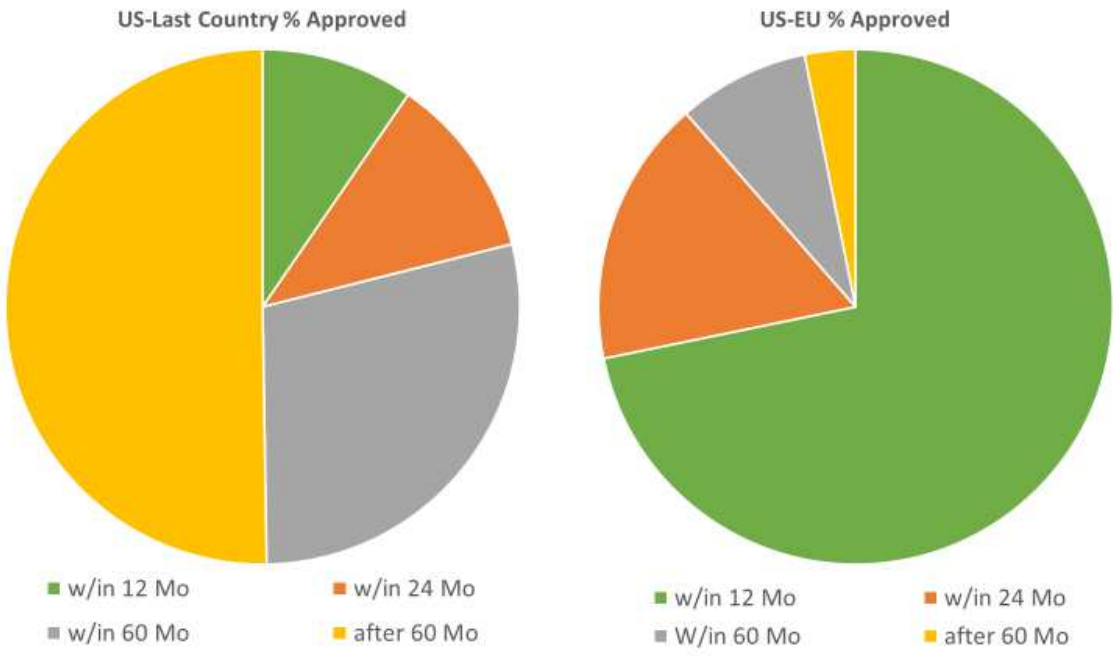

Figure 6. U.S.-last country drug lag versus U.S.-EU drug lag in months.

Figure 6 demonstrates the difference in drug lag, by time category, between the U.S.-Last country and the U.S.-EU, for the 157 products in the sample. The green color in the pie charts indicates the most expedient approval (approved within 12 months of U.S.A.) and the gold color indicates the least expedient approval (approved or unapproved after 60 months) of U.S. approval. The null hypothesis for the primary research question was that fewer than 66% of drugs would be approved in all host countries within 12 months of U.S. approval. As indicated in the US-Last Country drug-lag pie chart, 9.6% of products were approved within 12 months of the US approval, versus 72% for the EU. Therefore, while the null hypothesis for the primary research question is accepted for the US-Last Country drug lag, the null hypothesis would have

been rejected if the drug-lag of primary interest in this study was the U.S.-EU lag. Though the U.S.-EU lag is understandably shorter than the U.S.-LC and EU-LC lags based on the size of the EU market, premium pricing, transparency in the application and approval processes and the concentration of corporate headquarters in the U.S. and EU for sponsoring companies, the median difference in drug lag between U.S. and EU approvals to last country approvals remains striking at 63 months and 50 months, respectively. The Wilcoxon tests support that both the U.S.-Last country and the EU-Last country drug-lags are significantly greater, ($p < .001$) than the U.S.-EU lag. These data indicate that seeking tandem or rapid approval in the EU is a priority for US and EU sponsors, and that seeking approval in all countries participating in pivotal trials, outside the U.S. and EU is either a lower priority or a protracted endeavor.

