A SYSTEMS APPROACH TO UNDERSTANDING THE HISTORY OF U.S. PEDIATRIC BIOLOGIC DRUG RESEARCH AND LABELING

by

Edward William Wolfgang

Dissertation submitted to the faculty of Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy
in
Science and Technology Studies

Janet E. Abbate (Co-Chair)
Shannon A. Brown (Co-Chair)
Ann F. Laberge
Jeremy L. Wally
Lee L. Zwanziger

May 3, 2016

Falls Church, VA

Keywords: Large Technological Systems Theory, Organizational Theory, Collaborative Theory, Actor Network Theory, Biologics, Pediatrics, Medicine, Drugs

A Systems Approach to Understanding The History of U.S. Pediatric Biologic Drug Research and Labeling

Edward William Wolfgang

Abstract

Using a Systems Theory approach allows a person to analyze the intertwined elements of the drug development system and the potential influences of the environment. Thomas Hughes's Large Technological Systems (LTS) Theory is one that could be used for this purpose; however, it falls short in its ability to address the complexity of current day regulatory environments. This dissertation provides a critical analysis of Hughes's LTS Theory and his phases of evolution as they apply to the United States (U.S.) system for biologic drug research, development and labeling. It identifies and explains potential flaws with Hughes's LTS Theory and provides suggested improvements. As an alternative approach, this dissertation explores the concept of "techno-regulatory system" where government regulators play an integral part in system innovations and explains why such systems do not always follow Hughes's model. Finally, this dissertation proposes a hybrid version of Hughes's systems approach and uses it to explain the changes that occurred in the drug approval system in response to the push for, opposition, and inclusion of, pediatric research in drug development during the period 1950-2003.

Abstract (Public)

This dissertation explains Systems Theory and Thomas Hughes Large Technological Systems (LTS) Theory. Systems Theory helps to answer key questions such as why a certain technology advanced or failed and how it attracted the interests and support of social groups who are often outside the system of drug development and part of the environment (e.g., scientists, capitalists, politicians, advocacy groups and others). Hughes LTS Theory was chosen to help answer the question how and why pediatric research and drug development became a requirement in our society. However, when applying Hughes's LTS Theory to a case study of the United States system for biologic drug research to help answer the question why pediatric research and drug development became a requirement, Hughes's LTS Theory fell short in its ability to tackle the complexity of the current day regulatory environment of drug development. Because of the identified gaps in the LTS Theory, key pieces of historical information may be overlooked, such as the actors who were external to the system but strongly influential in pediatric research and development.

To tackle the shortfalls with Hughes's LTS Theory, additional system models principles from (Actor Network Theory, Organizational Theory, and Collaborative Theory) were included and applied to revise Hughes LTS Theory and make it robust

enough to encompass and explain the regulatory system that makes up drug development, also called in this dissertation a "techno-regulatory system". This hybrid version of Hughes's systems approach was then applied to explain the changes that occurred in the drug approval system in response to the push for, opposition, and inclusion of pediatric research in drug development during the period 1950-2003. The inclusion of these other models of investigation to the case study revealed deeper developments that led to the shaping of pediatric drug development by main system actors such as the Food and Drug Administration, and the drug industry, but also those from the system environment (e.g., scientists, the American Academy of Pediatrics, and others).

The knowledge gained from this new model approach can help improve written policy, guidance, and collaborative efforts by recognizing both the mainstream system actors and those who are part of the environment who play an influential role. While the focus of this dissertation has been limited to biologics, this revised system model could also explore other case studies involving the Federal Communication Commission, the United States Environmental Protection Agency, the United States Nuclear Regulatory Commission, Drugs, and others.

Acknowledgment

I would have never been able to finish my dissertation without the guidance, critical comments, and hard questions from my committee members: Dr. Janet Abbate, Dr. Shannon Brown, Dr. Ann Laberge, Dr. Jeremy Wally and Dr. Lee Zwanziger. They challenged my thinking and enabled me to notice the weaknesses in my dissertation and incorporate the necessary improvements. I would also like to express my sincere gratitude to my mentor, Dr. Janet Abbate, for her continued support and direction that helped me progress to complete my dissertation.

Besides my committee members, I would like to thank my branch chief, Dr. Elizabeth Sutkowski, and co-workers, Dr. Timothy Nelle and Dr. Kirk Prutzman, for their help and encouragement. Their discussion points, stories about their dissertation experiences, and occasional humor helped me persevere and stay focused on completing this dissertation.

Lastly, I want to thank my wonderful kids, Katelyn and Grant, who had to make sacrifices because of the time I needed to work on this dissertation. Finally, and most importantly, I would like to thank my wife, Heather, for her encouragement and support that allowed me the time to complete my studies.

Table of Contents

Table of Figures and Tables

Abbreviations

AAP	The American Academy of Pediatrics
AAPS	The Association of American Physicians and Surgeons
AMA	The American Medical Association
BLA	Biologics Licensing Application
BPCA	Best Pharmaceuticals for Children Act
BSE	Bovine Spongiform Encephalopathy
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DVRPA	Division of Vaccines and Related Products Applications
E.U.	European Union
FDA	The Food Drug Administration
FDAMA	Food and Drug Administration Modernization Act
IND	Investigational New Drug Application
LTS	Large Technological Systems
NIH	The National Institutes of Health
OPP	Obligatory Passage Point
OVRR	Office of Vaccines Research and Review
PREA	Pediatric Research Equity Act
SOPs	Standard Operating Procedures

Chapter 1: Introduction

Has the drug your sick child takes been studied or demonstrated to be safe and effective in children of his or her age? Perhaps not. Up until the last 20 years, a majority of medications prescribed to children have not been tested in controlled clinical studies to measure safety and effectiveness testing in children, only adults. Why did this type of practice continue for well over a half century? How and why did it change? This dissertation helps to answer these questions through the lens of Thomas Hughes's Systems Theory. By applying the theory to a sociotechnical system that differs in significant ways from Hughes's exemplars, this dissertation exposes weaknesses with Hughes's Systems Theory and suggests revisions to make it more relevant for today's systems that have a strong regulatory component, such as drug development, while strengthening and broadening Hughes's theory.

Pediatric research and drug development as a regulatory mandate did not happen overnight. It took years of debate between the drug industry, the Food and Drug Administration (FDA), the Congress, patient advocates and others. For years, white males in their twenties through fifties were the "standard human" from which knowledge about human health and illness

flowed.[1] The drug industry argued that it was too challenging to conduct such studies in pediatric populations because it was too hard to recruit pediatric subjects into clinical trials, was ethically wrong, and unnecessary as physicians could prescribe medications for off-label use (i.e., use for an drug indication that is not in the FDA approved labeling). The medical community argued that research with adults cannot be generalized or extrapolated to infants and children, as the pharmacokinetics and pharmacodynamics may be different.[2] Furthermore, off-label use could expose physicians to lawsuits for malpractice; thus, physicians argued that pediatric drug research was needed to show that drugs were safe and effective in children.

It was not one organization or individual that implemented this policy change, but many different people and organizations that comprise an interconnected system. Focusing on one organization or just a specific part of an investigation may help answer questions about the inner workings of the organization, or a specific group of individuals. However, this approach cannot explain what led to the pediatric drug development process. For example, if the investigative approach

---

[1] Steven Epstein, "*Histories of the Human Subject*," *Inclusion.* (Chicago: The University of Chicago Press, 2007), 31-52.
[2] Marilyn J. Field and Richard E. Behrman, "The Necessity and Challenges of Clinical Research Involving Children" in *Institute of Medicine (US) Committee on Clinical Research Involving Children*. (Washington DC: National Academies Press, 2004), 58.

was to focus on preclinical research, this approach might be limited to just the scientists and/or researchers who determine what germs cause specific diseases. Additionally, predisposing factors that led to certain conditions in the pediatric population, such as autism, might be included in this investigation, but the investigative approach would not identify who contributed to the pediatric drug development process. This difficulty is also found during the next stage of drug development, i.e., clinical trials conducted to determine if investigational products meet safety and efficacy regulatory standards, involve a different set of actors, organizations, and motives. This is further complicated in the fact that the actions of one group affect those of the others. As an alternative, a systems approach can investigate drug research at a much broader level as it identifies the many interconnected components of a system and their relationships with each other. As an example, Figure 1 (not exhaustive) illustrates a Systems Theory approach of the collaborative process that takes place between actors involved in the process of drug technology development. This system is not limited to strictly the FDA and drug industry. Instead, it includes many other actors such as Congress, laws, and others who play a key role in influencing drug technology. Some of these actors are not the mainstream players in the system of drug development, but are instead part

of the environment and choose to be part of the system to influence the technology. An advocacy group or organizations such as the American Medical Association (AMA) are just two examples of actors who may push their own interests (e.g., legislation to gain quicker access to certain drug technology) into the system.

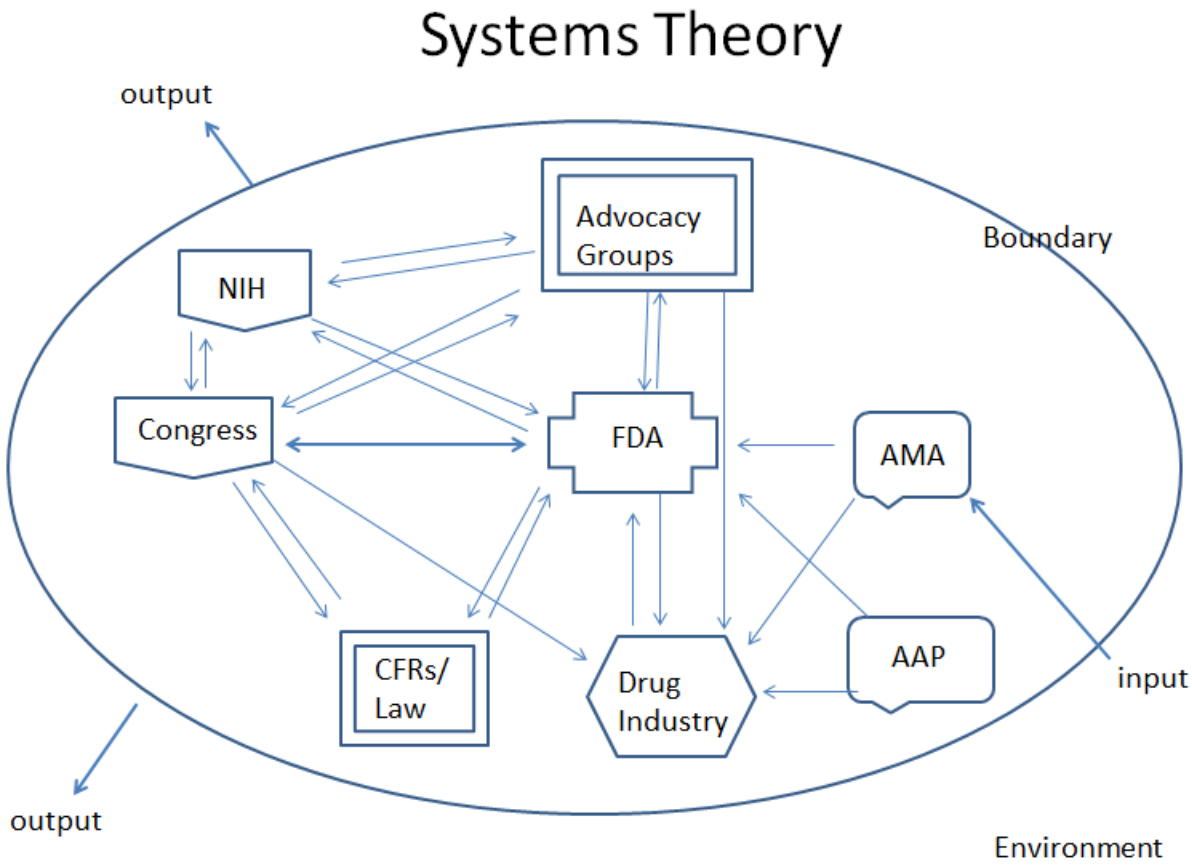

Figure 1: Systems Theory
This figure provides examples of actors who may be involved in the development of drugs, and the back and forth collaboration, and influences that these actors have on one another, the environment and vice versa. *AAP: American Academy of Pediatrics; *AMA: American Medical Association; *CFRs: Code of Federal Regulations; *FDA: Food and Drug Administration; *NIH: National Institutes of Health

This Systems Theory approach not only identifies key actors involved in the process being investigated, but also helps identify the collaborative approach necessary to make a social process change, such as the implementation of pediatric research and drug development. Systems Theory helps to answer key questions such as why a certain technology advanced or failed and how it attracted the interests and support of social groups, such as scientists, capitalists, politicians, and inventors. When investigating a technological change within a large technical system, analysis should not be limited to just the new piece of technology, but should also include the entire system of related components, linked institutions, and their values—all of which contribute to the shaping of the new technology.[3]

Systems Theory can help to answer how and why pediatric research and drug development became a requirement in our society. Systems Theory is particularly useful for studying the gradual emergence of such systems and the way they acquire inertia. Systems Theory provides general principles and laws for how a system is structured and works. Furthermore, one type of Systems Theory I call Large Technological Systems (LTS) can also help by identifying the actors and interests involved where no overall authority exists, the collaboration between actors is

[3] Arie Rip, "Citation for Thomas P. Hughes, 1990 Bernal Prize Recipient". *Science, technology & human values*, 16 (1991): 382-386.

required, and by focusing on the technical areas that affect policy goals concerning flexibility, fairness, efficiency and acceptability.[4] For example, today's drug development process is not centralized. Although each organization has its set of criteria to meet for a drug product to be developed, a drug product requires that multiple organizations work together. This involves a continuous exchange of information and collaboration. If one were to use a non-systems approach when investigating the historical development of pediatric research, key pieces of information that played a central role in a technological development might be overlooked. Such pieces of information could include the collaborative process of groups who work together to bring about a certain change, or perhaps those who were resistant to the change. It is through a system approach that we are able to understand the many actors involved in drug development and define their involvement in the total system.

In this dissertation, I discuss pediatric research and drug development as a current example of a LTS. I describe the interactions between consumers, health professionals, academia, researchers, government, Congress, and disease-focused

[4] Janet Abbate, "From control to coordination: new governance models for information networks and other large technical systems", in *The Governance of Large Technical Systems*, edited by Olivier Coutard, London: Routledge, 1999. 114-129.

organizations within this system. I explain how these actors are systematically linked to the drug approval system and provide specific examples of system changes that took place to incorporate pediatric research and labeling of pediatric drugs within the system. In the case study of pediatric research and drug development, I discuss system bottlenecks that impeded change and the collaboration between system actors who worked for change. The sources of data for the case study consist of published materials (books, journals, advertisements, guidance documents and laws that have played a critical role in the regulatory approval process).

In the first chapter of this dissertation, I provide a general overview of Systems Theory and the purpose of this dissertation. In chapter 2 I introduce Thomas P. Hughes and the Systems Theory of LTS. Hughes's theory focuses much attention on the economic, political and technical factors at work within LTS. Chapter 3 includes a critical analysis of Thomas Hughes's LTS Theory and suggests revisions using additional system models principles that include Actor Network Theory, Organizational Theory, and Collaborative Theory to revise Hughes LTS Theory and make it robust. In Chapter 4, I provide a general historical overview of the drug approval process as a system. Chapter 5 includes a case study of the challenges and actors involved in bringing about changes in drug development and an analysis of

the system expansion of pediatric research using my new theory improvements. Rather than examining the barriers to pediatric research and development in an individual and linear manner, I suggest a more contextual and circular or multidimensional causality in which subsystems influence one another and create unintended consequences. In the Conclusion, I summarize the presented work, the study conclusions, the benefits my suggested theory improvements offer when applied to techno-regulatory systems.

Please note that this dissertation and critique of Hughes's theory applies to mostly biologics. While this research analysis may also be applied to drugs, there are important differences in the definition, regulation, (i.e. Acts, Guidance's) and developmental pathways of drugs versus biologics. The Food and Drugs Act of 1906 and the Federal Food, Drug, and Cosmetic Act of 1938 define "drug" broadly to include, among other things, substances intended for use in the cure, mitigation, or prevention of disease.[5] The 1902 Biologics Control Act, applied to "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of

[5] Richard Kingham, Gabriela Klasa and Krista Hessler Carver,"Key Regulatory Guidelines for the Development of Biological in the United States and Europe" In *Biological Drug Products: Development and Strategies*, ed. Wei Wang and Manmohan Singh. (John Wiley & Sons, Inc. Hoboken, New Jersey), 75.

man".[6] Over the years, the Congress has expanded this list of covered products to include, vaccines, blood, blood products, allergenic products, proteins and those "analogous" to them.[7] Congress never defined the listed terms and, in particular, never defined "analogous," so the scope of the biological product definition remained unclear.[8] Today, the statutes do not clearly distinguish non-biological drugs from biological products. As such, I use the term "drug" and "biologic" interchangeably throughout this dissertation. While this may be an important distinction, it is not germane to this dissertation. Because of these differences, many of the examples used in this dissertation include regulations, and processes specific for biologics, unless otherwise indicated.

[6] Ibid.
[7] Ibid.
[8] Ibid.

Chapter 2: Thomas Hughes's Theory of Large Technological Systems

Large Technological Systems (LTS) play a pivotal role in the process of economic development and industrialization and have contributed to significant changes in the way in which we live.[9] While similar technologies may be adopted around the world, each technological society also develops unique forms of technology and ways of using them. Yet with all the different forms of technology in existence, few people take the time to think of the enmeshed systems of components that have influenced these technologies and provided direction and strength to their development.[10] Understanding technologies as systems can help inform the development of future technologies, policies, and decision-making goals.

One such example of system complexity is the development of the Ford Model A automobile. Inventors, engineers, factory owners, and manufacturers all had a stake in its development. These social groups saw that the wide use of the automobile could lead to job security, capital growth, and perhaps power.

---

[9] Renate Mayntz and Thomas P. Hughes, eds. *The Development of Large Technical Systems* (Frankfurt am Main: Campus Verlag 1988), accessed November 18, 2015, http://hdl.handle.net/2027/heb.01147.0001.001

[10] Thomas P. Hughes, *American Genesis: A Century of Invention and Technological Enthusiasm 1870-1970* (Chicago: University of Chicago Press, 2004),184.

Yet, other social groups such as farmers and the rural community thought they were an abomination. Farmers were upset with the automobiles being stuck on country roads and the loud muffler and engine noises that frightened their livestock. Rural communities rallied and passed laws banning autos or requiring a person to carry a red flag and walk ahead of the car. Anti-car groups formed and protested against the automobile. Eventually, however, the rural communities' idea of the automobile changed and the anti-car movement ceased. This was because automobile manufacturers responded to the influence of the environment (the farmers and rural community) on the automobile system by listening to the complaints of the consumer and communities and redesigning the automobile to handle the country roads. These automobile changes led to increased sales, decreased material costs to the manufacturer and lowered costs to the consumer. Where once advertisements and editorials negatively criticized the automobile, views changed and critics began promoting automobiles.[11] With the rural communities' increased acceptance of the automobile, new economic markets developed, leading to better road infrastructure, and automobile service centers began sprouting up in rural areas. Eventually, the farmers' thinking

[11] Ronald Kline and Trevor Pinch "*The Social Construction of the Automobile in the Rural United States," Technology and Culture* 37, (1996): 763-795, accessed February 22, 2016. doi: 10.2307/3107097

about the automobile changed from one of a menacing machine to an envied technology and power. For one to fully understand the technology of the model A automobile, a person needs to view it through a wide lens of complex systems of roads, regulations created in response to public outcry and need; and service stations and tolls and not just the manufactured product.

2.1 Thomas P. Hughes's Account

One well recognized systems theorist who changed the way we look at science and technology is Thomas P. Hughes. Thomas was born September 13, 1923, and graduated from the University of Virginia with an undergraduate degree in mechanical engineering in 1947.[12] He later obtained his Ph.D. also from University of Virginia in Modern European History in 1953.[13] Publications by Hughes include: *Networks of Power: Electrification of Western Society, 1880-1930, (1983); Elmer Sperry: Inventor and Engineer; American Genesis: A Century of Invention and Technological Enthusiasm, 1870-1970 (1989); Rescuing Prometheus (1998);* and *Human-Built World: How to Think about Technology and Culture (2004)*. In Hughes's works, he includes examples of engineering feats, scientific advances, and groundbreaking risks in designing and managing large-scale technological systems. Hughes chose to focus on inventors such as the Wright brothers, Thomas

[12] University of Pennsylvania, "Thomas P. Hughes," https://hss.sas.upenn.edu/people/hughes
[13] Ibid.

Edison, and others that he studied as a mechanical engineering student. However, instead of concentrating his discussion on one particular invention, he included these inventions as part of larger systems that shape and are shaped by a culture. In Hughes' examples, the term "system" is constituted of related parts or components which are connected by a network, or structure.[14] Technological systems include physical artifacts, and include organizations, legislative artifacts, and even natural resources.[15] Hughes argued that limiting our attention to a specific device or individual machine causes us to overlook how the technology is shaped by those who make up the technological system as well as those who are outside the system and are part of the environment.[16] Figure 2 shows an example of the interaction and input that different actors engage in when developing a technology such as a drug. The environment, which is represented as an oval in Figure 2, surrounds the system of drug development. Actors who are outside the oval are not the main actors involved in the system of drug development, but may become part of the system and the technology produced.

---

[14] Thomas P. Hughes, "Reverse Salients and Critical Problems," in *Networks of Power: Electrification in Western Society, 1880-1930,*(Baltimore: The John Hopkins University Press, 1993) 5.
[15] G. Pascal Zachary, "Remembering Thomas P. Hughes," *The New Atlantis 42 (published by Center for the Study of Technology and Society, 2014)*: 103-108.
[16] Hughes, *American Genesis*, 184-248.

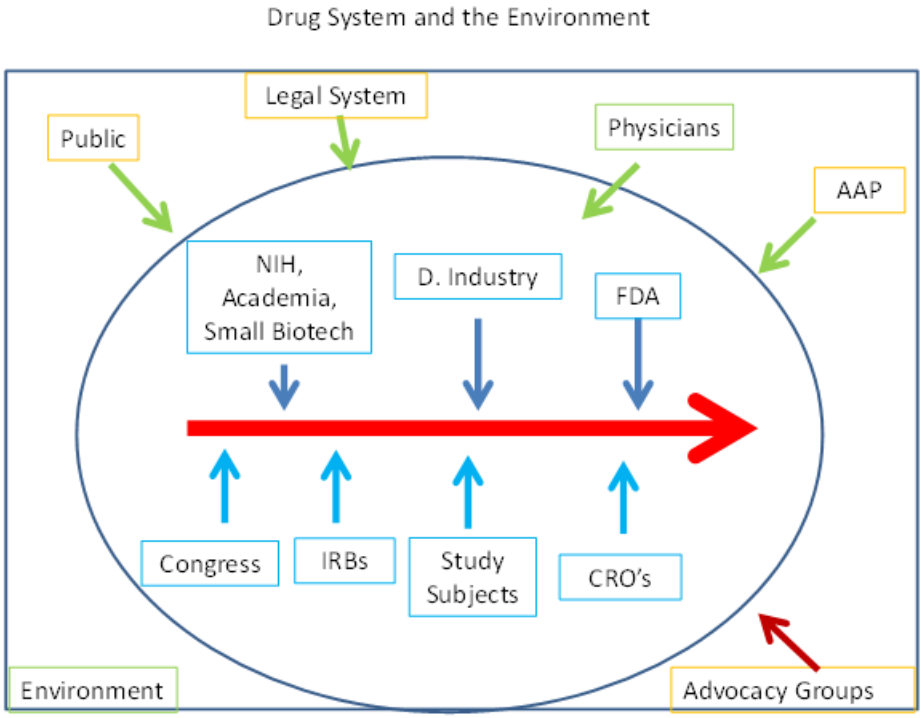

Figure 2: Drug System and the Environment
This figure illustrates the influences environmental actors have on drug system actors when developing a technology.
***AAP: American Academy of Pediatrics; *CRO's: Contract Research Organization; *D. Industry: Drug Industry; *FDA: Food and Drug Administration; *NIH: National Institutes of Health; *IRBs: Institutional Review Board**

In the book *Networks of Power: Electrification in Western Society 1880-1930*, Hughes developed his theory of LTS as a conceptual framework to investigate large infrastructure and production systems.[17] These system components are connected by a structure (or network) and share a unifying goal. Similar to Actor Network Theory, which integrates the conceptual framework of both human and non-human artifacts in the same conceptual

[17] Erik van der Vleuten, E. "Large Technical Systems". In Olsen, J.K.B, Pedersen, S.A & Hendricks, V.F (Eds), *A Companion to the Philosophy of Technology.* (Blackwell Publishing Ltd, 2009), 218-222.

framework and assigned equal amounts of agency,[18] Hughes viewed his historical subjects as complex, interactive systems whose components-whether mechanical, financial, social or political- were equally essential and could not be understood apart from one another.[19] This allows one to gain a detailed description of the concrete mechanisms that hold a system together, while allowing an impartial treatment of actors.

2.2 Hughes Systems Theory Contributions

Hughes is mainly known for his contribution of reshaping the academic field of Science and Technology Studies, especially the history of technology by advocating a shift from concentrating on isolated artifacts to investigating and looking at the totality of the many interrelated elements or artifacts.[20] In the early 1980s, scholars of Science and Technology Studies worked to develop theories to better understand how science, technology and society influence one another, and Hughes's theory of LTS greatly contributed to changing the way that

[18] Learning-Theories.com, Actor-Network Theory (ANT), http://www.learning-theories.com/actor-network-theory-ant.html
[19] Renate Mayntz and Thomas P. Hughes, "The Development of Large Technical Systems," *The Business History Review*, 65,(1991): 1002-1004.
[20] William Ravesteijn, Leon Hermans, and Erik van der Vleuten, "Participation and Globalization in Water System Building," *Knowledge, Technology, & Policy*, 14(4), (2002):4-12. accessed December 11, 2015, http://ocw.tudelft.nl/courses/sustainable-development/technology-dynamics-and-transition-management/readings/

scholars view technology. According to Hughes, what makes something a LTS (such as an electricity supply systems, the FDA, etc.) is that they are human-made "deep structures" that strongly influence where people live, work and play.[21] With the development of LTS came more actor involvement, greater achievements, complex technologies and a growing dependence of societies on these infrastructural systems.[22] Hughes's theory points out that social factors, such as specific interests and values of the interrelated elements that influence a technology, were as important as the technical parts. By investigating a technological object as part of a system (versus concentrating on the object itself), we can discover the origin, development, and the refinement of an object by the system actors and environment. When a form of technology is created and developed, other interests are drawn into the system to meet their own self-interest. These other actors contribute to shaping of the technology while also influencing the system with their own individual goals and interests.

According to Hughes, technological systems include complex problem-solving components. These problem-solving components include people, designers, operators, organizations,

[21] Erik van der Vleuten, "Infrastructures and Societal Change: A View from the Large Technical Systems Field," *Technology Analysis & Strategic Management*, 16, (2004) 395 accessed February 22, 2016, doi:10.1080/0953732042000251160.
[22] Ibid.

legislation, books, articles and regulatory laws, which adapt to societal influences to maintain the goal of the system.[23] These LTSs are made up of many organizations most of which are linked to one another because of their shared involvement and interests in contributing to a certain technology within the system. Some organizations within the system are fully enmeshed, and these dominant organizational actors may own, regulate or manage parts of the system and have strong links politically, legally and financially. Other organizations within the system are only partially involved and focus on managing their own subsystems while being dependent on other organizational services.[24]

Hughes focuses attention on what he terms "system builders" who are "heterogeneous engineers" that invent and develop system components for the overall functionality of the system. It is the concept of Hughes's system builders that brings the human agency (thoughts and actions taken by people that express their individual power to shape the thought, behavior, and experiences of people) in the analysis of sociotechnical system development by which the individual and (later) organizations do the

[23] Thomas P. Hughes, "The Evolution of Large Technological Systems," in *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology, ed Wiebe* Bijker and Thomas P. *Hughes (*Cambridge MA: MIT Press, 1987), 51.

[24] Bernward Joerges "Large Technical System: Concepts and Issues," in *The Development of Large Technical Systems,* Renate Mayntz and Thomas P. Hughes (Boulder: Westview Press, 1988),9-36.

sociotechnical weaving of bringing the technical and non-technical together.[25] The system extends beyond the engineering realm into intermeshing categories such as technical, administrative, and economical. It is through these various elements that the characteristics of system builders are clearly evident, because of their ability to "construct or to force unity from diversity, centralization in the face of pluralism, and coherence from chaos."[26] When system builders bring system components together, they have a vested interest in the system as a result of their invested time and money in offering a product and/or service in alignment with the views of the existing system.

2.3 Hughes Systems Theory Phases and Influencing Drivers

Hughes's Systems Theory framework provides a comprehensive and holistic view of organizations by focusing on the interactions between system components. In the chapter titled "The Evolution of Large Technological Systems", Hughes includes a description of a pattern a system goes through during its evolution. The first phase is *invention*. According to Hughes, an invention could be a power plant, light bulb or non-physical items such as holding companies, which often do not produce

[25] van der Vleuten, "Large Technical Systems," 218-222.
[26] Hughes, "The Evolution of Large Technological Systems," 52.

goods or services but rather own company shares.[27] Inventions that occur during the first phase are called *radical inventions* because they lead to a new system, rather than a component within an existing system. An invention that leads to the improvement and expansion of an existing technological system is a *conservative invention*.[28]

The second phase of evolution according to Hughes is *development*, during which the system builder expands his or her invention into a complete system. The social construction of technology becomes especially clear, as the invention is adapted to social, political and economic constraints by the inventor-entrepreneurs and their associates. One example that Hughes provides is the invention of a transformer that had varied levels of electrical output. This technical ability to have varied levels of electrical output was developed in response to the regulatory constraints of the British Electric Lighting Act of 1882 which encouraged competition by requiring that power companies accommodate all the different types of electrical appliances on the market.[29,30] This example, illustrates how a component may have its characteristics changed to be in

[27] Ibid., 57.
[28] Ibid., 56-57.
[29] Ibid., 64.
[30] "Miscellaneous News: Electric Lighting in the Metropolis" in *The Journal of Gas Lighting, Water Supply & Sanitary Improvement* (London: Walter King, 1889),863-893.

alignment with current social, political or economic conditions to better ensure the system's survivability. With a change in characteristics of one system component, other interrelated system components will have to change to adjust accordingly.[31]

The third phase of system evolution is *innovation*, during which the inventor-entrepreneurs along with the associates (industrial scientists, other inventors, etc.) push for the use of the invention. During innovation, those who had collaborated and had a vested interest during the invention and development phase of the product continue to work together as a complex system of sales, manufacturing services, and other types of organizational contributions. Hughes's Systems Theory expands the view of organizations to include technical components and the wider social environment, in contrast to theories such as Organizational Theory, which focuses its investigation on human aspects of the organization itself. In the article "Designing, Developing and Reforming Systems", electrical power systems are part of a larger sociotechnical system that includes not only utilities and generating stations but also research laboratories, brokerage houses, regulatory bodies and other organizations that have their own power structures and goals in addition to the shared goals of the electrical power system.[32]

[31] Hughes, "The Evolution of Large Technological Systems," 63.
[32] Thomas P. Hughes, "Designing, Developing, and Reforming

Once a system has been initially established, it goes through what Hughes terms "systems growth". During this phase, the system builder identifies reverse salients and critical problems within the system to diagnose and correct system imbalances. Hughes borrowed the concept of a reverse salient from military history in which military commanders defined it as a reverse bulge that results at various points on the front line as influenced by the relationship between soldiers and their war equipment.[33] For example, if both soldiers and supplies were ample in a section of the front line, both the soldiers and equipment would move forward. Yet, inversely, if soldiers or supplies were in short supply in a section of the front line, that section would progress slower than the neighboring sections causing a reverse bulge to form. It is the reverse salient that can be looked at to identify key issue or factors that influence the components of a system. Reverse salients can lead to a technological, social, economic and/or political change to correct system imbalances.

Once a critical problem is identified, whether it be technical, economic or political in nature, there are ways of resolving it. Perhaps, the development of a new tool or revised legislation is needed to correct the reverse salient and bring

---

Systems," in *Daedalus, (Cambridge: MIT Press, 1998), 215-232.*

[33] Ibid.

the system back into alignment. Eventually, the system will go into imbalance again as the technological system once again goes through further development to expand or improve the system.[34] Reverse salients can emerge in all system phases. The nature of the reverse salient will determine which problem solvers are needed to tackle the critical problem and find a solution. Most technological developments result from efforts to correct reverse salients.[35] Problem solvers include managers, financiers, inventors, and legislative individuals who have relevant experience or expertise in tackling certain problems.[36]

In *Networks of Power*, Hughes argues that the technological advances of power and electrical lighting after 1880 were a direct result of the corrections of reverse salients. One of the reverse salients that affected both power and electrical lighting was the high economic cost of electrical distribution. To tackle the high cost problem, inventors hired industrial scientists through business enterprises to investigate this critical problem and find a solution.[37] Hughes provides an

---

[34] Thomas P. Hughes, "The Evolution of Large Technological Systems," in *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology, ed. Wiebe* Bijker et al *(Cambridge*: MIT Press, 1987), 13.
[35] Thomas P. Hughes, "*Reverse Salients and Critical Problems"*.80
[36] Renate Marntz and Thomas P. Hughes, eds., *The Development of Large Technical Systems* (Boulder: Westview Press, 1988), accessed March 2, 2016, http://www.mpifg.de/pu/mpifg_ book/rm_lts.pdf
[37] Hughes, "*Reverse Salients and Critical Problems,"*.80.

example of a direct-current system that evolved over the years from the work of inventors and engineers to overcome reverse salients that led to improved generators and the introduction of a three-wired system that lowered the cost of electrical distribution over a wide area while also saving sixty-percent of the copper needed to operate the two-wired network.[38]

Once a reverse salient is corrected, the system grows if there is adequate demand for its product.[39] On occasion, a critical problem within an existing system cannot be solved and a new system develops. This occurred in the 1880's involving direct current electricity in that the existing transmission was not economical and system engineers could not find a solution. As a result other inventors outside the system found a solution and the two systems existed until the newer system eventually dominated the market and replaced the other. Once a system is established and is in use, people and companies have an investment in it, and they often resist system change. Hughes calls this resistance "momentum". While a manufacturer is often willing to manufacture a "conservative invention," which often strengthens and develops existing technologies, they are often reluctant to adopt "radical inventions" since they usually require new tooling equipment, validation studies, training and

[38] Ibid.
[39] Ibid.

other costs.[40] Radical inventions often result in the re-skilling of workers (managers, laborers, etc.) who need to learn the newly introduced technology and go against the grain of the existing system of organizations.

The fourth phase of the systems model is *technological transfer*. In this phase, a system is adapted to meet the needs of a particular time and place. Hughes again uses the electrical transformer as an example. In the 1880s, Lucien Gaulard and John Gibbs introduced an electrical transformer to meet the requirements of British electric lighting legislation. After seeing the transformer on display, countries, such as the United States (U.S.) and Hungary, redesigned and adapted the transformer to meet their own countries' legislative and market needs.[41]

Systems Theory allows us to look at a complex problem through a wider lens. Organizational systems are complex, and understanding them can be a daunting task and may overwhelm most people. Instead of focusing on a piece of the system and reducing it to smaller parts for a better understanding, Systems Theory provides a new perspective and methodology of investigation by seeing the system of different, yet linked, organizations. If a non-LTS approach were to be used to

[40] Hughes, "The Evolution of Large Technological Systems".,64-65.
[41] Ibid.

investigate the development of pediatric drug regulation, the investigational analysis may only capture the attributes of the individual actors and not the collaborative process that takes place between the different actors. Information overlooked may include the negotiating challenges, power issues, and actor conflict, all of which influence the decision making process. The creation, development, and adaptation of drug technology is a collective process and cannot be understood by investigating each actor separately. Instead, the research analysis of actors needs to be looked at as a unit (i.e., a holistic approach), something that the LTS approach is well suited to handle. Using a LTS approach to investigate the actors as a unit provides a better understanding of the complex mandated collaborative actor process that takes place in the system of drug development.[42]

2.4 The Prefilled Syringe: A Systems Theory Approach

To see how Systems Theory can be applied to the drug industry, let us briefly look at the development of the prefilled syringe. For years, multi-dose vials (Figure 3) have been used for the storage of a drug product for administration.

[42] Mats-Olov Olsson, and Gunnar Sjostedt, "Large Technical Systems a Multidisciplinary Research Tradition" in *System Approaches and Their Application Examples from Sweden* (Berlin: Springer Science & Business Media, 2004), 301-306.

Figure 3 [Fair Use]: A Multi-dose Vial[43]
This figure is a picture of a multi-dose vial with a needle inserted into the rubber diaphragm.

When drugs stored in such vials were to be administered to a patient, the health care worker, such as a nurse, would attach a needle to a syringe, insert the needle into the multi-dose drug vial through the rubber diaphragm and draw up the liquid medication into the syringe. Before giving the medication to the recipient, a new needle would replace the needle that had been used to draw up the medication from the multi-dose vial. This method of drug administration has resulted in years of drug waste and potential medication errors as a result of too much or too little medication being drawn up and given to the intended recipient. Furthermore, to ensure a multi-dose vial had enough

[43] "Vaccine Resistance Movement," http://vaccineresistance movement.org/?page_id=7452 [fair use].

doses of medication, manufacturers needed to over-fill the drug vial by as much as 20-30% to account for potential waste.[44] While the drug industry and the health care industry were well aware of the long history of drug waste and medication errors using a multi-dose delivery system, the key factor that led to the technological change in the medication delivery system was the public's fear of thimerosal, a mercury-containing preservative. Each time a health care worker uses a needle to puncture the rubber diaphragm of a multi-dose vial, there is the risk of introducing bacteria into the vial, which can lead to contamination and bacterial and fungal growth within the medication. To prevent this from occurring, drug manufacturers have added small amounts of thimerosal to vaccines that are packaged in multi-dose vials since the 1930s.[45]

What prompted a change in system components from the multi-dose vial to the prefilled, single-dose syringe technology was not the cost savings to manufacturers (since they no longer needed to overfill the drug product), but changes in regulatory

[44] Sagar Makwana et al., "Prefilled syringes: An innovation in parenteral packaging," *International Journal of Pharmaceutical Investigation*, 4 (2011): 200, accessed March 2, 2016, doi: http://dx.doi.org/10.4103%2F2230-973X.93004

[45] U.S. Department of Health and Human Services, Food and Drug Administration, "Thimerosal in Vaccines," http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228 (accessed March 22, 2016).

aspects of the system due to public pressure. In 1994, the Environmental Protection Agency (EPA) lowered the acceptable reference dose for methylmercury after reviewing two Iraqi longitudinal studies with adverse neurological events reported in infants and children following exposure to methylmercury. In 1998, a British gastroenterologist named Dr. Andrew Wakefield published a report that claimed that a small number of children had developed autistic regression following immunization with measles-mumps-rubella vaccine, which included thimerosal as a preservative. While Wakefield's conclusion was later discredited, these reports fueled public fears about a link between vaccination of children with vaccines containing preservatives and children developing autism. This resulted in many parents not immunizing their children because they feared that their child might develop autism due to exposure to thimerosal. Eventually, this concern worked its way to U.S. Congressman Dan Burton, who began a series of congressional hearings on autism after his granddaughter was diagnosed. The hearings led to a provision for a comprehensive review of the use of thimerosal in childhood vaccines in the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA).[46] This

[46] Ellen Watkins, "*Sick With Fear: Popular Challenges to Scientific Authority in the Vaccine Controversy of the 21st Century,"*(n.d.) http://digitalcommons.Providence .edu/cgi/viewcontent.cgi?article=1008&context=auchs

FDAMA provision led to committee meetings with representatives from the American Academy of Pediatrics (AAP), the Centers for Disease Control and Prevention (CDC), and the FDA. Based on a review of the data and committee meeting discussions, the FDA concluded that the maximum cumulative exposure to mercury from vaccines was within acceptable limits. However, because the risk of exposure to the thimerosal was uncertain due to the variable weight of infants receiving thimerosal-containing vaccines, the committee decided to explore the possibility of eliminating the use thimerosal.[47] On July 1, 1999, a letter was sent to vaccine manufacturers asking them to provide a listing of products that contain thimerosal, their intentions to remove the thimerosal from their products, and the manufacturers' proposed clinical studies to assess the effect of removing thimerosal, as related to potency, stability and immunogenicity.[48] To avoid any potential public concern, the AAP, U.S. Public Health Service, and vaccine manufacturers agreed that thimerosal should be removed from vaccines as soon as possible. European regulatory agencies and European vaccine manufacturers also discussed this

[47] Ibid.