The secondary research question finding of an association of last host country World Bank income category with drug lag, ($p < .001$) with a moderate to large effect size, and post hoc sensitivity testing indicates with confidence that this association is real. While the sample size is relatively small, of the 157 products tested in 82 countries between 2006 and 2015, 65 of those countries were World Bank high income, 47 were upper-middle income, and 45 were lower-middle income. There were no World Bank low income countries included in the sample. It should be stated however that World Bank low income countries do participate in US and EU sponsored clinical research, none of those trials met the inclusion criteria of this study, as either an NME, first approval of the NME in the United States or deemed by the FDA as a pivotal trial to US approval. Figure

7 illustrates the World Bank Host Country Income results and associations with drug lag by category.

Figure 7. World Bank host country income category and drug lag in months.

Figure 7 compares World Bank high income countries in the sample (n=65) to the combined upper-middle and lower-middle income countries (n=92). Interestingly, in the combined lower-middle income and upper-middle income countries, 1 of 92 products, or 1.1% were approved within 24 months of the U.S. approval. For the 45 countries in the lower-middle income group, there were no products approved within 24 months, with the majority of approvals, 58%, taking 60 months or longer. Finally, for the 65 high income countries, the distribution of approvals was approximately equal over each of the 4

categories of drug lag, with 49% of approvals happening within 24 months, indicated by the green and orange sections of the diagram.

Combining the significant regional drug lag findings from research question 1, and the strength of the association between World Bank last host country income, a picture consistent with an economic model for drug approval and marketing appears (Poitras, 2009). The data support both a pursuit of prioritizing registration in the EU than in other, non-EU countries when the U.S. is the first approving country. The data also demonstrate that a prioritization of registration in World Bank high income countries versus upper-middle and lower-middle income countries, though these samples are smaller. Other descriptive but not statistically tested data are supportive of this observation, namely that the mean number of countries participating in pivotal trials in this sample was 16 and that 72 of the 157 products remain unapproved in at least 1 of the 81 countries included in this sample.

The independent variable year of FDA approval, as one of the 7 tested in research question 2, originally demonstrated an association with the dependent variable, drug-lag category, ($p < .001$) with a moderate to large effect size. I noted that 3 elements of this association were potentially problematic, however. The first was variability in the number of approvals per year, from a low of 9 in 2008, to a high of 24 in 2015. I also noted that the approvals largely increased on an annual basis between 2006 and 2015, with 57 approvals in years 1-5 and 100 approvals in years 6-10 of the sample period. Finally, with respect to the dependent variable, drug lag category, I noted that, considering the cutoff date of April 1, 2019 for all approvals, that for the years 2014 and

2015, for the majority of products the maximum drug lag category would be the Delayed category, i.e. between 25 and 60 months. These concerns prompted me to perform additional, post hoc sensitivity testing which included combining the categories for each variable. First, I combined the individual years of approval into 2 categories, 2006-2010 and 2011-2015, and left the 4 categories of the dependent variable the same, yielding a 4x2 table for chi square testing. This resulted in the significance of the association remaining the same ($p < .001$), but with a reduction in the effect size from the original moderate to large effect size (Cramer's V = .461) to a moderate effect size of (Cramer's V = .367). As second step of sensitivity testing was conducted by reducing the dependent variable to 2 categories, with 0-12 months as 1 category, and 13 months or greater as the other category, resulting in a 2x2 table for chi square testing. The second step results indicated a non-significant *p* value ($p = .801$) for association between FDA approval year and drug lag category.

None of the other 5 independent covariates tested by chi square analysis as part of research question 2 were found to have an association with the categories of U.S.-Last country drug-lag. Given the strength of the association observed between World Bank last host country income category and drug lag, it was somewhat surprising that neither orphan indication nor FDA review type, nor sponsor market capitalization had any association with drug lag category, however given the clear prioritization of EU approval observed in this study, this assumes an economic model for prioritizing global drug approvals prevails in this sample.