[48] U.S. Department of Health and Human Services, Food and Drug Administration, "Letter to Vaccine Manufacturers Regarding Plans for Continued Use of Thimerosal as a Vaccine Preservative," http://www.fda.gov/biologicsbloodVaccines /safetyavailability /ucm105875.htm (accessed March 23, 2016).

issue with the FDA and reached a similar conclusion.[49] To avoid using thimerosal, drug manufacturers packaged the vaccines in single dose syringes, which do not require the thimerosal preservative. In this example, the fears of consumers represented a reverse salient whose solution would require changes in other system components.

2.5 Unique Aspects of Regulated Systems

While the multi-dose vial to a prefilled syringe example is similar to Hughes's examples in that they both showed how different components of a system require adjustments to work together toward the system goal, there are key differences. In a clinical phase drug development system, the technology must stay within the lines that are predefined by regulators, technology designers, and others to ensure what can and cannot be done with the technology. This is different from Hughes's examples in that regulators play a key role in system innovations from the very beginning, rather than simply reacting afterwards. These regulators work within the regulatory framework of drug development that is based on laws. One example of the integral role of regulation in the drug system involves controlling the

[49] "Notice to Readers: Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the U.S. Public Health Service." *CDC Morbidity and Mortality Weekly Report (MMWR)*,(July 9, 1999),563-565. http://www.cdc.gov/mmwr/preview/mmwrhtml /mm4826a3.htm

risk for bovine spongiform encephalopathy (BSE), more commonly known as Mad Cow Disease, which is believed to be related to the fatal variant Creutzfeldt-Jakob disease in humans. In 2000, the FDA learned that drug manufacturers were using bovine-derived materials as a source of nutrients for the growth of bacteria and cells that are used to grow viruses used in the manufacture of certain vaccines. Some of the bovine material used for vaccine development came from countries the U.S. Department of Agriculture identified as having BSE. The FDA took a proactive approach by having public BSE forums, issuing letters to drug manufacturers and developing guidance documents that advised drug manufacturers to take steps to reduce the theoretical risk of exposing individuals to the infectious agent that causes BSE (i.e., a prion) as a result of vaccination. The FDA requested that drug manufacturers submit detailed information about the cell lines used in the production of biological products. This information include such details as the cell culture history, isolation, and adventitious agent testing. In letters to manufacturers, the FDA strongly recommended that manufacturers not use bovine-derived material sourced from countries where BSE was known to exist. Because of the FDA's actions, drug manufacturers only used bovine derived materials from countries where BSE was not known to exist. Alternatively, drug manufacturers redesigned their products to be free from bovine

derived products by using alternatives to bovine serum to avoid potential product market delays and product recalls due to BSE concerns.[50]

Regulation helps ensure that *d*rug technology stays within the lines defined by drug regulators, to make certain behaviors impossible and/to prompt others. Under 21 Code of Federal Regulations (CFR) 314.70, drug manufacturers must notify the FDA about each change in condition established in an approved application beyond the variations already provided for in the application.[51] In other words, drug manufacturers cannot just take their own initiative to change their product or product labeling without first getting approval or concurrence by the FDA. If a drug manufacturer made a change in a licensed product's characteristics without the FDA's concurrence, the FDA could determine the drug to be adulterated or misbranded and take regulatory action to remove the drug product from the

[50] U.S. Department of Health and Human Services, Food and Drug Administration,"Recommendations for the Use of Vaccines Manufactured with Bovine-Derived Materials Transcript of 27 July 2000, Joint Meeting of the Transmissible Spongiform Encephalopathy and Vaccines Related Biologicals Advisory Committees", http://www.fda.gov/BiologicsBloodVaccines /SafetyAvailability/ucm111476.htm (accessed March 23, 2016).

[51] Federal Register: Electronic Code of Federal Regulations, "CFRs are general and permanent rules of the Federal Government developed by federal departments and agencies which are published in the Federal Register. Within the Federal Register are public notices of rulemaking, proposed rules, final rules and other types of public interests," http://www.ecfr.gov/cgi-bin/text-idx?rgn=div5&node=14:1.0.1.1.1

market. The FDA has had this authority to regulate drugs since the passing of the Pure Food and Drug Act of 1906, which provided both civil and criminal penalties for violation of its provisions.[52] Unless a significant public safety issue is identified involving a drug product, the FDA cannot make unilateral changes either; it can only urge and incentivize drug companies. In the previously mentioned thimerosal example, the FDA's 1999 letter to drug manufacturers included the following text:

> "Please note that the FDA regulations do not require use of preservatives in biological products formulated for single-dose containers and that the FDA encouraged discussions with manufacturers as to what additional data, if any would be required to effect such a change".[53]

This letter suggested a pathway to be used by drug manufacturers to address the public's fear of thimerosal-containing vaccines and to help revert the system back to alignment and normal

---

[52] David L. Stepp, "The History of FDA Regulation of Biotechnology in the Twentieth Century". *Food and Drug Law,* Harvard University's DASH repository, 1999,.6 https://dash.harvard.edu/bitstream/handle/1/8965554/Stepp,_David_00.pdf?sequence=1

[53] U.S. Department of Health and Human Services, Food and Drug Administration, (2015) "Letter to Vaccine Manufacturers Regarding Plans for Continued Use of Thimerosal as a Vaccine Preservative." http://www.fda.gov/biologicsbloodVaccines/safetyavailability/ucm105875.htm

functioning following the damage created by Dr. Wakefield's report and public health concerns. To bring the system back into alignment and ease environmental fears and concerns, the system components needed to adapt. The FDA coaxed the drug manufacturers to decrease their use of preservatives in vaccines by suggesting that single-dose prefilled syringes could be used an alternative. The drug industry in turn worked with syringe manufacturers and provided the FDA with study proposals to test these prefilled syringes and their effect on drug product's potency, stability and immunogenicity. In order for the proposed technological change of using prefilled syringes to solve the problem, the clinical studies proposed for testing the prefilled syringes had to meet the requirements of the FDA reviewers responsible for reviewing the study proposals and non-human actors, such as the established regulations and drug guidance.

Once a drug product was available in prefilled syringes without the preservative thimerosal, drug manufacturers (with FDA concurrence) advertised their product prominently as being "preservative free" on the product carton and/or container to ease public fears. Drug manufacturers such as Medimmune LLC, whose influenza vaccine Flumist® never contained the preservative thimerosal, advertised this fact to consumers. The Drug maker Merck & Co. announced in September 1999 that the FDA approved a preservative-free version of its hepatitis B vaccine and its

press release stated, "Now, Merck's infant vaccine line is free of all preservatives."[54] In November 2009, the FDA issued a public press release that the influenza vaccines for 2009-2010 would be offered to consumers either with or without thimerosal as a preservative. Newspapers such as the Union Tribune - San Diego advertised mercury-free influenza vaccine as options for those consumers fearful of mercury.[55] This illustrates how various components of the system—labels, advertising, and marketing—had to be adjusted in order to bring the system into alignment.

While the thimerosal example shows the applicability of Hughes's system model to the case of drug development and labeling, it also reveals key differences. Unlike Hughes's paradigmatic system builders in the electric power industry, the managers of drug companies could not make significant changes to their systems without prior coordination with regulators. Since biologics regulations apply to all of vaccine manufacturers, they also act to synchronize changes across the vaccine industry. The unique characteristics of this type of system will be the topic of the next chapter.

---

[54] Myron Levin, "Merck Misled on Vaccines, Some say," *Los Angeles Times,* March 7, 2007, http://articles.latimes.com/2005/mar/07/business/fi-merck7

[55] Richard Harkness, "Mercury-free flu shot vaccine is an option," *Union Tribune San Diego*, October 24, 2006, http://www.utsandiego.com/uniontrib/20061024/news_lz1c24qanda.html

Chapter 3: A New Theory for Highly Regulated LTS: The Techno-Regulatory System

However, Hughes focused his analysis on systems that were less complex in some ways than today's drug regulation systems. Hughes's Systems Theory has many investigative benefits. The systems analysis approach can reveal the weak links (critical problems) in a complex interconnected system and be useful for analyzing how and why system components are adjusted and/or fine-tuned to fit with each other. Actors are anyone and anything that has an interest in an item, product or idea. For example, with the drug approval process, the human actors could be the participants (or study subjects), researchers, study staff, personnel, scientists, researchers and others. Nonhuman actors include the study protocols, lab equipment, testing equipment, informed consent forms, monitors, room equipment, policies and documentation associated with conducting drug trials. Systems Theory also works well to recognize the effect of outside stakeholders on the organization and the impact of environment on organization structure and function.[56]

Thomas Hughes's Systems Theory case studies include examples that occurred before World War II, such as the

[56] Jo Luck, "You think you have problems with your research participants? My research subjects don't have a pulse!" Faculty of Informatics & Communication, Central Queenland University, http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.214.6491&rep=rep1&type=pdf

airplane, the incandescent light, and the gasoline-driven automobile, in which one or a few inventors led the creation or improvement of and expansion of a technological system. His later works provide examples of technical systems on a much larger scale that include many agents of change. For example, in his book *Rescuing Prometheus,* Hughes discusses a refined systems approach that facilitated the management by one authority over the collaborative effort of many system actors (such as Bell Aircraft, General Electric, North American Aviation, Northrop Aircraft and the Air Force) to research and develop long-range ballistic missiles.[57] Yet even in its later expanded form, Hughes's theory overlooks key characteristics of today's techno-regulatory systems. I propose the term techno-regulatory system to describe systems in which multiple system builders, none with complete authority over the system, must collaborate within a single technical and regulatory regime. Additional characteristics of a techno-regulatory system include a regulatory framework that involves regulatory guidelines to ensure compliance in the technology itself, specified responsibilities, an open system, and no central decision making authority over other system actors. The U.S. system for research, development, and labeling of pediatric biologics

[57] Thomas P. Hughes, "Managing a Military – Industrial Complex: Atlas," *Rescuing Prometheus* (NY: Random House, 1998),78.

provides an example of such a techno-regulatory system. When applying Hughes's LTS to the techno-regulatory system of drug development, I have identified the following list of weaknesses. Hughes theory:

- is limited to system builders who have complete authority over the system,
- has many pathway approaches a system builder can take to develop a technology but does not address the limitations of a single pathway approach such as the regulatory pathway used in drug development,
- neglects to address conflict and internal power relations within organizations, and
- neglects to identify the collaborative process needed by different organizations to meet their own interests and those of other organizations for a technology to advance and be developed.

For example, I argue that the development of pediatric research that led to labeling of drugs for pediatric use had many system builders (none of whom had complete authority over the others) who were required to combine their resources and authority to produce a system technology. In *The Evolution of Large Technological Systems*, Hughes argues that, for system builders, the construction of a technology often involves the destruction of alternative systems in which the system builder has no personal stake.[58] Yet, in a techno-regulatory system such as drug development, there may only be one system approach for a drug

[58] Hughes,"The Evolution of Large Technological Systems",52.

technology and this requires that actors work with governmental regulator's in the statutory role as gatekeeper. For example, for licensure of drug products, development is a protracted process involving product development, preclinical testing, and clinical testing over the course of several years. There often is interplay between the small biotechnology and pharmaceutical companies and between clinical trial managers, various national regulatory agencies, and the Food Drug Administration (FDA) reviewers from different disciplines, all of whom must have their requirements met for a product to develop. Another characteristic overlooked by Hughes's theory is collaboration between drug producers and regulators. Collaboration occurs daily in a large techno-regulatory system. The following sections will elaborate these five gaps or weaknesses in Hughes's model.

3.1 Techno-Regulatory Systems Have Divided Authority and a Single Mandated Pathway

In drug development, different organizations often must meet both their own interests and those of other organizations for a technology to advance and be developed. For example, a drug manufacturer may push its internal resources to promote the further development of a drug for its own interests and not the collaborative interests of other organizations. Yet, if a regulatory agency makes a determination that the drug company's

goals are not in alignment with their own, further drug development can be halted. This can occur during both the pre-licensure and post-marketing phases of drug development, e.g., when issuing a clinical hold letter, or a complete response letter.[59] Within these letters issued to the drug manufacturer, the FDA must list its concerns, along with the information or modifications needed to resolve the issues. Asking for additional information (e.g., safety data) from the drug manufacturer can be one way of slowing or halting drug phase development.

Unlike other types of organizations that have the option of seeking other suppliers or organizations to work with, if conflict exists, key organizations that make up techno-regulatory systems are required to work together. Multiple actors from across different agencies are required by law to collaborate with one another to develop a drug technology and maintain system alignment. Because the modern system of drug development is a regulatory process with many actors involved, system evolution or innovation by just a few actors (as in Hughes's examples) would not be feasible today.

In the chapter *The Evolution of Large Technological Systems,* Hughes describes system builders as having the ability

[59] Complete Response Letter to the Applicant, 21 CFR 314.110 (2015)

to "construct or to force unity from diversity, centralization in the face of pluralism, and coherence from chaos".[60] However, this type of control does not exist in techno-regulatory systems. During the pre-IND phase scientists in biopharmaceutical research companies, academia and research institutions can be creative in developing a new drug technology and individual authority can exist. However, central authority does not exist in a techno-regulatory system of drug development. Individuals and organizations involved in drug development often do not have authority over other components of the system and cannot control the coordination and incentives used to motivate people to achieve certain goals. Although each organization has its own staff, leadership, management style, and chain of command, these different organizations are required by law to combine their resources and authority to produce a system technology.

In a Techno-regulatory system the main players involved in drug development do not have the option of changing whom they need to work with for drug approval. While a drug manufacturer may be able to change from one device manufacturer to another for supplying syringes for use with their drug product, drug manufacturers cannot change the regulatory agency that is

[60] Hughes, "The Evolution of Large Technological Systems",p.52.

responsible for regulating drug technology. In the U.S., the FDA has this regulatory responsibility for protecting and promoting public health through the regulation of drugs, food, devices and other products. The government's role is also constrained. Congress oversees the FDA, and the Congress has enacted legislation that grants the FDA the enforcement authority to ensure drug compliance is met through fines, injunctions and withdrawal of drug approval. However, no authority exists to require the drug industry to develop drug products that the FDA would like developed. Instead, Congress has provided the FDA with incentives to offer the drug industry to develop these drugs. For example, under the Orphan Drug Act if the FDA determines a product meets the criteria of an orphan drug (drug used to treat a rare medical condition), the drug sponsor is entitled to tax credits of up to 50% of research and development costs, waiver of prescription drug user fees[61] and enhanced patent protection.[62] The E.U. has enacted similar legislation to

[61] The Prescription Drug User Fee Act was passed by Congress in 1992 which allowed the FDA to collect fees from drug manufacturers at the time a BLA was submitted to fund the drug approval review process. FDA in turn was required to meet performance benchmarks related to the speed of BLA review process. U.S. Department of Health and Human Services, Food and Drug Administration, "Prescription Drug User Fee Act (PDUFA)," http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

[62] U.S. Department of Health and Human Services, Food and Drug Administration, "Orphan Drug Act," http://www.fda.gov/For Industry/DevelopingProductsforRareDiseasesConditions/

treat rare diseases and conditions, and they also provide marketing exclusivity for up to 10 years post approval.[63]

3.2 Organizational Internal Differences and Conflict.

Another way techno-regulatory systems differ from Hughes's examples is in the importance of conflict and internal power relations within large regulatory organizations. For example, federal agencies such as the FDA, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) are vast and touch many aspects of society. This can make their purpose, goals and procedures seem confusing compared to organizations in the private sector. While corporations are accountable mainly to their shareholders, governmental organizations are less autonomous and are more subject to laws, administrative regulations, executive orders, and outside interest groups.[64] This results in leaders and managers being pulled in different policy directions, which can lead to internal conflicts and power struggles within and between organizations. While some organizations may accept a

---

HowtoapplyforOrphanProductDesignation/ucm364750.htm

[63] Michelle Lang, "Pervasis drug candidate gets EU orphan drug status," Mass High Tech, http://www.bizjournals.com /boston/blog/mass-high-tech/2011/03/pervasis-drug-candidate-gets-eu-orphan-drug.html

[64] Joseph LaPalombara (2001). "Power and Politics in Organizations: Public and Private Sector Comparisons," in Dierkes, M., Berthoin Antal, A., Child, J., and Nonka, (Eds.), *The Handbook of Organizational Learning and Knowledge* (New York: Oxford University Press, 2001).557-581.

newly-implemented policy that applies across multiple organizations, others may argue against it. Power is held unequally by organizations and their members, and its distribution is in constant flux, which can lead to tensions within organizations.[65] For example, for years the FDA regulators have had to consider only the safety and effectiveness of a new drug before granting its approval. Yet quite recently, there have been discussions on whether the FDA clinicians and scientists may need to also assess the financial impact of a drug before granting approval, as is the case in the United Kingdom and Germany, where price is a deciding factor in the approval process. This potential change in review practices would give the FDA new power to influence pricing, which might lead to internal resistance from the FDA staff as well as pressure from the pharmaceutical manufacturers to have their products evaluated favorably to justify the costs of new drugs.[66] If the FDA was mandated to take on this practice of assessing the financial impact, one might expect that U.S. regulatory agencies would be resistant to weighing the cost of a product against the perceived health benefits.

---

[65] Ibid.

[66] Laura Lorenzetti, "Is it time for the FDA to consider cost when it comes to new drugs?," *Fortune, February 4, 2015, accessed March 6, 2016,* http://fortune.com/2015/02/04/is-it-time-for-the-fda-to-consider-cost-when-it-comes-to-new-drugs/

3.3 Large Heterogeneous Organizations, not Tight-knit Independents

In *American Genesis*, Hughes uses the term *inventor-entrepreneurs* to describe independent inventors who customarily worked with few assistants, mostly craftsman, in small workshops or laboratories that they designed and owned, while being free from organizational entanglements.[67] Examples of these "independent inventors" include Thomas Edison, The Wright Brothers and Thomas Bell. Hughes's focus on these independents causes him to overlook the internal pressures within organizations that are often faced by managers who try to maintain a balance of controlling the activities necessary to achieve overall system goals.[68] Organizations are made up of many different stakeholders with each seeking rewards for their efforts, including money, prestige, power, or a sense of accomplishment. While stakeholders cooperate with one another within the organization to produce a good or service, they also compete for the organizational resources. An organization must maintain balance between cooperation and competition among the stakeholders to maintain viability. At times organizational conflict occurs because one group may not have the same goals as

[67] Thomas P. Hughes, *American Genesis: A Century of Invention and Technological Enthusiasm, 1870-1970*, (Chicago: The University of Chicago Press, 2004), 21.
[68] Gareth Jones, *Organizational Theory: Text and Cases* (Boston:Addison-Wesley Publishing Company, 1995),14.

another.[69]

Unlike the inventor-entrepreneur's tightly run shop, the system of drug development does not have a centralized decision hierarchy; instead these organizations are made up of additional sub-organizations who are responsible for their own specialty and decision-making. The organization of the FDA is made up of Centers, Offices, or Divisions with each having its own mission, goals, and culture. The organizational structure of the FDA **(Figure 4)**[70] shows the multiple Offices and Centers within the FDA that are involved in regulating the development, approval, and monitoring of food, devices, and drugs. These different Offices/Centers have different specialties, goals, cultures, and priorities that can potentially come into conflict within or between one another.[71]

[69] Ibid.
[70] U.S. Department of Health and Human Services, Food and Drug Administration "FDA Organization Overview" accessed May 6, 2016, http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm393155.htm
[71] Ibid.

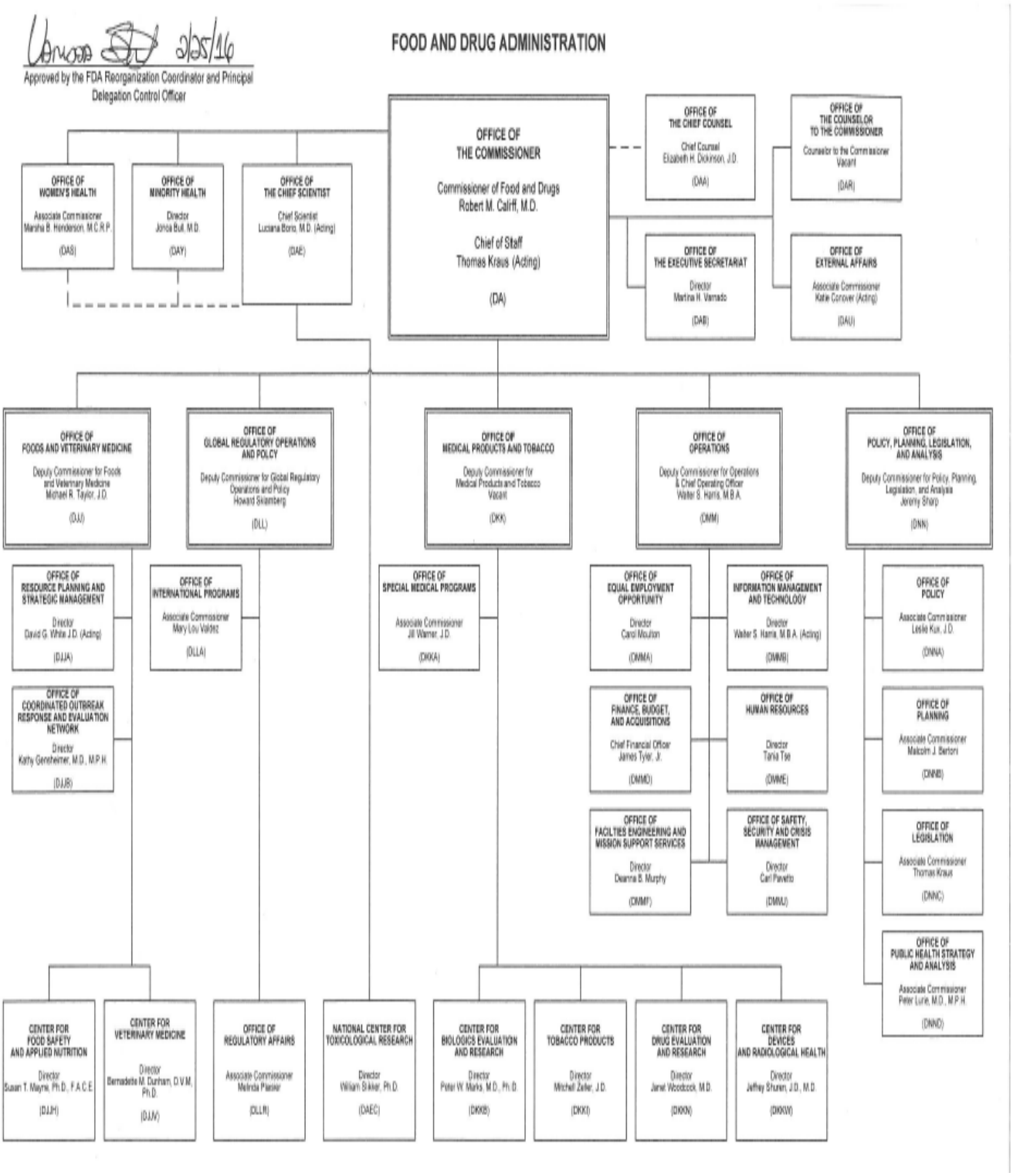

Figure 4: [Public Domain] Organizational Structure of the FDA (2016)

This figure illustrates the many layers of organizations that make up the FDA.

3.4 Internal Conflict in a Techno-Regulatory Environment

One example of an organizational conflict occurred within CBER of the FDA in the Office of Vaccines Research and Review (OVRR). OVRR is responsible for three dominant activities related to preventative and therapeutic vaccines for infectious diseases: (1) taking action on Investigational New Drugs (INDs) and Biologic Licensing Applications (BLAs), (2) developing policies and procedures governing the review of regulated products, and (3) conducting research related to the manufacture, evaluation and development of vaccines and related products for the consumer.[72] Divisions that fall under the authority of OVRR (Figure 5) include the Division of Viral Products, the Division of Bacterial, Parasitic and Allergenic Products and the Division of Vaccines and Related Products Applications (DVRPA). Each of these divisions includes a staff of regulatory scientists, medical officers and research/review scientists who contribute to the review of sponsor's submissions for vaccine development. In DVRPA, personnel are primarily made up of medical officers, scientists and regulatory reviewers who are assigned to review, manage, and support the managed review of a sponsor's IND or BLA

[72] U.S. Department of Health and Human Services, Food and Drug Administration, *Overview of the Office of Vaccines Research and Review*, http://www.fda.gov/downloads/BiologicsBloodVaccines/InternationalActivities/UCM273206.pdf (accessed March 6, 2016).

submissions.[73]

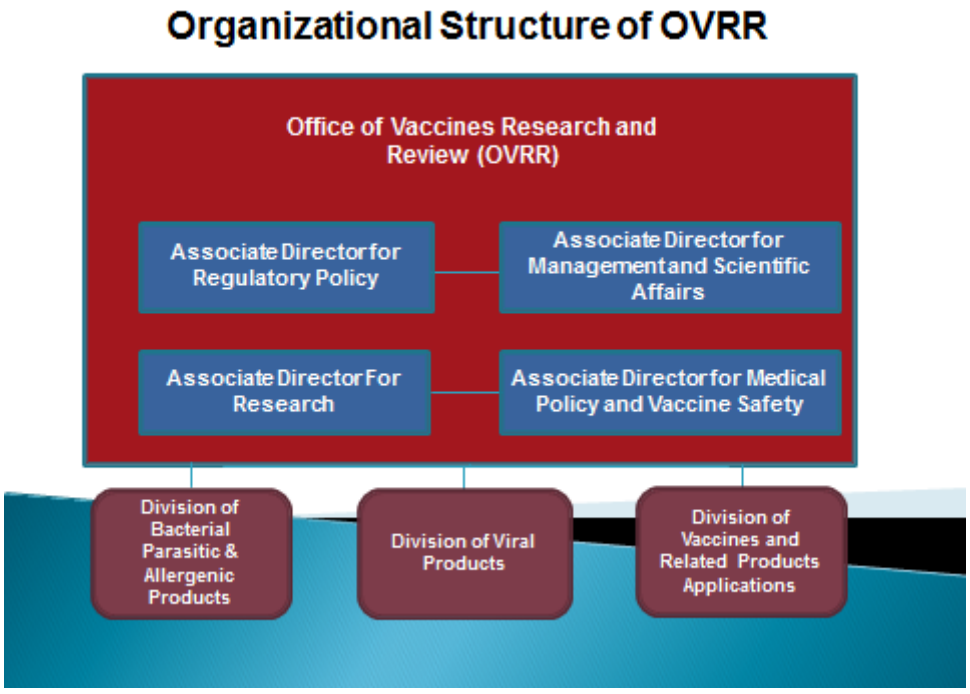

Figure 5: Organizational Structure of Office of Vaccines Research and Review
This figure illustrates the layers of organizations that make up the Office of Vaccines Research and Review

As with any organization, internal conflict can arise. This was the situation within DVRPA/OVRR during the review of the BLA for a vaccine against a pandemic influenza virus, H5N1. Unlike seasonal influenza, from which most people suffer mild to serious infection symptoms, infection caused by pandemics such

[73] U.S. Department of Health and Human Services, Food and Drug Administration, "Overview of the Office of Vaccines Research and Review," http://www.fda.gov/downloads/BiologicsBlood Vaccines/InternationalActivities/UCM273206.pdf (accessed March 6, 2016).

as the H5N1 subtype strains are far more severe, with quick onset of symptoms that cause many persons to develop pneumonia and systemic organ failure.[74] Because of public concern over H5N1, there was pressure to approve a new vaccine, Q-Pan, as soon as possible and under accelerated approval licensure regulations (21 CFR 314, Subpart H) (see Appendix A regarding accelerated approval licensure pathway description) was chosen. Because the approval under the regulatory pathway relies on surrogate markers of efficacy, confirmatory studies are require post-approval in order document true efficacy and convert the drug license to that of traditional (standard) approval.

FDA informed GlaxoSmithKline (GSK) that following the traditional approval of GSK's non-pandemic vaccine, FluLaval (a product that was also approved under accelerated approval regulations, study FLU Q-QIV-006 which studied product made with the same manufacturing process as the Q-Pan H5N1 vaccine, the data from the Flulaval BLA could also serve as the required confirmatory trial information to fulfill the accelerated approval requirements and support the traditional approval of

[74] U.S. Department of Health and Human Services, Food and Drug Administration, "FDA Approves First U.S. Vaccine for Human Against the Avian Influenza Virus H5N1," http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108892.htm(accessed March 6, 2016).

the Q-Pan H5N1 vaccine.[75] On February 22, 2012, GSK submitted to the FDA a BLA containing clinical study reports, publications from two Canadian vaccine effectiveness studies, and other supportive evidence for the Q-Pan H5N1 vaccine to the FDA. During the course of the review of the Q-Pan BLA, the efficacy of GSK's seasonal influenza vaccine FluLaval was confirmed based upon the results of study FLU Q-QIV-006 and was granted traditional pathway approval by the FDA. Following the approval of FluLaval, GSK requested to use the clinical data from FLU Q-QIV-006 in support of the traditional approval of Q-Pan H5N1 vaccine, as previously discussed and agreed to by the FDA.[76]

During the review of the BLA, differences of opinion developed between the assigned BLA reviewers, their supervisors, and the Director of the OVRR concerning the licensure pathway, and whether a confirmatory study was required post licensure.[77] These differences in opinion resulted in a system imbalance and bottleneck that impeded the approval of the BLA. The DVRPA clinical reviewer and her immediate supervisor wrote review memos to the BLA file that expressed their opinion that the effectiveness of the Q-Pan H5N1 vaccine could only be confirmed

[75] Carmen Collazo-Custodio, "Summary Basis of Regulatory Action (SBRA)," U.S. Department of Health and Human Services, Food and Drug Administration, http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM379624.pdf
[76] Ibid.
[77] Ibid.

by a study conducted using the Q-Pan H5N1 vaccine in a scenario where the H5N1 virus is in circulation (e.g., during an H5N1 influenza virus pandemic or outbreak) or in a high risk population, such as poultry workers in a country where the H5N1 influenza virus is endemic. Therefore, they contended that data collected for other influenza virus subtypes (irrespective of the manufacturing process) could only be considered supportive, but not confirmatory. Instead, the reviewer recommended that the Q-Pan H5N1 vaccine be maintained under accelerated approval until such time as its efficacy could be confirmed during an H5N1 influenza virus pandemic or outbreak. The Chemistry, Manufacturing and Control reviewers assigned to the BLA, who concurred with the regulatory strategy proposed by GlaxoSmithKline, expressed a contradictory view. These reviewers recommended allowing study FLU Q-QIV-006 to be used in verifying the clinical benefit of the Q-Pan H5N1 vaccine.[78] OVRR agreed with this review team that the sponsors had provided adequate data to support the safety and immunogenicity of Q-Pan, rejecting the conclusions reached by the assigned DVRPA clinical reviewer, and her immediate supervisor.[79] The OVRR argued that

[78] Ibid.

[79] Marion Gruber, "OVRR Office Director's MEMORANDUM," U.S. Department of Health and Human Services, Food and Drug Administration,http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM378662.pdf (accessed March 6, 2016).

verifying the clinical benefit of GSK's H5N1 pandemic influenza vaccine for traditional approval was met per the guidance provided in the FDA May 2007 Guidance for Industry entitled "*Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines*." In the Director's Memorandum, the Office of Vaccines Research and Review acknowledged DVRPA's argument that there were differences in pathogenicity and clinical disease between the H5N1 influenza virus and seasonal influenza viruses. However, they argued that the biological mechanism for protection from disease is similar to the induction of hemagglutination inhibition (HI) antibodies and that "Numerous independent studies have supported that serum HI antibody titers are associated with protection against influenza A viruses." Furthermore, the manufacturing process of the seasonal influenza vaccine is the same as the pandemic vaccine. Likewise, the Office of Vaccines Research and Review argued that this licensure approach is consistent with previous regulatory decisions related to pandemic influenza virus vaccines, per regulatory discussions in April 2007 for Sanofi Pasteur Inc.'s vaccine for the Strategic National Stockpile.[80] Furthermore, they

---

[80] The Strategic National Stockpile is the U.S. national repository of vaccines, antibiotics, antitoxins and other supplies that can be distributed to address a public health

argued that the February 2007 Vaccines and Related Biological Products Advisory Committee reviewed the pandemic study data and recommended that the data available were sufficient to support the safety and effectiveness of the vaccine. The Office of Vaccines Research and Review overruled the decision made by DVRPA and determined that the traditional pathway would be the approach used since the same manufacturing process is used with a U.S. licensed seasonal influenza virus and the clinical benefit of the Q-Pan H5N1 vaccine could be verified from the efficacy data generated with FluLaval.

The internal organizational conflict described above is just one example of how managers try to maintain a balance of controlling activities necessary to achieve the overall system goals despite internal and external pressures. Furthermore, Hughes's LTS methodology does little to investigate the rules, procedural directives in place and the collaborative process that organizations follow when addressing internal conflict and how these decisions may have influenced certain outcomes. While the individual BLA reviewers assigned were responsible for the regulatory decision to determine if the data provided in the BLA was adequate to approve the BLA, the OVRR was pulled in many

---

emergency (flu outbreak, earthquake, and terrorist attack) when local supplies run out. Centers for Disease Control and Prevention "Strategic National Stockpile (SNS)," http://www.cdc.gov/phpr/stockpile/stockpile.htm.

different policy directions to address its larger number of stakeholders that included internal staff, drug industry, the public and other environmental components. OVRR had to take into consideration the actors affected by the decision of which licensure pathway to use to help avoid immediate conflict, while trying to not alienate other actors, which could lead to conflict later. The Director's memorandum acknowledged the DVRPA reviewer's concerns and the reasons for the disagreements, but still granted traditional approval to GSK's Q-Pan H5N1 vaccine.

3.5 The Package Insert: A Collaborative Process

A drug package insert provides detailed information on product administration, use, and risks and is compiled and distributed by the drug manufacturer for the use of consumers, healthcare providers and others.[81] There are regulations, such as the biological products regulations under 21 Code of Federal Regulations 600s, which describe the required contents of a package insert that drug manufacturers must follow to ensure drug system compliance. The information in the package insert is used by the manufacturer to help with advertisement claims, but also limits the product claims that can be made. From a typical

[81] Robert H. Vander Stichele, "*Impact of written drug information in patient package inserts: Acceptance and benefit/risk perception*," *Doctoral dissertation., Ghent University*, 2004, Accessed March 3, 2016, https://books.google.com/books?isbn=9038206186

150,000 to 225,000 page biologics license application (BLA), key information is condensed into a twenty to thirty page document that provides the approved chemical and proprietary names, product description and classification, clinical pharmacology, approved indications and usage, contraindications, warnings, precautions, manufacturing facilities authorized to produce and handle the product, adverse reactions, dosage and administration, and appropriate references.[82] The package insert is negotiated between the manufacturer of the product and the assigned FDA review team. As part of the licensure process, the drug manufacturers provide a draft package insert, which follows the FDA's labeling guidance on certain content and format requirements, to the FDA for review and consideration. Various labeling guidances are publicly available and posted on the intranet for drug manufacturers, drug industry labeling consultants, and health care agencies to reference and ensure labeling standards are met. Application reviewers from a broad range of disciplines and work divisions review the draft package insert to ensure it meets regulatory requirements. As part of the review process for a package insert, reviewers from various disciplines (Figure 6)[83] are required to assess whether the

[82] The Free *Dictionary by Farlex. Package Insert.* Accessed May 9, 2015. http//medical-dictionary,thefreedictionary.com /package+insert.

[83] U.S. Department of Health and Human Sevices, Food and Drug

supportive data and analyses are relevant and appropriate.

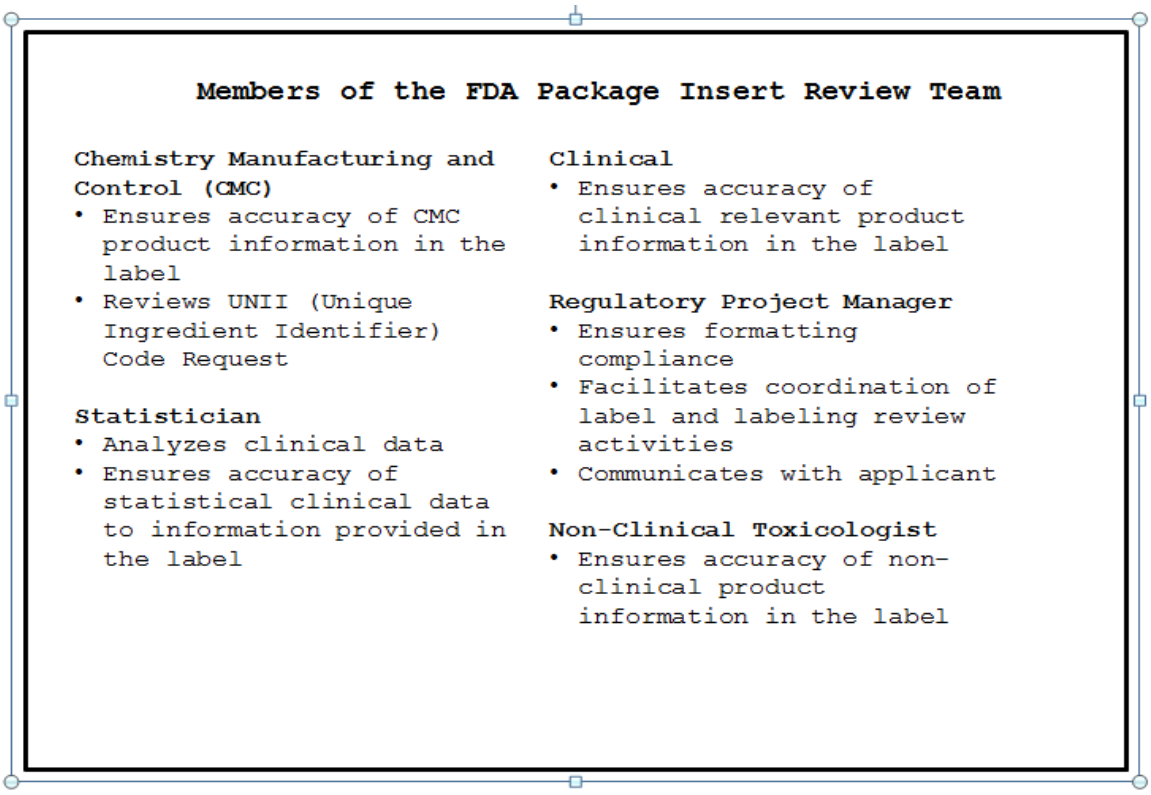

Figure 6: Members of the FDA Biologics Package Insert Review Team
This figure lists a typical review team assigned to review a package insert and the work responsibilities of each member.

The reviewers check the text for accuracy, missing relevant information, and fraudulent or promotional claims, and suggest or require certain revisions to the proposed package insert. Next, there are negotiations that often consist of a series of back and forth communications resulting in a compromise between

---

Administration, Center For Biologics Evaluation and Research *SOPP 8412: Review of Product Labeling*, http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM277726.pdf

the drug manufacturer and the FDA. After a drug product is approved, drug product changes, manufacturing changes, or any other type of change that may impact the drug product must be reported to the FDA and the package insert updated with this information.[84]

At times, labeling changes include changes to promotional materials that again require mutual compromise between the FDA and the drug manufacturer or the entire drug industry. One example of such a compromise includes the use of a "Latex-free" labeling statement in the package insert and on the carton label. Under 21 CFR 801.437 there is a requirement for drug manufacturers to include a statement in product labeling when latex is used in their products, but there is no regulation allowing a drug manufacturer to claim a product is 'latex-free' when latex is not part of the product.[85] So, the drug manufacturer could not normally insert a claim in the labeling unless they demonstrate it was relevant to the safety, efficacy, or manufacture of the drug product. One vaccine manufacturer; Sanofi Pasteur, argued that having this latex language on the

[84] Code of Federal Regulations, Application for FDA Approval to Market a New Drug, Title 21, sec. 314.70.
[85] U.S. Department of Health and Human Services, Food and Drug Administration, (2014) *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex - Guidance for Industry and Food and Drug Administration Staff, http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm342872.pdf*

carton was useful information for health care providers since allergies to latex are relatively common and can be life threatening. The FDA compromised and allowed this information in product labeling. Thus, Sanofi Pasteur prominently marketed the latex-free text in the product labeling (Figure 7). This example shows that while the manufacturer had to follow labeling regulations, the FDA does allow exceptions by accommodating drug industry if a case can be made that the information presented in the labeling is for the better good of the public.