It is also noted that there is no easily accessible information on what trials are considered pivotal versus supportive, and there is significant variability in access to information about what countries participated in those pivotal trials. Ready, on-line access to information regarding the approval dates and availability of drugs on a country-by-country basis in English was available in approximately 70% of the countries in this study, whereas for the remaining 30% a combination of direct sponsor contacts and a free subscription to a proprietary database, ADIS insight from Springer Publications assisted in completing the collection of the missing approval dates and data. Several sponsor practices were noted on clinicaltrials.gov, one of the main sources for participating country information, which complicated data collection on specific pivotal trials and participating countries were; failure to include the specific protocol number in the posting, and a practice of designating one point of contact to distribute information on the location of participating sites. These practices made it challenging at times to determine if a trial was pivotal, and/or which specific countries participated in that trial.

Aristotle's concept of a society's duty to contribute to the flourishing overall health is the foundational concept of both the Health Capability paradigm and the RHJ framework, which is most relevant to the role of medical research in enriching societal health, particularly in low-and-middle-income countries (Papadimos, 2007; Pratt & Loff, 2014; Ruger, 2010; Taylor, 1956). The fundamental premise of the health capability paradigm is that societies, be they state or federal governments have an interest and mandate in both promotion of overall health but also to decrease inequalities, by ensuring just distribution of benefits throughout the population (Ruger, 2010). In cases where

states or countries themselves may lack the resources or necessary expertise to provide for their populations, then this paradigm proposes that more affluent states, countries, organizations and corporations are ethically bound to contribute goods, services and know how to address these gaps in health and the capability of becoming as healthy as the most affluent, healthiest nations (Pratt & Loff, 2014; Ruger, 2010). The health capacity model also states that a state of health capacity justice can only exist when, global organizations continuously monitor the status of countries which have health related shortfalls and actively assist these states to reduce those health and health capacity shortfalls (Pratt et al., 2012). This concept is directly relevant to the development of a new drug treatment by international pharmaceutical companies headquartered in affluent regions. As the state of knowledge and therapeutic armamentarium increases through new drug development, whether or not the populations with health capacity shortfalls participated in pivotal clinical trials, if global access is not provided to those therapeutic advances, an injustice has been created with respect to health capacity, as the ability to flourish of the under-served population is diminished in comparison to the countries which have access to the advanced treatment.