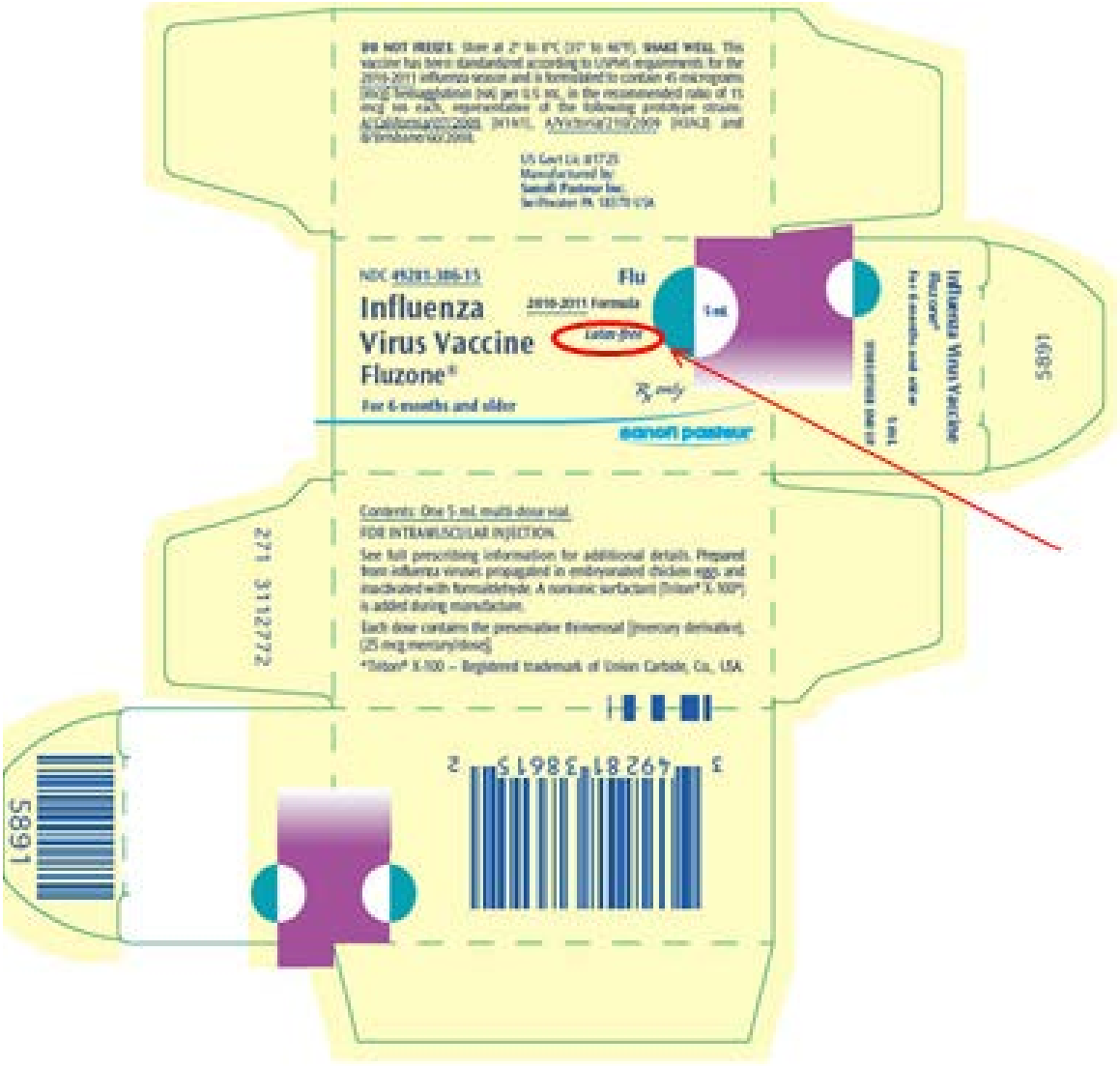

Figure 7 [Fair Use]: Fluzone Carton Label[86]
This figure is an image of Sanofi Pasteur's 5 mL Fluzone® vial container with the words "latex-free" circled to show promotional wording.

3.6 Drug Development: A Collaborative Effort.

The package insert is just one example of mandatory collaboration within the drug development and approval system. An overview of the system as a whole shows sharp differences

[86] Drugs.com, *Fluzone*, http://www.drugs.com/pro/fluzone.html (accessed March 6, 2016).

from Hughes's paradigmatic cases. Hughes's examples include independent inventors who customarily work with few assistants and often own the organization. In contrast, many people today have a stake in the system of drug development. Throughout the process of drug development, regulators and industry work together in the development of a drug. This collaborative effort goes back to the Biologics Act of 1902, which was created following the death of several children from contaminated smallpox vaccines and diphtheria antitoxins in 1901, and required that the federal government grant premarket approval for every biological drug and the facilities that produce them.[87] Before this Act, premarket control did not exist in the U.S.[88] The control described in the Biologics Act of 1902 occurs from the very early stages of drug research and development for a potentially promising drug to well after approval and marketing of a drug to the consumer. In early product development, a drug manufacturer often tests the investigational product in animals to study the safety, immunogenicity, and proposed dosage. Not all sponsors conduct their own pre-clinical investigations, but instead may contract them out. These contract organizations specialize in certain drug development functions, and may be

[87] Henry Miller, "Failed FDA Reform". *Regulation* 21 (1998)(3), accessed March 6, 2016, http://object.cato.org/sites/cato.org/files/serials/files/regulation/1998/7/v21n3-ftr2.pdf
[88] Ibid.

more cost-effective or provide better reliability in being compliant with current regulatory standards. When a product shows promising results, the next step is usually to study the investigational product in humans by submitting the preclinical testing information and a protocol to conduct the studies in humans as an investigational new drug application (IND).

The FDA reviews the submitted IND information to make a determination if the investigational product can move forward to be studied in humans or if the proposed clinical study should be placed on clinical hold (e.g., due to patient safety concerns). A clinical hold is an order issued by the FDA to the sponsor to delay a proposed investigation or suspend an ongoing clinical investigation. When a study is placed on clinical hold, no investigational drug may be given and no new subjects may be recruited to participate in the study. Study subjects are not allowed to receive the investigational drug unless specifically permitted by the FDA in the interest of patient safety. When product information is submitted to the FDA in the form of a new IND, the FDA reviews the material to assure the safety and rights of subjects. In later phases of drug development (Phases 2 and 3), the FDA assures that the quality of the scientific investigation of a drug is adequate to permit an evaluation of the drug's effectiveness and safety, and that the investigations will yield data capable of meeting statutory standards for

marketing approval.[89] Reasons for placing clinical studies on hold include the following 1) an unreasonable and significant risk of illness or injury if exposed to the investigational drug, 2) the clinical investigators named on the IND are not trained and qualified, or 3) the investigator brochure is misleading, erroneous, or materially incomplete; 4) lack of sufficient information for the FDA to assess the risks to subjects.[90] The reviewers assigned to the IND make the determination of whether the product information and clinical data provided from one phase of an investigation support proceeding towards the next phase of clinical investigation.

A BLA is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce, and a BLA is submitted after the FDA requirements at the earlier stages of IND development have been met.[91] During the review of the BLA, questions often arise and communication between the FDA and manufacturer flows two ways to ensure information is shared and all requirements are addressed. Furthermore, the FDA takes into consideration the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks,

[89] Investigational New Drug Application, 21 C.F.R.§ 312.42 (2015)
[90] Ibid.
[91] U.S. Department of Health and Human Services, Food and Drug Administration, "Biologics License Application (BLA) Process (CBER)" Last Modified November 5, 2015, http://www.fda.gov /BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/default.htm (accessed March 8, 2016).

and data obtained during the developmental phase of the drug.[92]

At times, interactions between the sponsor and the FDA can become heated. For example, this can happen during the IND stage if the clinical trial is placed on hold or if additional safety study information is requested but the manufacturer disagrees. This can cause IND delays moving forward to the next phase of development. Another delay can occur during the BLA stage if a Complete Response letter is issued because additional information is needed and another nonclinical or clinical trial is requested. To help ensure system alignment and avoid conflicts, sponsors often request or are encouraged by the FDA to request formal meetings (such as teleconferences or face-to-face conferences) with the FDA to discuss product and clinical development and to avoid potential disagreements and/or development delays. The document *Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants of Prescription Drug User Fee Act (PDUFA) Products* explains three different kinds of meetings that may be held between sponsors and the FDA on various topics depending on the stage of development such as pre-investigational new drug application meetings, end of phase 2 meeting, and pre-new drug application or pre-biologics licensing application meetings.[93] The purpose of

[92] Investigational New Drug Application, 21 C.F.R.§ 312.42 (2015)
[93] U.S. Department of Health and Human Services, Food and Drug

these meetings maybe to address outstanding questions, resolve identified problems, facilitate the evaluation of drugs or agree on a potential regulatory pathway forward towards licensure. The meetings provide a mechanism that both the FDA and drug sponsor can use to communicate and avoid or resolve system flow impediments. The centrality of these meetings to the drug development process illustrates the fundamentally collaborative nature of the system.

3.7 Improved Systems Theory Approach: Large Technological Systems and Organizational Theory Principles Combined

While Hughes's Large Technological Systems (LTS) provides a conceptual framework for investigating large infrastructure and production systems, it lacks certain investigative principles. Techno-regulatory systems are very complex, and applying only one theoretical approach to investigate a techno-regulatory system may overlook key knowledge. One theory that could help strengthen Hughes's Systems Theory to address today's modern systems is Organizational Theory. Organizational Theory is the study of how organizations function and how they affect and are affected by the society in which they operate and by the people

---

Administration. *Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,* (2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM437431.pdf

who work in them.[94] Within an organization, a system of rules, tasks, and authority relationships control how people use resources and cooperate to achieve organizational goals. The principle of Organizational Theory is to control the actions of staff and the means used to motivate people to achieve the organization's goals. By applying the principles of Organizational Theory to Systems Theory one can investigate the collaborations between the different organizations and the inner workings of each organization to reveal how these technical systems function, respond to societal influences, and affect society. For example, organizational power is (according to Max Weber) the ability of one person or group to overcome resistance by others to achieve a desired objective.[95] By virtue of their positions within an organization, actors may wield powerful tools to bring about outcomes they desire over the opposition of other actors, as was the case with OVRR and its overriding decision.[96] Organizational Theory also provides a set of ideas and study methodology to investigate how people interact in groups.[97] In any type of business, it is important to understand the principles of how employees act around one another,

[94] Gareth Jones, (1995). *Organizational Theory: Text and Cases* (Boston:Addison-Wesley Publishing Company, 1995),14.
[95] Ibid.
[96] Ibid.
[97] Tiffany Wright, "Principles of Organizational Theory," Small Business Chron, http://smallbusiness.chron.com/principles-organizational-theory-75374.html

including how they act towards management and what motivates employees, such as performance incentives.[98] Furthermore, Organizational Theory contributes to the investigating and exploring the rules within an organization. In a techno-regulatory system this Organizational Theory contribution can help to understand an implemented rule, why an organizations criterion was or was not met which led an organization to make a decision that impacted the drug development system.

The focus of Organizational Theory has shifted over time from the hierarchic structures of the industrial age to the broader, less stringent structures of today's technological modern age. Theories that have contributed to and become enmeshed in the principles of Organizational Theory include the Classical Organization Theory, Bureaucratic Theory, Administrative Theory, Contingency or Decision Theory, and Modern Systems Theory.

Classical Organization Theory includes a combination of basic principles of Administrative Theory, Scientific Management and Bureaucratic Theory. Bureaucratic Theory and Administrative Theory were built upon the principles of a specified standard in that a scientific method exists to perform each task; employees are to be closely supervised and workers are to be

[98] Ibid.

selected, trained and developed for a certain task.[99] Followers of Contingency Theory, also referred to as Decision Theory, view conflict as manageable. This theory espouses the principle that organizations act rationally and linearly to adapt to environmental changes. Contingency Theory assesses management effectiveness by evaluating management's environmental adaptation abilities. In addition, in volatile industries, managers at all levels must have the authority to make decisions in their area, contingent on what is happening. Companies and managers must adjust their managerial styles and techniques based on the conditions occurring around them.[100]

The foundation of Modern Systems Theory is the principle that all of an organization's components interrelate nonlinearly; therefore, making a small change in one variable impacts many others. A small change can cause a huge impact on another variable or large changes in a variable can cause a nominal impact. Another principle is that organizations operate as open systems in dynamic equilibrium as they constantly adjust and adapt to changes in their environment.[101] Hughes's Systems Theory can be improved by incorporating some principles of Organizational Theory, in particular its observations about the importance of rules, organizational culture, and national or

[99] Ibid.
[100] Ibid.
[101] Ibid.

international context.

Actors within the drug development system collaborate with one another much more today than they did a half-century ago. The federal government, often fund academic drug research, and government organizations such as the NIH, which contains 27 individual Institutes and Centers, and are the largest contributors of funding for research in the world.[102] Even though these funds are dispersed among many actors, no sole authority exists to control the organizations receiving these funds. Instead, control is dispersed among many other actors, including the drug industry, the FDA, Institutional Review Boards, Congress, drug contracting corporations, and study advocacy groups. All of these organizations fall into one system of collaboration, from the research funding, to the development of the drug product, to having industry transform the academic drug product into a good and/or service that is used by the public.

While the practical goal of drug development is bringing drugs to market, which drives the intellectual focus of demonstrating safety and efficacy, each system component has its own agenda stemming from its own goal.[103] For example, the drug

[102] U.S. Department of Health and Human Services National Institutes of Health, "Turning Discovery into Health," http://www.nih.gov/about/

[103] Joga Gobburu, "*Learn-Apply Paradigm: Re-Configuring Drug Development Goals,"* U.S. Department of Health and Human Services, Food and Drug Administration, http://www.fda.gov/down

industry may be more focused on the development of a long-term use product that has the potential for large profits, while academics, such as Baylor College of Medicine, may focus their goals on generating drug research, publications, and new knowledge. While academia and industry have some converging interests, especially in the wake of the 1980 Bayh-Dole Act that allowed universities to profit from patents on government-funded research, there are still important differences in their goals and incentives. Consumers, in turn, may push for the development of a drug technology for specific ailments, such as cancer, autism, and others. In response to the environmental pressures, institutions like the NIH may change the focus of their research funding to meet public interest. All of these factors are taken into consideration when exploring the development of a technology and the actors' individual goals and influences on the development of a technology.

One way in which Organizational Theory can add insight to LTS Theory is by drawing attention to the way rules, tasks, and authority relationships control people to align their behavior with an organization's overall goal.[104] For example, to better understand the decision making process as it relates to the

---

loads/Drugs/NewsEvents/UCM209136.pdf

[104] Gareth Jones, *Organizational Theory: Text and Cases* (Boston: Addison-Wesley Publishing Company, 1995),12.

changes, development or perhaps non-development of a technology, one should be aware of the written rules, procedural directives, mission and penalties that each organization or sub-organization has in place. Do the decisions come from management down through the hierarchy to employees, who are then given a set of strict guidelines to follow, or are employees empowered to make decisions but management is brought in for larger issues?[105]

In a techno-regulatory system many different sub-organizations may be involved in the development of a technology, each with its own management style. Unlike private organizations, government organizations such as the FDA post their standard operating procedures publicly on their home web page, which allows both the FDA employees and those outside the organization to review these operating procedures. These posted standard operating policies and procedures cover not only procedures that the FDA overall needs to follow but procedures specific to each Office and/or Division for use by staff in the performance of their duties. These standard operating procedures and policies show the public how governmental organizations operate, which leads to public scrutiny of the FDA, e.g., if the actions of an FDA element does not follow the written norm. This

[105] George N. Root, "Differences Between Horizontal & Vertical Organizations," Chron Small Business, http://smallbusiness.chron.com/differences-between-horizontal-vertical-organizations-20335.html

gives formal rules extra importance in the functioning of techno-regulatory systems.

Another variable highlighted by Organizational Theory is the values, norms and culture of an organization, which may be transmitted through employee performance reviews, teaching, peer pressure, and socialization, and which help the organization meet its goals and objectives. One normative goal for drug regulation is that the FDA's process for making decisions on the development of a drug technology must be consistent across all drug manufacturers, especially since their decisions are public and will be scrutinized by the drug industry. For example, when a new drug is approved, the product's package insert is posted on the FDA website along with the regulatory documents generated by the FDA that are relevant to the approval. This leads to a flurry of activity by the drug's manufacturer, (including the launching of product ads) and news reports and by the drug company competitors who evaluate the reviews and the package insert for wording that could be viewed as a marketing advantage over their product. If inconsistency between drug manufacturers is noted or the package insert wording puts any drug manufacturer at a marketing disadvantage, they may complain to the Agency and the FDA office responsible for approving the product and packet insert may need to argue their position as to whether consistency between different drug manufacturers was

maintained. To ensure consistency in the treatment of drug manufacturers, organizations such as the Center for Drug Evaluation and Research have review teams' recommendations reviewed by discipline-specific supervisors or team leaders, the division directors, and at times the office directors before they are finalized.[106] This process shapes work behavior and ensures that a drug application is viewed from many different perspectives and concerns. More experienced reviewers teach new review team members to perpetuate the organization's knowledge base and status quo.[107] This helps to ensure that work standards are being upheld between the different manufacturers and consistency is maintained.

3.8 International Techno-Regulatory Systems Differences

Techno-regulatory systems of drug development are especially complex when developing a drug technology for use internationally, which often occurs with many large multinational pharmaceutical companies.[108] When these large drug manufacturers submit an investigational drug to a regulatory

---

[106] U.S. Department of Health and Human Services, Food and Drug Administration, "*Office of the Center Director: Resolution of Disputes: Roles of Reviewers, Supervisors, and Management Documenting Views and Findings and Resolving Differences, Manual of Policies and Procedures MAPP 4151.1*," http://otrans.3cdn.net/8eaee20f2088e70485_38m6iyd3k.pdf

[107] Ibid.

[108] "Global 2000: The Biggest Drug Companies of 2014," *Forbes*, www.forbes.com/pictures/eedh45fhhmf/no-1-pfizer

agency such as the European Medical Agency to seek approval, they often simultaneously submit another application to a regulatory agency in another country for the same or similar product. The application, language and technological setup of each application submitted must be formatted and geared towards a particular country's drug application requirements. To minimize regulatory differences between countries and to avoid duplicating many time-consuming and expensive test procedures, drug companies follow International Council for Harmonisation guidance. In response to rising health care costs, public expectations and increased research and development costs, in the 1980's the European Union (E.U.) began to harmonize the regulatory requirements for safety, quality and efficacy to encourage the development of a single market for pharmaceuticals. This led to a meeting in April 1990 in Brussels that included regulatory agency representatives from Europe, Japan, the U.S. and many from drug industry.[109] This collaborative approach eventually produced the Common Technical Document (CTD), which provides a standardized format where specific IND and BLA information is to be placed in specific modules for ease of review. This standardized format by the E.U., Japan and the U.S., eliminates the need for applicants

[109] "ICH Harmonization for Better Health, History," accessed March 6, 2016, http://www.ich.org/about/history.html

from the drug industry to reformat the information for different regulatory authorities.[110] By responding to public concerns and rising health care costs, the harmonization of testing standards has resulted in less repetitive animal tests being performed and has revolutionized the regulatory review processes to shorten the review time needed to introduce the drug product to the market. For industry, it has eliminated the need to reformat the information for submission to the different international regulatory authorities saving time and money for them and perhaps the consumer.

As captured in Figure 8, international differences in regulation remain, so system components must have the flexibility to adapt to different markets. For example, drug industry needs to address both the U.S. and the E.U. regulatory requirements, environmental influences (actors outside the system), and reverse salients, if they intend to market the drug product in both countries. The needs of the American Medical Association (AMA) and the European Medical Association (EMA) along with any cultural differences between countries must be met. Drug industries quite often request from the different regulatory agencies that study information from other countries be used as supportive information when seeking a drug indication

[110] "ICH Harmonization for Better Health, M4: The Common Technical Document," accessed March 6, 2016, http://www.ich.org/about/history.html

to lower cost and redundant testing. These regulatory differences between different geographical regions may include the manufacturing process of a product, product testing, safety, efficacy standards, and research ethical guidelines.

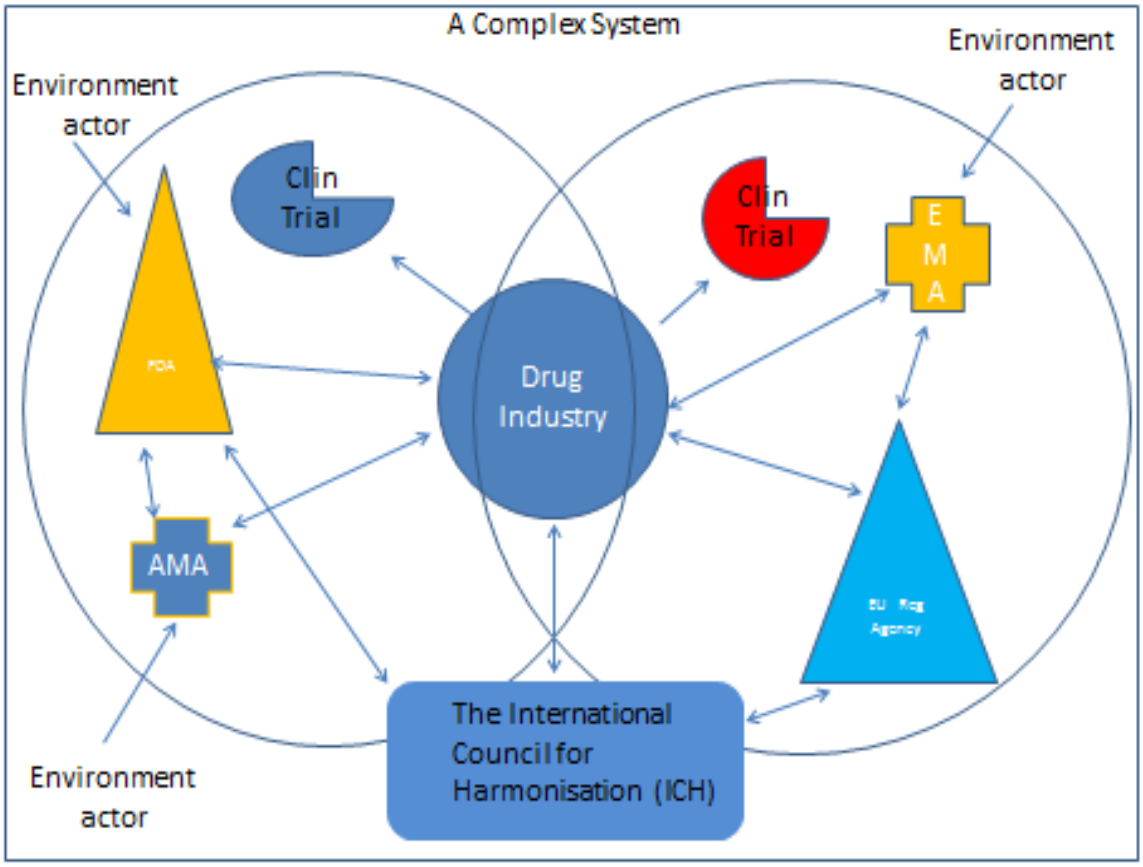

Figure 8: A Complex System
This figure illustrates different international regulatory, environmental, and overlapping challenges actors must overcome for a drug technology to develop.

Suppose, for example, that a drug manufacturer has a goal of submitting a new investigational drug product for an adult indication and has no interest in pursuing a childhood

indication because adult drug trials may be easier to conduct and have fewer ethical and liability challenges than pediatric drug trials. In the U.S., current legislation provides drug manufacturers with the option to waive or defer the research conducted in the pediatric population until years after drug approval in adults or perhaps not at all. In contrast, the E.U. requires studies for all pediatric indications and conditions for which the medicinal product may be useful.[111] These legislative differences can influence the decision as to whether and where to pursue approval of a drug technology. For example, a drug manufacture may decide to develop a drug technology strictly in the U.S. and not in the E.U. to avoid conducting pediatric trials altogether, or to seek a pediatric indication after approval and marketing of the product for adults when the product is well recognized by the public and it is a better financial position from product sales. Alternatively, because the E.U. requires studies on all pediatric indications, pediatric study discussions and collaboration between the drug manufacturers and the E.U. regulatory agency may take place

[111] Julia Groger, "*Studiengang, Master of Drug Regulatory Affairs Master Thesis Comparison of the Pediatric Drug Legislation between US and EU Food and Drug Administration safety and Innovation Act (Title V) versus EU Paediatric Regulation (EC) NO 1901/2006"*(master's theses, Kooperation Universitabonn 2014) accessed March 6, 2016, http://dgra.de/deutsch/studiengang/master-thesis/2014-Julia-Gr%C3%B6ger-Comparison-of-the-Pediatric-Drug-Legislation-between-US-and-EU-F?nav=studiengang

earlier than discussion with the FDA.

Since many large U.S. drug manufacturers have geographical locations in the U.S., Asia and Europe, they must be knowledgeable about manufacturing regulations in all of the regions that they market their products to. System components involved in manufacturing in an international technological regulatory system are more heterogeneous than the examples provided by Hughes. In order to minimize regulatory conflicts and avoid reverse salients, a drug company might establish multiple manufacturing sites in different regions to allow it to tailor its manufacturing location to the regulatory environment. An additional complication is that pediatric drug development today often involves the conduct of clinical trials outside the U.S. Drug manufacturers may choose to conduct drug trials in developing countries for many reasons including substantial cost savings. The cost to conduct a clinical trial in India may be one-tenth of the cost in the U.S.[112] Also, certain diseases may be more prevalent in developing countries than in the U.S., making study subject recruitment easier.[113] The prescription drug Cetirizine (Zyrtec®), to treat urticaria, perennial and seasonal

[112] Andre Ourso, "Can the FDA Improve Oversight of Foreign Trials?: Closing the Information Gap and Moving Towards a Globalized Regulatory Scheme," *Annual of Health Law* 21 (2012): 2, accessed March 6, 2016, http://lawecommons.luc.edu/cgi/viewcontent.cgi?article=1008&context=annals

[113] Ibid.

rhinitis in children, is just one example of a drug that had clinical trials conducted in the U.S. and other countries to support licensure.[114] Conducting studies abroad creates even more challenges to avoid deviations from U.S. drug approval standards and maintaining cultural norms in each country where study sites are conducting pediatric subject recruitment into studies. Other system complexities include international differences in the roles of reviewers in the review process and differences in decisions about data needs to determine the safety and effectiveness of a drug. For example, as shown in Table 1, different regions rely on different scientific methods to determine the safety and effectiveness of a technology. In Japan, there is considerable statistical information used in the popular press and on television, as part of Japanese culture, but biostatistics is given low importance in drug approval process.[115] In the U.S., much emphasis is placed on data that help determine the statistical significance when deciding to approve or not approve a drug product.[116]

---

[114] "Zyrtec Product Information" UCB Pharma, accessed March 6, 2015, https://gp2u.com.au/static/pdf/Z/ZYRTEC-PI.pdf
[115] Thomas J. Cook, "Differences in Clinical Drug Development in Europe, Japan, and the United States: A Biostatistician's Perspective," *Therapeutic Innovation & Regulatory Science* 29 (1995) 4 accessed March 6, 2016, http://dij.sagepub.com/content/29/4/1345
[116] Ibid.

Professional Environment			
	Japan	**Europe**	**U. S.**
Statistical information in popular culture	Much	Some	Little (except in sports)
University department of biostatistics	Very few	Few	Many
Educational emphasis in training biostatisticians	Theoretical	Theoretical	Applied
Importance of biostatistics in drug approval	Little	Some	Much
Biostatisticians in the pharmaceutical industry	Very few	Few	Many

Table 1 [Fair Use]: Professional Environment[117]
This table provides the cultural differences concerning statistics and how cultural differences can influence the regulatory process

Unlike in Europe and the U.S., in Japan most biostatistians do not have advanced degrees and often are taught on the job. While this helps to ensure statistical consistency within a Japanese agency, it may limit the statistical methods that can be used in drug development in Japan as compared to Europe and the U.S. These educational differences affect the conduct of

[117] Thomas J. Cook, "Differences in Clinical Drug Development in Europe, Japan, and the United States: A Biostatistician's Perspective," *Therapeutic Innovation & Regulatory Science* 29 (1995) 4 accessed March 6, 2016, http://dij.sagepub.com/content/29/4/1345

clinical trials as well as regulatory requirements.[118] Furthermore, drug development phases are carried out in specific order in Japan, with one development phase being completed before moving on to the next phase of development. Yet, in Europe and the U.S., this is not a requirement, and a later phase of drug development can begin before an earlier phase is completed to shorten product development time.[119] While Hughes discussed how "technological style" varied between countries, in his examples each system was confined to a single country and responded to local constraints. In contrast, the development of drug technology in an international techno-regulatory system is much more complex and makes system alignment much more challenging. Use of the principles of Organizational Theory to investigate and understand the networks of interactions that take place within different organization, can reveal why and how an organization behaves a certain way in a given environment and in a different set of circumstances.

3.9 LTS and Collaborative Theory Principles Combined: A Suggested Improved Approach

I have argued that Thomas Hughes's existing Systems Theory can be improved by incorporating some of the principles of Organizational Theory. However, incorporating the principles of

[118] Ibid.
[119] Ibid.

Collaborative Theory can also make additional improvements, since pediatric drug development depends heavily on collaboration.[120] Within a complex open system such as drug development, collaboration between actors varies in terms of level and degree of integration with cycles of inquiry.[121] As an investigational drug product advances through phases of development, more actors become part of the product's techno-regulatory system. This leads to an increase in collaboration between system actors, and with it system momentum (relationship between technology and society over time). When a product reaches late phase development, more system actors become invested in the success of the process, which increases the system's momentum. Higher cost and greater actor involvement in later drug development demands greater degrees of connection, responsibility and accountability.[122] For example, small errors such as a drug manufacturer's printing the product labeling before all parties (drug industry and regulatory agencies) agree to the final wording can result in tens of thousands of dollars in lost revenue and the termination of those responsible. Furthermore, ensuring that all required tasks and perhaps

[120] Rebecca Woodland, and Michael S. Hutton, "Evaluating Organizational Collaborations: Suggested Entry Points and Strategies," *American Journal of Evaluation* 33 (2012): 366-383.
[121] Ibid.
[122] Woodland, "Evaluating Organizational Collaborations: Suggested Entry Points and Strategies," 366-383.

personal goals have been completed before approving a product helps further spur drug development activity. With the increased activity of the system comes more scrutiny of system actors by the larger public. At this phase in development, any technological delays or safety concerns can tarnish the public's perception of both the drug industry and regulatory agencies.

Collaborative Theory can help to identify and map communities of practice or teams who have the responsibility for making key decisions or establishing policy that is to be followed in carrying out certain tasks and activities that are central to the organization.[123] Once these teams and committees are identified, one can investigate the strategic alliances of the team, their relative importance for the system's vision, mission, and goals, as well as the systems primary purpose and task.[124] Using this theory can led to quicker product approval time, improvements in policy, ensuring the inclusion of overlooked actors, and building actor relationships to tackle complex issues that often occur in the technological regulatory system of drug development.[125]

Unlike the drugs that were developed in the mid to late 1800's like Stanley's Snake Oil, which claimed to treat rheumatism, neuralgia, sciatica, lame back, lumbago, contracted

[123] Ibid.
[124] Ibid.
[125] Ibid.

muscles, toothache, sprains, swellings, etc.,[126] drug development today is not a "closed system". Compared to the past, today's system of drug development, is much more of an "open system" that requires actors' collaboration to reach goals, accomplish tasks and address societal issues.[127] Data needed to support a drug claim requires the collection of information across many disciplines other than drug industry and the FDA, which may include the scientific community, universities, research councils, hospitals, clinics, scientific, and clinical experts and more. Actors involved in drug development often come together to support the innovation of new drugs for use as a new disease indication. While drug development in the past may have been possible with just a few individuals selling the product directly to the consumer, drug developers today could not and would not be allowed to do this alone.

Despite the weaknesses, Hughes's LTS Theory was chosen over others because the research methodology used is able to unravel the diverse efforts of the many actors who are part of the system of drug regulation, and the actors who are part of the environment that contribute to the complex shaping and

[126] Joe Nickell, "Peddling Snake Oil". The Committee For Skeptical Inquiry, http://www.csicop.org/sb/show/peddling_snake_oil/

[127] Woodland, "Evaluating Organizational Collaborations: Suggested Entry Points and Strategies," 366-383.

functioning of the sociotechnical construction process of drug development. Other theory approaches if used, may be too narrowly focused and overlook actors who may not be the main players in the drug development process, but play a significant role in shaping the system. Furthermore, by incorporating the principles of Organizational and Collaborative Theory with Systems Theory, a better overall investigative approach towards an understanding of actor collaboration, interactions, and intra-organizational and inter-organization dynamics within a techno-regulatory system can be used. This improved LTS approach can help better explain why the practice of drug research excluded children for so long and why it did eventually change. First, however, we need to know how and why the drug regulation system came to be as it is today.

Chapter 4: A Historic General Overview of the Regulatory Drug Approval Process

In this next section, I discuss the history of drug development, and the changes that have taken place over the years concerning the system of regulatory drug development. Drugs help millions of people by treating or preventing diseases that both adults and children experience that would otherwise cause pain and suffering while diminishing the quality and length of a person's life. While pharmaceuticals are important products that save lives, incorrect administration of them can result in serious damage or even death. Because of these concerns and the history of deaths that have resulted from mishaps involving pharmaceuticals, modern governments strictly regulate the research, development, manufacturing, and delivery of drug products.

In the United States (U.S.), drug development, safety and efficacy are under the purview of the Food Drug Administration (FDA), but government organizations are not the only system regulators. The system of drug development consists of many actors who may influence the regulatory process. Besides the FDA these include the drug industry, clinical research organizations, the American Academy of Pediatrics (AAP), legislators, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), academic

researchers, investigational review boards, advocacy groups, and the general public. These actors view the regulatory process through the lens of their own individual goals. Some may look at the approval of a drug as a source of monetary gain, while others may view it as introducing technology to address a public health need.

The system of drug development began well over a hundred years ago, beginning with family home remedies and the selling of drug products from the back of horse drawn carts. By 1890, drug research was being conducted at universities. Scientists at the University of Berlin found that when certain animals were injected with diphtheria and tetanus toxins, they produced antitoxins that provided these animals with immunity against diphtheria and tetanus. This led them to try inoculating other animals and eventually led to the discovery that humans could also be inoculated with these antitoxins and that the serum containing these antibodies could prevent these diseases. A sample of diphtheria toxin was sent from Europe to the Hygienic Laboratory (later called the NIH in 1930 by the Ransdel Act) in Washington D.C., where the immunization of horses yielded large quantities of the serum to meet the public need for vaccination.[128]

[128] Ramunas Kondratas, *"Biologics Control Act of 1902". In The Early Years of Federal Food and Drug Control,* 8-27. (Madison,

The production, testing, standardization and application of this type of therapeutic product began with the public health departments. Before 1902 any person with a little nerve and ambition could work autonomously to produce and sell drugs.[129] These individuals created their own drug concoctions to sell while promoting unproven medical claims about the product.[130] However, a series of tragic events changed the public's acceptance of this practice. On October 16, 1901, a 5-year-old girl died as a result of receiving tetanus-infected antitoxin. The child's medical doctor reported the incident and an investigation was conducted by members of the District of Columbia City Council, the mayor, and the Board of Health, focusing on the toxin preparation methods and the testing of the serum. Following the death of the 5-year-old girl, an additional 12 children died and the news media widely publicized this childhood tragedy. The investigation revealed that the horse that had been used to make tetanus antitoxin had recently developed tetanus and had been killed. The doctor responsible for the antitoxin serum neglected to destroy all the serum after discovering that tetanus had infected the horse, and the adulterated serum was distributed. The committee found and

---

Wis.: American Institute of the History of Pharmacy, 1982):8-27.
[129] Ibid.
[130] Ibid.

reported that the serum was not properly tested for purity and strength before being distributed and no general safety test was performed to check the serum for remaining toxins. The committee also discovered that the bottles used in the laboratory were not properly labeled and identified.

The incident was widely reported in the press, and the Congress responded to the public outcry by passing the Biologics Control Act, signed into law on July 1, 1902, to regulate the sale of serums, toxins, viruses and other products.[131] This was the first modern federal legislation to control the quality of drugs. The 1902 Biologics Control Act provided the Hygienic Laboratory with the inspection authority to control the production of biological products.[132] The Hygienic Laboratory was given the authority to promulgate regulations for licensing establishments engaged in the manufacturing and sale of biologics, and only establishments with a license number could sell and manufacture biologics for interstate commerce.[133] The Act provided the Hygienic Laboratory with the authority to set laboratory standards in areas such as preventing cross-contamination, maintenance of product temperature, and maintaining aseptic technique; develop standard operating procedures; create standards for product purity, potency and

[131] Ibid.
[132] Ibid.
[133] Ibid.

labeling; and conduct inspections of facilities both before and after licensing to evaluate a manufacturer's product claims. Laboratories that did not meet the scientifically set requirements were not issued licenses or their license was suspended if an inspection found the lab was not in compliance.[134] Regulation enforcement was used to ensure that pharmaceutical companies interested in developing drugs followed certain practices consistently. Once one pharmaceutical organization within the drug development system adopted a certain method of practice, others followed suit. Those who attempted to become part of the system of drug development and did not follow established drug standards would not have their product approved for licensure and sales. Thus, formal rules became a crucial part of the system.