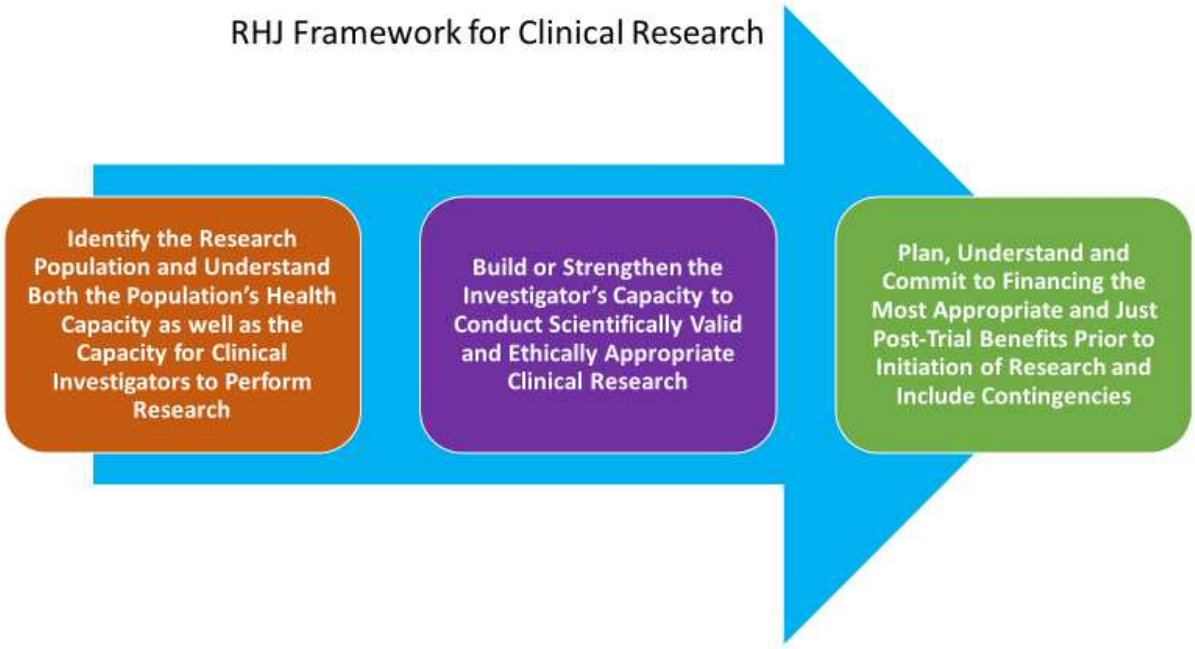

Figure 8. Research for health justice framework.

Specifically, as it pertains to international clinical research, the RHJ framework, figure 8, builds upon the tenets of the Health Capability paradigm to guide the conceptualization of clinical trials on a global scale, particularly when trials include Low and Middle income countries (Pratt & Loff, 2014; Pratt et al., 2012). Conceptualizing specifically what, or who the research targets are, with knowledge and appreciation of the state of health and development in the proposed population is an important consideration from the outset of research design. However, with the globalization of clinical research, clinical protocol design strives largely for consistency and portability to a variety of healthcare settings, with the goal of international regulatory approval for the drug being tested and therefore is often insensitive to local population considerations (Tufts Center

for the Study of Drug Development, 2009). The second tenet of the RHJ framework, strengthening of research capacity at the local level is frequently fulfilled by the sponsors of clinical trials, as it is in their interest to train the clinical investigators and their staff in the research protocol, to provide any necessary supplies, equipment and instruments which potentiate objective measurement of clinical data. Finally, the RHJ framework requires, from the time of research conceptualization, the consideration of post-trial benefits, and what forms those benefits may take (Pratt & Loff, 2014).

Because globalization in clinical research into lower-and middle-income countries has happened relatively quickly, many sponsors, investigators and contract research organizations have viewed each clinical trial on a single transactional basis, versus as a part of a continuum of health benefits or elements contributing to the overall health capability of a population. There has also been a failure of sponsoring companies and contract research organizations to appreciate that the burdens, risks and benefits of the research are experienced not just by the research participants themselves, but their communities (Pratt & Loff, 2014; Pratt et al., 2012) International organizations, local Ministries of Health, clinical investigators, advocates, ethics committee members must all have the benefits of training and interactions with research sponsors who propose to introduce a potential new treatment into their communities (NCOB, 2005; UNAIDS, 2012).

Finally, while it is logical to require that sponsors make all drugs available to all populations which hosted the research, there are situations which may ethically preclude doing so, and an alternative post-trial benefit is of equal or greater value to the host

country's population (Pratt & Loff, 2014). Some examples where post-trial access to the drug under study is precluded; if the drug has an unpredictable safety and efficacy profile, calling the benefit to risk into question, a change in access to properly trained practitioners familiar with the drug's use, infrastructure elements such as cold-chain transport and storage, access to necessary monitoring equipment to ensure safe use which cannot be replaced, and others. In such cases, there may be an alternative treatment or intervention that the research sponsor can provide increases community health capacity, without the accompanying risks introduced by the new drug. Regardless, all communities where research is performed and inequalities exist must be monitored for opportunities to increase health capacity by more affluent countries, companies and international organizations (Pratt et al., 2012).

Limitations of the Study

All data in this study were collected from secondary sources, which I neither designed nor administered, and thus, is an inherent threat to internal validity if the sources themselves were not constructed or maintained in a high-quality manner. Sources including the FDA, EMA, dozens of national ministry of health websites and downloadable formulary spreadsheets, as well as centrally maintained data archives such as clinicaltrials.gov, the EU clinical trials registry, the World Bank, the New York Stock Exchange, NASDAQ and the ADIS Insight data aggregation product from Springer Publications all have differing specifications and procedures for quality control. Errors of inclusion or omission could be present within each source, which could impact the internal validity of the data set I derived for the primary and secondary analyses. I also

hand-entered portions of the data, such as those portions from the FDA websites which were all available only in PDF format. If there were systematic, entry, or random errors in any of these secondary sources, then the observations, analyses and inferences relying on incorrect or discrepant data could be incorrect (Creswell, 2014).