Even with the provisions of the 1902 Act, drug-manufacturing problems continued, from adulterated products to false labeling claims. The 1906 Food and Drug Act dealt with adulteration and was the government's attempt at setting standards and providing penalties to prevent the distribution of unsafe or unfit products.[135] The Act provided definitions for

[134] Harry Marks, *Cambridge History of Medicine, The Progress of Experiment Science and Therapeutic Reform in the United States, 1900-1990*. Cambridge MA: Cambridge University Press, 2000.
[135] Daniel P. Carpenter, "Pure Food and Drug Act (1906)," Major Acts of Congress. 2004. *Encyclopedia.com.* (accessed March 6, 2016). http://www.encyclopedia.com/doc/1G2-3407400257.html

adulterated and misbranded products and gave the U.S. Department of Agriculture's Bureau of Chemistry (which later became the FDA) the authority to seize these articles and seek criminal prosecution of the person responsible.[136]

Because of the advances in technological changes that revolutionized the production and marketing of feed, drugs, and related products, the 1906 law became obsolete.[137] With the economic hardships of the 1930's, some manufacturers intentionally modified their products to save money. These practices led to a new consumer movement that voiced concerns about receiving "honest products"; products are as safe and potent as advertised.[138] In response to this movement, officials of the FDA and members of the Department of Agriculture revised and strengthened the existing 1906 Food, Drug, and Cosmetic Act in 1933 to what eventually became the 1938 Food, Drug, and Cosmetic Act. Before the passing of the 1938 Food, Drug and Cosmetic Act industries were informed of its progression through drug journals, annual meetings and other drug development associations; this led to a number of objections.[139] One major

---

[136] Ibid. The Food, Drug, and Insecticide Administration was created in 1927 and changed its name to FDA in 1930.
[137] Wallace F. Janssen, "The Story of the Laws Behind the Labels," U.S. Department of Health and Human Services, Food and Drug Administration, http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm
[138] Ibid.
[139] David F. Cavers, "*The Food, Drug, and Cosmetic Act of 1938:*

issue was that the proposed law would allow the FDA to make multiple seizures of a product if it considered the product adulterated. Industry wanted this authority removed from the bill. A second issue was whether the control of advertising of food, drugs, and cosmetics by manufacturers should be transferred to the FDA or remain with the Federal Trade Commission as industry preferred. The Federal Trade Commission already had jurisdiction of interstate advertising but lacked a strong deterrent other than a judicial order to prevent repeat offenses of inappropriate advertising.[140] Industry protested the proposed bill in periodicals and public meetings of the trade. Industry tried to get public support by charging that the bill deprived the American people of their right to "Self Medication". Although, the FDA was not allowed by law to spend public funds to influence members of Congress concerning pending legislation, it did make vivid attempts to get the message across to the Congress that the current Food and Drug Act of 1906 needed to be replaced. It did this by creating what the press called the "Chamber of Horrors". The Chamber of Horrors was a traveling exhibit containing an array of labels, pictures

---

Its Legislative History and Its Substantive Provisions," Law and Contemporary Problems, no 6 (1939):39, http://scholarship. law.duke.edu/cgi/viewcontent.cgi?article=1937&context=lcp

[140] Ibid.

and advertisements of ineffective or dangerous products, which were considered adulterated or deceptively packaged but which the FDA, under the existing Food and Drug Act, lacked the authority to do anything about. Many public health officials and those who wrote the draft of the 1938 Act feared it was just a matter of time before industry introduced a competing bill. Special interest groups who favored industry and had congressional support to further attack the drafted bill exerted constant pressure. President Franklin Roosevelt sent a message in March of 1935 urging them to provide this legislation, but it would take a tragic event to persuade them to pass the Act.[141]

In 1937, S. E. Massengill Co., a pharmaceutical manufacturer, created a preparation of sulfanilamide using diethylene glycol as a solvent in the preparation Elixir Sulfanilamide. Before the elixir formulation, sulfanilamide was only available in powder and pill form. After adding diethylene glycol and raspberry flavoring to the product to make it an elixir, the manufacturer conducted testing for flavor, but no animal or human testing for safety was performed since premarket safety testing of new drugs was not required before the 1938 Act. A month after the product was distributed to the public, the first report of a death reached the FDA.[142] The FDA began

[141] Ibid.
[142] Carol Ballentine, "Sulfanilamide Disaster: Taste of

seizing and holding the Elixir Sulfanilamide. While the manufacturer quickly recalled the product, it caused over 100 deaths, mostly children. At the time, the laws only required Massengill to pay only a minimum fine (under provisions of the 1906 Pure Food and Drugs Act that prohibited labeling the preparation an "elixir" if it had no alcohol in it). Congress responded to the public outrage by passing the 1938 Food, Drug, and Cosmetic Act, which required that companies perform safety tests on their proposed new drugs and submit the data to the FDA before being allowed to market their product.[143]

4.1 Drug Regulations, Authority and Guidance

Since the creation of the FDA, there has been a steady increase in the amount of scientific research and regulatory oversight required before an investigational drug can be approved.[144] The Federal Food Drug & Cosmetic Act, which has been amended many times since it was originally passed in 1906, gives the FDA authority to prepare and implement standards or requirements of conduct for industry to follow. If drug industry

---

Rasberries, Taste of Death. The 1937 Elixir Sulfanilamide incident," *FDA Consumer Magazine.* (1981), http://www.fda.gov /aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm

[143] Juliana D. Anderson, "Elixir Sulfanilamide." *Toxipedia (2013),* http://www.toxipedia.org/display/toxipedia/ Elixir+Sulfanilamide

[144] John, P. Swann, "FDA's Origin," U.S. Department of Health and Human Services, Food and Drug Administration, http://www.fda.gov /AboutFDA/ WhatWeDo/History/Origin/ucm124403.htm

violates these established regulations, the FDA can have the offending product seized or seek criminal penalties.

An important component of the FDA's regulatory practice is public notification and feedback on its regulations and guidance documents. The Office of the Federal Register publishes regulations to provide notice and give interested persons an opportunity to participate in the rule making prior to implementation of the final rule(s). The information published includes a description of the situation or problem, the regulatory action that the agency intends to take, and requests for public comment concerning the necessity for the regulation and the Agency's anticipated regulatory action.[145]

Guidance documents are documents that are drafted and posted on the FDA's website and provide the FDA's current thinking about a topic. These guidance documents provide clarifying information about requirements issued in regulations or imposed by the Congress to provide awareness so that the drug industry can take necessary steps if needed to remain in compliance with the laws or regulations concerning a topic or issue. Unlike regulations, guidance documents do not have the force of law, but they do represent the FDA's current thinking and provide advice to manufacturers and sponsors on important

[145] U.S. Government Publishing Office (n.d.) "ABOUT FEDERAL REGISTER". [Weblog], http://www.gpo.gov/help/about_federal_register.htm

aspects of drug development, testing and product marketing.[146]

4.2 Drug Development Process as a System

Many stakeholders are involved in the distinct yet connected processes of drug development, which forms a network of interwoven complexity and multilevel connectivity. As we have seen, the required determination of safety and effectiveness of an investigational product in the U.S. is under the purview of the FDA. But the initial stages of drug development involve a diverse set of other actors. Seeking a drug indication for a new product is often under the control of large drug manufacturers. While small start-up drug companies and academia may have flexibility in deciding what type of research and drug development they want to pursue, many of these small organizational entities lack the necessary financial resources to bear the huge cost of Phase 3 drug development and the manufacture of the product at large scale. Of the companies that do pursue the development of a drug product and spend the estimated $800 million dollars to gain marketing approval, most fail to market the drug due to lack of proven efficacy or safety or insufficient funds for clinical trials or business

[146] U.S. Department of Health and Human Services, Food and Drug Administration. "Guidance & Regulation," http://www.fda.gov/Food/GuidanceRegulation/ (accessed March 6, 2016).

expenses.[147] Large drug manufacturers have a financial interest in decisions related to which investigational drugs will actually be developed for the consumer, and therefore are one of the main system components involved in developing the drugs that reach consumers.

On the demand side of the system, important components include organizations such as the American Medical Association (AMA) and the AAP who promote the science of medicine, the improvement of public health[148] and the health and well-being of infants through young adults.[149] These organizations have the expertise, authority and voice to push for change. Patients and health advocacy groups also play a part in this techno-regulatory system by collaborating with the pharmaceutical industry throughout the drug development and review process. Advocacy groups and patients who live with a disease have a direct stake in the outcome of drug development and the drug review process from the very beginning, not just when the drug product comes to consumer market. The patient's perspective provides industry with important context about the market need

[147] Wendy Tsai and Stanford Erickson, "Early-Stage Biotech Companies: Strategies for Survival and Growth," *Biotechnology Healthcare* 3, no. 3 (2006), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571061/

[148] American Medical Association, "AMA Mission & Guiding Principles," http://www.ama-assn.org/ama/pub/about-ama.page?

[149] The American Academy of Pediatrics, "About the AAP," https://www.aap.org/en-us/about-the-aap/Pages/About-the-AAP.aspx

for a certain drug indication and can influence the FDA's regulatory decision-making about an investigational drug. For example, the history of investigational new drug trials involving research subjects with Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome shows how the patient's perspective and influence affected the review time of an investigational new drug product. Patient activism led to a regulatory policy change that included an expedited approval approach for certain drugs for life-threatening diseases and expanded pre-approval access to drugs for patients who are unable to obtain the investigational drug or to participate in a clinical trial.[150,151]

Another part of Organizational Theory involves understanding the cultural differences between system actors in the development of a technology. What makes sense in one culture may not make sense in another. In the system of drug development, the FDA's culture is devoted to averting risks and protecting the public, while also guiding new medical innovations to market. Others have viewed the cultural priority of protecting the public negatively because of the FDA's

[150] Expanded Access to Investigational Drugs for Treatment Use, 21 C.F.R.§ 312.42 (2015)

[151] Steven Epstein, "The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials," Science, Technology, & Human Values 20, No. 4, (1995):408-437, http://ambounds.org/docs/716/Steven%20Epstein.pdf

cautious approach to prioritize safety over speed, which has resulted in slowing new technology innovation. Yet, the culture of the pharmaceutical industry is principally focused on bringing new products to market quickly and promoting corporate profit. Twenty years ago, about 20% of an executive's compensation was in the form of stock; today, in large companies, it accounts for about 60%, and this reality drives the mission, behavior and attitudes of its members.[152] Doctors on the other hand, do not sell drugs to patients, but they are often responsible for encouraging patients to participate in clinical trials, and study participants often first learn about clinical trials through a doctor than by other means.[153] The culture of medicine values research and nourishes evidence-based medicine and practice to improve patient care. This system of drug development contributes to the expanding knowledge base of medicine and provides physicians an opportunity to offer patients the latest cutting-edge therapies. In years past, the traditional hierarchical model whereby a "doctor knows best" may have applied. Today, especially in Western culture, parents

[152] Mark Kessel, "Restoring the pharmaceutical industry's reputation," Nature Biotechnology 32.(2014):983-990, http://www.nature.com/nbt/journal/v32/n10/full/nbt.3036.html

[153] Department of Health and Human Sevices, National Institutes of Health, "The Need for Awareness of Clinical Research," http://www.nih.gov/health-information/nih-clinical-research-trials-you/need-awareness-clinical-research (accessed March 6, 2016).

question the treatment, diagnosis, or plan of care involving their child. Parents are stakeholders alongside doctors, academics, and drug companies in working out the best course of action for children with certain conditions and at times these parents are strong advocates for lobbing for social change such as an unmet need (e.g. pediatric drug indication).[154]

Other system actors get involved in drug development by contributing substantial funding and advocacy types of research, which may be conducted by academia, small drug firms, or large drug manufacturers. One such actor is the NIH which conducts its own intramural clinical research, funds researchers throughout the nation and abroad and advocates research by offering interested researchers financial incentives. Organizations such as the FDA, drug industry, and NIH provide workshops to bring together key government, academic, and industry leaders to explore clinical regulatory and scientific challenges encountered in the development of drugs, to provide awareness of the new technology, and to discuss approaches to help overcome technological barriers.[155] These workshops are often open to the

[154] Alastair Kent et al. "Paediatric Medicine: A View from Patient Organizations," in *Guide to Paediatric Clinical Research,* ed. Klaus Rose and John Van den Anker.*(Switzerland: S Karger AG.), 27.*

[155] U.S. Department of Health and Human Services, National Institute of Allergy and Infectious Diseases, "RSV Vaccine Workshop National Institute of Allergy and Infectious Diseases," https://respond.niaid.nih.gov/conferences/RSVWork

public, as well as these agencies.

If we look at an overview of the system of clinical research for drug development, actors responsible for the success or failure of these activities and procedures include the investigators, sponsors, ethics committees, contract research organizations, and regulatory authorities.[156] A contract research organization may be commissioned to conduct product testing, development, or manufacturing of an investigational drug product under development. Developing a product at commercial scale is one example of when a sponsor may hire an outside contract organization. If a contract organization is found to have regulatory noncompliance issues during the FDA inspection, product development can be halted. To ensure that drug products meet and maintain certain established parameters these contract organizations are inspected by the FDA and the drug organization who hired them. The FDA conducts these inspections before licensure of a new product and throughout the life cycle of the marketed product. If during an inspection of a manufacturing organization a drug product failed to meet established analytical testing parameters, the FDA has the

---

shop/Pages/Logistics.aspx (accessed March 12, 2016).

[156] The World Health Organization, "Handbook For Good Clinical Research Practice Guidance for Implementation 2002," www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf

authority to order the facility to halt drug production and product distribution until the violations are resolved.

In order for a product to be licensed, it must conform to rigorous standards. Investigations designed to evaluate the safety and efficacy concerning toxicity, administration and dosage, interactions, and effects in target populations must be met. The drug sponsor, in consultation with clinical investigators, often develops the clinical trial protocol. Within the U.S., clinical trial protocols include information on risk identification, control groups and statistical methodology. In addition, the sponsor or the party who oversee, conduct, or support the clinical research draws up a contract or an agreement that defines each party's responsibility, the methods to be used and followed for study activities, and the standard operating procedures (SOPs).[157] Parties who are involved in these activities include independent ethics committees, Institutional Review Boards, and the others previously mentioned. To ensure a drug product meets the safety and efficacy requirements needed for approval, the FDA makes guidance documents available for drug manufacturers and other drug researchers to follow to

[157] SOPs capture the activities and responsibility of study personnel, such as procedures to capture study data, obtaining informed consent, administering the investigational product and more. Ibid, "Handbook For Good Clinical Research Practice (GCP) Guidance for Implementation 2002"

assure that the required testing, development, clinical reporting, and follow-up are met. Sponsors may choose to use an alternative approach, if such an approach satisfies the requirements of the applicable statute, regulations, or both. Guidance for Industry documents are critical to support industry's efforts to comply with the law and to develop new products that may benefit the public health. Having guidance documents in place helps ensure that the system remains in alignment.

Unlike the case study examples provided by Hughes, the small sub-organizations within an organization specialize and contain the expertise necessary for certain aspects of drug development. These sub-organizations develop and provide insight into the development and issuance of guidance that covers areas that fall under their experience and expertise for the parent organization. For example, a drug manufacturer may present to the FDA a new testing method to discuss its applicability to drug development. Yet, at the FDA, it is the expertise at the sub-organization level that is responsible for reviewing drug testing. Thus, reviewers at the sub-organization level will provide the critical advice needed for the FDA upper management (and for the drug sponsor) to either accept the new testing method or guide it through further development. The determination regarding the use of the presented drug testing

technology would be based on the knowledge gained from the sub-organizational evaluation of thousands of product applications from many different sponsors. The successful development of an investigational new drug to consumer market takes years of research, testing, and evaluation. Reverse salients must be overcome or the development of an investigational drug product can be halted. For example, a common clinical deficiency found by the FDA when reviewing submitted IND clinical protocols is the "unreasonable and significant risk to the human subject". If this determination is made, the FDA will notify the sponsor that their IND has been placed on clinical hold and all study activity must cease.[158] For sponsors to overcome this reverse salient, certain deficiencies will need to be addressed, e.g., the protocol might need to be rewritten to change the eligibility criteria, increase the safety-monitoring plan, or add additional information to better assess the potential risks to trial subjects. A study investigation may only be initiated or resumed after the agency agrees that the deficiencies have been corrected. Additionally, Institutional Review Boards (IRBs) have the authority under the FDA regulations to review and monitor biomedical research involving humans to protect the welfare and rights of human subjects participating in research

[158] Clinical holds and requests for modification, 21 C.F.R.§ 312.42 (2015)

trials.[159] This board also has the authority to suspend the conduct of a study if new information is found that alters the original IRB approval decision or if the principle investigator of the study fails to comply with federal regulations regarding the protection of human subjects.

The FDA's legal authority for the regulation of drugs and vaccines derives primarily from section 351 of the PHS Act and from sections of the federal Food, Drug, and Cosmetic Act. The Code of Federal Regulations is another actor included in this subsystem. This is an official and complete text of Agency regulations, also known as administrative laws by executive departments and federal government agencies. When Congress enacts Federal laws or statutes, they do not include detailed information that explains how industry, people and government organizations are to follow the law. Instead, the Congress authorizes Federal Agencies such as the NIH, the FDA and others to develop the operational, technical, and legal details in the form of regulations or rules for people and industry to follow to make the law work.[160]

---

[159] U.S. Department of Health and Human Services, Food and Drug Administration, "Institutional Review Boards Frequently Asked Questions - Information Sheet," http://www.fda.gov/Regulatory Information/Guidances/ucm126420.htm (accessed March 12, 2016)

[160] National Archives, "About the CFR," http://www.archives. gov/federal-register/cfr/about.html

4.3 Phases of Drug Development

Drug manufacturers or researchers initiate preclinical studies because either no current disease intervention exists or the current intervention is sub-optimal. Drugs are often tested in animal models prior to studies in humans to study the immunogenicity, proposed dosage, and preliminary safety. If the results from these tests support safety and efficacy of the drug, manufacturers or academic researchers often publish the study results in science articles or present them at public forums to help promote further research and exploration. This helps to spur the interests of others outside the existing system, resulting in more collaboration, organizational contribution and growth of vested interests.

Following animal testing, drug manufacturers may choose to submit an investigational new drug application (IND) to the FDA for testing of their product in humans. The pre-market clinical testing of drugs consists of three phases, which may overlap. Phase four clinical trials are trials conducted during the post-marketing stage, which occurs after the drug has been licensed. Table 2 summarizes the four phases of clinical trials as described in 21 Code of Federal Regulations (CFR) 312.21 and 312.85.[161] Please refer to **Appendix 1** for further discussion and

[161] Darlene Martin, "A Comparison of the Food and Drug Regulations That Provide the Framework for How Probiotics are

a more detailed description of the phases of drug development. This overview of the development, actors, and processes constituting the drug development system sets the stage for understanding how pediatric drug research and development was eventually incorporated into the system.

Four Study Phases of an IND			
Phase	Purpose	Population Size	Population Demographic
Phase 1	Primarily safety to evaluate side effects, metabolism, and PK using escalating doses	Small – up to 20-80	Healthy adults
Phase 2 Randomized, Blinded; placebo controlled	Safety and initial effectiveness for a specified indication; determine common short term side effects; determine final dose and dosing regimen	Small/Medium – up to several hundred	Subject with disease or condition – typically adults
Phase 3 Randomized, Double blinded; placebo controlled	Safety and effectiveness for a specified indication/population; Pivotal trial to evaluate risk-benefit and provide basis for label (also includes lot consistency studies)	Large/Very Large – several hundred to tens of thousands	Subject with disease or condition – typically adults

Regulated in the United States"(Unpublished master's thesis, Hood College, Maryland, 2014)

Phase 4 Randomized, Double blinded; placebo controlled	Post-marketing studies to delineate additional information about the drug's risks, benefits, and optimal use (may provide basis for a label change)	Small/Medium/Large – depending on the study endpoints	Population dependent on the study endpoints

Table 2 [Permission Granted]: Four Study Phases of an IND
This table summarizes the four phases of clinical trials as described in 21 Code of Federal Regulations (CFR) 312.21 and 312.85.

Chapter 5: The Push for Pediatric Research and Drug Development: Conflict and Collaboration in a Techno-Regulatory System

Since the 1906 Pure Food and Drug Act, which first focused on governmental drug labeling requirements, few drug labels had included safety and effectiveness information for the pediatric population. According to the Physicians' Desk Reference surveys conducted in 1973 and 1991, as much as 80% of the listed medication labeling disclaimed usage or lacked dosing information for children.[162] Medications not labeled or approved for use in infants and children, or not available in pediatric dose form, were often compounded on an ad hoc basis by pharmacists to reduce the drug dose or made into a liquid for ease of swallowing. In the absence of pediatric drug labeling, the medical community and the public had no information on the safety and effectiveness of these drugs. Furthermore, health care providers had no clear and concise reference information on pediatric prescriptions to help them ensure the safe and optimal use of a prescribed drug for their pediatric patients.[163] As a

[162] Jean Temeck, "Pediatric Product Development in the U.S." (Slides presented at the symposium conducted at the FDA Seminar, Copenhagen, November 2010, http://www.fda.gov/downloads /ScienceResearch/SpecialTopics/PediatricTherapeuticsRe search/UCM262309.pdf

[163] U.S. Department of Health and Human Services, Food and Drug

result, medical personnel could not provide consistent information to patients or parents about the potential safety and effectiveness of the drugs they prescribed.

Changes in pediatric practice regarding drugs began to emerge in the 1950s. Following the Great Depression and World War II, the 1950s were a more prosperous period. Unemployment was at an all-time low as compared to previous years. With fewer cases of malnutrition, disease, and other ailments seen by pediatricians, many physicians started to question the future direction of pediatric practice.[164] This led the pediatric medical community to push for expanding the role of pediatrics by broadening the scope of pediatric research and to look at the concept of the "whole child" and the "concept of the patient as a person".[165] By assessing the "whole child", physicians could then increase the number of patient practice appointments while also increasing their revenue and not be limited to seeing mostly sick children. Over the next 20 years as the medical community began the transition from focusing on sick children to that of the whole child, the medical culture began to change and

---

Administration. *The FDA Announces New Prescription Drug Information Format,* http://www.fda.gov/Drugs/GuidanceCompliance RegulatoryInformation/LawsActsandRules/ucm188665.htm (accessed March 12, 2016).