External validity is threatened when there are conclusions reached, or over-broad generalizations made which extend, inappropriately, beyond a reasonable scope of what the sample can represent (Creswell, 2014). Limitations to external validity and the introduction of bias are possible any time inclusion and exclusion criteria designed to sample a population, including groups of studies included in meta analyses are implemented (Ahn & Kang, 2018). The inclusion criteria and sampling method and several of the sources in my study was similar to 3 other studies which considered 1-year, 2-year, and 10-year reviews of FDA NME approvals for different objectives, therefore I have confidence that the sampling criteria and sampling method are valid and acceptable (Homedes & Ugalde, 2016; Larochelle et al., 2017; Wileman & Mishra, 2010).

Importantly, this study examines the drug-lag between therapeutic NME products first approved by the FDA between the years 2006 and 2015, which included pivotal trials with at least 1 host country outside the United States. 92% of the sponsoring companies were headquartered in the United States or EU. The sample also represents 54%; or 157 of the 291 FDA NME approvals which occurred during the sampling period, therefore inclusion and exclusion criteria reduced the eligible sample size by approximately 46%. This study also does not consider overall FDA annual approvals during the sampling period which include generic medications and new formulations of

previously approved products. While the data provide actual approval dates, or a cutoff date for each product in each country which participated in pivotal trials, there is no information on corporate prioritization, decision making, or country-by-country regulatory challenges which may have been faced by sponsoring companies which impacted the approval date, or lack thereof, recorded for each host country. It should also not be assumed in all cases when a drug is not yet approved in a host country, that all research participants have had their treatment discontinued, as continued access to new products may be available by extension protocols, compassionate use or expanded access. Results and inferences, therefore, should be interpreted and extrapolated with caution beyond those contexts.

Recommendations

Awareness of ethical considerations of globalization of clinical research sponsored by pharmaceutical and biotechnology companies headquartered in high income countries is present in the peer-reviewed literature and among various international organization documents relating to human rights (CIOMS, 2016; NCOB, 2005; WMA, 2013). However, quantitative evaluation of the magnitude of drug-lag from the perspective of the ethical principle of justice is lacking. Because the enterprise of drug development involves research in human subjects who take risks for potential but unknown benefits, sponsors of global drug development must include contingency plans for success and failure which consider the human right to well-being, and the social justice of access to new treatments for disease. Using U.S.-EU, U.S.-Last country and EU-Last country drug-lags as surrogates to measure how sponsor companies prioritize

access to new treatments, the regional differences in prioritization elucidated by this study can offer insights into improving justice for research participants and overall global access to new treatments.

To add transparency to the clinical research and development process, sponsoring companies could adopt a culture of greater public disclosure of their research and development activities. Details such as listing all countries hosting their clinical trials, providing protocol numbers and dossiers organized by product and indication on public registry websites such as clinicaltrials.gov and the EU clinical trials registry could be updated more urgently and frequently and improved organizationally and for content. Regulatory agencies could provide searchable versions of their review and approval documents and organized, product specific meta-data on public websites to facilitate research on product development. Sponsors themselves and/or individual ministries of health could host web-interactive drug formularies in English including details on all approved products, in each country, their date(s) of approval, indications, doses, availability and retail prices.

To add specificity to this study's findings, future studies could use a survey methodology to explore the specific reasons that sponsoring companies do not pursue or achieve global approval of their products receiving approval in the United States and the EU. Such a method would depend upon significant disclosures from sponsor companies, portions of which some may consider to be proprietary information, therefore interjecting the potential for missing data. Future studies would also depend upon sponsoring

companies' buy-in to the validity of drug lag as a surrogate for justice and equality of access, particularly to prior research participants and their communities.

Implications for Professional Practice and Positive Social Change

Professional Practice

This study illustrates expediency in the time to new drug approval for the European Union and World Bank high income countries versus other countries which participated in pivotal clinical trials outside the EU. Whether this difference results from strategic economic corporate decision making, or complicated regulatory processes in ex-U.S., ex-EU countries is unknown. The results of this study could benefit pharmaceutical and biotechnology corporations sponsoring global clinical research to hasten the approval of their new treatments, by elucidating the need for transparency among all companies engaging in global clinical trials. Improving transparency of companies, regulatory agencies and ministries of health will allow identification of countries where injustices in new treatment access are greatest and allow focus on solutions to diminish those inequalities.

Methodologically, encouraging a culture of social responsibility and transparency among those sponsoring global clinical research as can be measured by metrics such as drug-lag sets a standard for new companies entering the environment and allows a more ready identification of the most appropriate population(s) in which to conduct clinical research. Identifying minimizing the gaps in global access to new treatments as one of the key company values and an important performance indicator can generate a culture of shared responsibility of improvement in global health. If more sponsors responsibly

invest in the healthcare infrastructure of emerging countries as part of pre-trial capability building, and/or as part of post-trial responsibility, the health capability of societies is improved. Finally, an increase in valuation of the social responsibility component of the corporate bottom line in the pharmaceutical and biotechnology industries, if accepted by company executives, industry trade organizations and shareholders, must occur for truly positive professional changes to maximized. Such changes involve modification of the current thinking of the pharmaceutical and biotechnology industries that new treatments are to be regarded as more similar to other consumer products than they are different. If the differences in corporate responsibility between developers of new therapeutic treatments for diseases and other consumer products can be ubiquitously acknowledged, then a new standard for transparency, access and justice may have a greater probability of adoption on a global basis.

Positive Social Change

My study has identified an opportunity in which sponsoring companies can improve the time to providing global access to their products, particularly to each country which hosted the clinical trials deemed as pivotal to the product's FDA approval. By elucidating what appears to be a corporate prioritization of approval in the largest, highest income and most premium priced markets, an opportunity exists for companies to take a more holistic approach and to ensure accessibility of their products not just to the direct research participants themselves, but to the entire communities an societies which supported the clinical trials responsible for the approval of new and valuable advances in the treatment of disease. Corporate leaders, ministries of health, members of ethics

committees, legislators, clinical investigators, community leaders, trade organizations and corporate shareholders are all stakeholders in the positive social changes which could drive a re-direction in the company priorities for those involved in the research, development, approval and access to new treatments for disease.

Conclusion

This study was built upon three main premises. The first is that new molecular entities approved by the U.S. FDA represent therapeutic advances in the treatment of disease. The second is that drug-lag is a reasonable quantitative measurement and a surrogate for the ethical principle of justice, as it relates to the availability of new treatments to the populations of research subjects and their communities which took the risks to test these therapeutic advances in clinical trials. The third premise was pragmatic, and assumes that availability of these new treatments within 12 months of FDA approval is a reasonable and ethical time-frame, given administrative requirements for registration of new drugs in different countries.

The results of this study demonstrate that, for drugs in this sample first approved by the FDA between 2006-2015, there is a significant difference between the lag time to European Union approval, and approval in the last country which hosted pivotal clinical trials for each product. The majority of these new treatments were approved by the EU within 12 months of the FDA's approval, whereas in the last host country, the majority were not approved within 5 years of the FDA's approval. A significant association was also found between the World Bank income level of the host country and the magnitude of the drug-lag, showing that high income countries are more likely to have approval of

new drugs sooner than upper-middle and lower-middle income countries. Finally, nearly half of the products in this sample which were FDA approved between 2006 and 2015 remain unapproved in at least 1 host country, as of April 1, 2019.

To date, host country drug-lag has not been included as a surrogate for justice in the availability of treatment advances for disease. Given the increase in globalization of clinical research in the past 2 decades and predominance of U.S. and EU sponsoring companies developing new treatments for disease, drug-lag is a simple measurement of social justice and corporate social responsibility which could easily benchmark companies ethical performance to each other. Such objective benchmarking may ultimately increase global access to new treatments and diminish inequities in social justice relating to access to new treatments for disease, simultaneously.

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