[164] George Wheatley, "Pediatrics in Transition," *Journal of the American Medical Association, 168, (1958):856-859.*

[165] Ibid.

question the differences between pediatric drug research and that of adults. The medical community discovered that investigational drug pharmacology research neglected children, yet in the areas of therapeutic research involving adults it was booming.[166] Instead of a "drug-oriented" approach where pharmaceutical manufacturers once studied and received licensure for "one level dose for all", the medical community now began to explore the "patient oriented" research approach by asking themselves what drug, what dose, and what route of administration should be provided to the pediatric population.[167]

The negotiation of pediatric research, from its virtual nonexistence in the 1970s to its mandated requirement today, involved much collaboration and eventual compromise between organizations. Unlike Hughes's many examples of electrical and engineering systems that focus on a top down hierarchical business approach, the system of drug development (and many other contemporary systems) is horizontally structured, with no one organization or individual entirely holding a position of power over others. The Hughesian model pays little attention to human conflict and to examining system building that involves

[166] Stuart MacLoed , "Therapeutic drug monitoring in pediatrics: how do children differ?" *Therapeutic Drug Monitoring* 32,no. 3 (2010):253-256.
[167] Jeffrey Blumer, "Origins of the PPRU - Therapeutic Orphans," *Pediatric Pharmacology Research Units (PPRU)*, http://www.Ppru .org/reports.aspx

actor negotiations to resolve conflict.[168] Yet, without a collaborative effort by system actors on the techno-regulator system of drug development, the system change for the inclusion of pediatric research and development may not have taken place.

In this chapter I draw on the concept of "obligatory passage point" from Actor Network Theory to capture key actors who played a substantial role in changing the system of drug development but would be excluded from Hughes's systems approach. I also incorporate the principles of Organizational Theory such as rules to explain organizational limitations, decision-making, authority, or lack of it, and the functional specialty, or expertise of organizational subcultures; all of which provide a better explanation of how techno-regulatory systems change.

5.1 Expert gatekeepers as change agents in the pediatric drug research system

Dr. Harry C. Shirkey greatly influenced the push for pediatric research and labeling. As a member of the AAP, he began to introduce his own agenda and goals toward the inclusion of pediatric research in drug development in the 1960's. Shirkey's ability to change the drug approval process is an example of how a techno-regulatory system depends upon, and

[168] Van der Vleuten, "Large Technical Systems," 220.

grants agency to, multiple sources of expertise and authority.

Shirkey's agenda and goal fit well within the vision of the AAP's founder James W. Rosenfield, M.D., who in 1929, during the American Medical Association (AMA) section on Diseases of Children meeting in Portland Oregon, invited all of the section attendees (35 Pediatricians) from around the country to a dinner at his home to discuss childhood diseases.[169] From this meeting these practicing pediatricians decided to form a unified group of members to advance the field of medicine, pediatric research, and the social needs of children, which eventually paved the way for the AAP.[170] In July 1930, the incorporation of the AAP was official with a stated goal to:

> Foster and encourage pediatric investigation, both clinically and in the laboratory, by individuals and groups.[171]

In the late 1960s, Dr. Shirkey advocated the need to differentiate drug use indications for adults from those used in children. He acted as an intermediary by bringing network actors like the AAP, the AMA, drug industry, and the Food Drug Administration (FDA) together to transform this once-radical idea into a part of mainstream thinking. He argued to these different drug actors that there were important differences in

[169] The American Academy of Pediatrics, "*AAP History,*" https://www.aap.org/en-us/about-the-aap/Pediatric-History-Center/Pages/AAP-History.aspx (accessed March 6, 2016).
[170] Ibid.
[171] Ibid.

the pharmacodynamics of drugs used for adults versus those used in children. He played a huge role in identifying this problem by articulating the need for a solution and acting as a representative between drug development actors and community. In the article *The Evolution of Large Technological Systems* Thomas Hughes describes an inventor as a person who independently created and developed a technology.[172] An individual like Dr. Shirkey would not fit into Thomas Hughes' model of system evolution because he was not directly involved in developing or regulating drugs. To explain how a seemingly "outside" actor like Dr. Shirkey played such a key role, I draw on the concept of obligatory passage point that is associated with Actor Network Theory as an additional element to work into my expanded system model. An obligatory passage point is an actor who has positioned themselves within the system in such a way that other actors must deal with this actor in order to meet their own objectives. But first, physicians are also an obligatory passage point for the drug system because they hold the power to prescribe drugs to patients and are often the primary sources for raising awareness to their patients about drug treatment options, barriers to potential treatment, and clinical drug trials.[173] This social

[172] Hughes, "The Evolution of Large Technological Systems," 58.
[173] Department of Health and Human Sevices, National Institutes of Health, "The Need for Awareness of Clinical Research," http://www.nih.gov/health-information/nih-clinical-research-

awareness (influencing the environment) from physicians can lead many to push for social change and a change in technology.

Dr. Shirkey became a focal actor who drove the new approach by framing the problem, defining the identities and interests of other system actors and acting as an intermediary between system components. Dr. Shirkey was the first chairperson of the AAP Committee on Drugs, which formed in 1968 to replace the Committee on Dosage (formed in 1950) and to review, monitor and resolve issues resulting from the therapeutic orphan dilemma (see below).[174] Dr. Shirkey and the AAP Committee on Dosage questioned the status quo of pharmacology research being limited to adults and advocated changing the drug development process to incorporate pediatric research in clinical drug trials rather than rely on extrapolation from adult efficacy data. The AAP raised awareness of the drug treatment differences between adult patients and children in both the medical community and the public. In the 1960's and 1970's, Dr. Shirkey argued to the medical community that infants and children were becoming

---

trials-you/need-awareness-clinical-research (accessed March 12, 2016).

[174] Sumner J. Yaffe, Harry C. Shirkey, Arnold P. Cold, Frederick M. Kenny, Mary Ellen Avery, Harris D. Riley, Jr., Irwin Schafer, Leo Stern, Henry L. Barnett, Alfred M. Bongiovanni, Robert J. Haggerty, American Academy of Pediatrics Committee on Drugs Statement of Purpose, Scope and Functions," *Pediatrics* 41 (1968):534, accessed March 6, 2016, http://pediatrics.aappublications.org/content/pediatrics/41/2/534.full.pdf

"therapeutic or pharmaceutical orphans".[175] He raised drug safety concerns for pediatric age populations because a vast majority of medications prescribed to children were never tested in children.[176] This spreading of social awareness of the differences between children and adults and the need for further exploration of drug research resulted in many pediatricians becoming reluctant to prescribe existing medicines for their pediatric patients.

The *Journal of Pediatrics* devoted much of its May 1965 edition to aspects of pharmacology on pediatric therapeutics versus those found in adults.[177] This issue's purpose was to promote social awareness to the medical community about drug action differences between adults and children. It included a discussion about the vast pharmacological differences between adults and children, while emphasizing that the doctor is "entirely responsible for his treatment, including his use of drugs".[178] The intent was to spur physicians to take some form of

---

[175] Harry.C. Shirkey, "The Package Insert Dilemma," *The Journal of Pediatrics* 79 (1971)4:691-693.
[176] William B. Abrams, "*Rescuing the Therapeutic Orphan: The Potential of Pediatric Pharmacology Realized," American Society for Clinical Pharmacology and Therapeutics,* http://www.ascpt.org/About-ASCPT/Awards/ASCPT-FDA-William-B-Abrams-Award-Lecture/2010-William-B-Abrams-Lecture (accessed March 6, 2016).
[177] Harry C. Shirkey, "Pediatric Pharmacology and Therapeutics: Drug Administration," *The Journal of Pediatrics* 66 (1965)5:909-917.
[178] Shirkey, "The Package Insert Dilemma," 691-693.

action to close the drug treatment knowledge gap between adults and children. Furthermore, it provided awareness of potential litigation suits against physicians for not following established drug treatment standards.

The article sparked the interest not only of the medical community but also that of the FDA, the National Institute of Medicine and other advocacy organizations. In the late 1960's, the AAP continued publishing articles that pushed the drug industry and the FDA to collect pediatric data that could be added to package inserts and thereby lessen the danger of lawsuits against physicians for prescribing medications that are not indicated for pediatric patients.[179] The AAP leveraged the physicians' position as an obligatory passage point intermediary between drugs and patients to demand system change.

Other than providing important information about a drug, such as the indication for use, dosage, and administration, a key role of product labeling and standards is to determine the legal liability and the practice of physicians highlights the importance of formal rules in the techno-regulatory system. Formal rules create control of the anticipated and unanticipated consequences.

[179] Ibid.

5.2 Components Within a Horizontal Multi-Organization System Resist Change

For years, drug research had focused on the adult population and extrapolated from that data indications in the pediatric population. In response to the push for mandating pediatric drug research by the AAP and the FDA, the drug industry argued that the existing drug system already addressed gaps in pediatric drug indications through off-label use, and that making decisions about such use falls under the standard practice of medicine and not the regulation of the FDA.[180] If doctors had to base their off-label prescriptions on limited knowledge rather than full clinical data, which could make these physicians vulnerable for lawsuits, prescribing off-label medication alone may not result in liability under medical negligence standards. When considering negligence, one must establish that the prescribing physician deviated from the standard of medicine practice.[181] Hence, many physicians could

[180] Off-label use is when a licensed physician prescribes a drug to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling. FDA does not have the authority to regulate health care providers' use of prescribed drugs for other than what the package insert indicates. Dresser, R., Frader, J. (2009, Fall) Off-Label Prescribing: A Call for Heightened Professionals and Government Oversight *Journal of Law, Medicine and Ethics*, 37(3), 476-496.

[181] Susan Thaul, "*FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective," Congressional Research Service website: http:www.*fas.org/sgp/crs/misc/RL33986.pdf

turn to articles published in peer-reviewed journals that claim evidence for a drug indication given off-label, but also to show that they are following the standard of medicine practice.[182]

For the drug manufacturers, however, off-label use is a free ride. The FDA has no authority to review whether a drug should be used off-label. In contrast, each drug indication sought by the drug industry requires that the FDA and the drug companies reach concurrence for required safety and effectiveness studies. These clinical trials cost the drug industry millions of dollars and years of research, and not all drug trials are successful in resulting in licensure. Additionally, drug organizations were resistant to include pediatric research in drug development because of the expected high upfront cost to implement clinical trials before any product sales. Because diseases often occur more frequently in adults than in the pediatric population, fewer product sales would result. Finally, if pediatric trials identified safety issues, the FDA may have required updated safety information in the existing product package insert to warn prescribing physicians, pharmacists, and the public, which could result in decreased off-label sales of the product. To protect their

[182] Christopher M. Wittich, Christopher M. Burkle and William Lanier, "Ten Common Questions (and Their Answers) About Off-label Drug Use," *Mayo Clinic Proceedings 87 (2012):* 982–990, http://doi.org/10.1016/j.mayocp.2012.04.017

favorable status quo situation, the drug industry addressed the conflict with the FDA and the AAP by disputing the need for the expansion of the existing drug system and arguing that a system mechanism already existed (e.g., off-label use).

Since the FDA and the AAP had no authority over the drug industry, they could only ask the drug industry to include pediatric study research as part of their drug development. This request required that the drug industry change their normal organizational practices of disseminating off-label information though peer journals and word of mouth and instead organize and plan pediatric clinical trials that would need to be completed and finalized before any marketing sales. The drug industry responded to this request by arguing that off-label use should continue to be the mechanism to address pediatric drug needs. That way, the drug industry could still receive sales revenue from drug products in the pediatric population without conducting costly drug trials and changing the current system process. The off-label liability would remain with the doctors, who risked potential malpractice litigations and the health of their pediatric patients. This misalignment of norms and interests between the organizational subsystems of drug development led to system turmoil, major debates, and conflict.

The AAP mobilized physicians to push for change by making visible the inequitable distribution of risk within the system.

In October 1971, *The Journal of Pediatrics* released an article entitled "*The package insert dilemma",* which emphasized that the package insert is the official reference resource information for drug information and that any physician who chooses to ignore its contents runs the risk of a lawsuit for malpractice.[183] Litigation examples against physicians for treating both adults and pediatric patients with a drug not approved according to the package insert were included in the article. Furthermore, the article spurred physicians to insist that the pharmaceutical companies give greater recognition to the needs of children and the effects that drugs have on children regardless of sales potential. It recommended that if physicians were to demand pediatric studies to establish the safety and efficacy of drug products for children, package inserts would be updated with this information, thereby lessening the danger of lawsuits for malpractice.[184] Furthermore, the article served as awareness for change where these physicians might one day need to solicit, recruit, or support studies involving pediatric patients. These articles provided awareness to the medical community about liability concerns and the lack of pediatric standardization, and helped to provide momentum for change by influencing other components of the

[183] Shirkey, "The Package Insert Dilemma," 691-693.
[184] Ibid.

system such as the FDA and drug industry.

In the early 1970's the FDA began to argue that "drugs used for children should be tested in children" and made attempts to motivate the drug industry to conduct pediatric clinical trials in order to update labeling with pediatric safety, efficacy and indication information; yet few pediatric clinical trials were conducted by the drug industry.[185] While the FDA had the authority to require the drug industry to conduct trials in populations for whom it was seeking an indication, the FDA lacked the authority to require that the drug industry pursue pediatric drug product indications. There were also cultural obstacles to pediatric testing. For decades, researchers encouraged the recruiting of a homogenous subject population of mostly white adult males in clinical studies. The extrapolation of this study data would then be applied to other social groups who were often excluded.[186] This homogenous group was preferred over others since it minimized the impact of variables outside the study and made the success of meeting clinical endpoints more likely. The drug industry again resisted the AAP's and the

---

[185] Sumner J. Yaffe, and Jacob V. Aranda, "Introduction and Historical Perspective," in *Neonatal and Pediatric Pharmacology Therapeutic Principles in Practice, ed.* Sumner J. Yaffe, and Jacob V. Aranda (Philadelphia, PA: Lippincott Williams & Wilkins, 2010),2.

[186] Steven Epstein, *Inclusion: The Politics of Difference in Medical Research* (Chicago: University of Chicago Press, 1989), 43-45.

FDA's attempts to change the system by arguing that there were liability issues involved in conducting pediatric clinical trials and ethical issues involving children.[187] One reason for the exclusion of children from drug trials was that many people in society thought it would be unethical to enroll a child in clinical research since he or she cannot give consent. The public's reaction to the Tuskegee Study and the Willowbrook State School experiments are two study examples that influenced the public to want to protect "vulnerable populations" (that included women and children) and to not enroll the disadvantaged, mentally ill, and children in clinical research.[188] The Tuskegee Study included 600 impoverished African American men to study the natural progression of untreated syphilis from 1932-1972 and that these men were never told they had syphilis even after treatment was available.[189] The Willowbrook experiments used coercion, in that the parents of children were informed that the institution might close due to overcrowding only to be contacted some time later that room vacancies were available if the child lived in the "hepatitis

---

[187] Kurt R. Karst, "Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry." *American University Law Review* 49 (2000)(3),739-772.
[188] Epstein, *Inclusion*, 43-45.
[189] U.S. Public Health Service Syphilis Study at Tuskegee, "The Tuskegee Timeline" Centers for Disease Control and Prevention http://www.cdc.gov/tuskegee/timeline.htm, February 19, 2016.

unit" and was enrolled in a hepatitis research study.[190] Children at Willowbrook State School received free room and board between 1938 and 1987 because of their sever mental retardation, and were unable to care for themselves.[191]

5.3 AAP – A Hughesian System Builder for the sub-system of pediatric drug research

At this point in history, the AAP behaved like a Hughesian system builder by making a determination of whether their desired technology (pediatric drug testing) could function in the larger techno-regulatory environment of drug research and labeling. As Hughes describes, system builders must take into account the economic, political and other characteristics of the environment in the design of their technology to better assure its survival.[192] The AAP responded to an environment that was wary of pediatric drug trials both by arguing for pediatric drug testing and by designing and disseminating a model for conducting pediatric trials that would make such trials easier to perform. In July 1974, the AAP's Committee on Drugs attempted to bring pediatric drug trial technology into alignment with the drug industry, the FDA, and others by authoring a report

[190] M.H. Pappworth, "The Willowbrook Experiments", *The Lancet*, June 5, 1971.
[191] Michael Ely "Disinterestedness at Willowbrook" COLFA Conference, http://colfa.utsa.edu/colfa/docs/conference/2014/Conference-Work-Ely.pdf
[192] Hughes, "The Evolution of Large Technological Systems".,62-63.

entitled "G*eneral Guidelines for the Evaluation of Drugs to Be Approved for Use During Pregnancy and for Treatment of Infants and Children."* This report that was submitted to the FDA, pointed out the differences affecting safety and efficacy of investigational drugs in pediatric subjects versus adult subjects and argued for the need for separate pediatric and testing adult. The AAP's report took into consideration the mindset of the drug industry and the FDA by providing the groundwork for to designing pediatric trials, thus decreasing the risk and/or investment required for industry. The report provided direction towards defining pediatric trial procedures, criteria, and necessary endpoints to help bring the subcomponents of drug industry, the FDA, and the AAP into system alignment. While the report acknowledged that ethical, practical and legal considerations might preclude an ideal experimental approach, it added that this was not an insurmountable obstacle.[193]

The AAP's efforts were not initially successful due to several issues. One was a practical issue in that the drug industry was accustomed to clinical protocols that had well-

[193] U.S. Department of Health and Human Services, Food and Drug Administration, *"Guidance for Industry: General Considerations for the Clinical Evaluation of Drugs in Infants and Children,"* September 1977, http://www.fda.gov/downloads/drugs/guidance complianceregulatoryinformation/guidances/ucm071687.pdf (accessed March 12, 2016).

known predefined endpoints in adults, but pediatric trials had very uncommon and lacked established safety standards, efficacy endpoints, study trial procedures, and specialized equipment. Another issue, regulatory in nature, was that the drug industry followed the standards set by the FDA, not the AAP, and there were no FDA established pediatric clinical trial standards in place to follow. Perhaps the biggest obstacle that pharmaceutical industry and clinical research organizations had to overcome was parents' reluctance to expose their child to a clinical trial. Since the children themselves are too young to give consent (or are not giving consent alone), the parents need to make the decision for the child, making the parents another obligatory passage point in the system. While some parents are willing to enroll sick children in cancer research trials because of the potential benefit to those children, a real challenge is the recruitment of healthy children into clinical trials. Understandingly, parents have reservations about exposing their child to an investigational new drug. They may ask themselves will this investigational drug do more harm than good and what is the drug benefit. They may question if the drug will have any long-term effects. Often diseases found in adults are not as common in children, and this makes recruitment efforts much more challenging. Because of this complex set of issues, both system components and the social environment

(public, physicians) needed to change. With the push for pediatric standards, the AAP was designing a new subsystem that was to reside within the larger existing system of drug development. Unlike the examples by Hughes, there is no sharp boundary between the system and its environment; the environment is also part of the larger system (e.g., study participants, public vaccine forums).

5.4 FDA - An Inventor-Entrepreneur joins the AAP's effort to build the new system

In 1977, to provide industry with motivation and direction, the FDA adopted the AAP's 1974 guidelines and provided them in the guidance entitled *General Considerations for the Clinical Evaluation of Drugs in Infants and Children.* The guidance included a statement that pediatric use of a drug must be based on substantial evidence derived from adequate and well-controlled pediatric studies, unless the requirement was waived. This had little effect on industry, since the FDA's guidance documents only provide the FDA's current thinking about a topic and do not establish legally enforceable responsibilities.

In 1979, the FDA issued a regulation requiring all drug product labeling to include a pediatric section for dosing and safety. However, this did not necessarily produce useful information, since the FDA lacked the authority to have the drug industry conduct pediatric research to update a product.

Instead, this only led to the following clause in product labeling:

> "... safety and efficacy of (drug name) in paediatric patients below the age of *x* has not been established".[194]

As before, few pediatric clinical trials by the drug industry took place, leading the FDA, the AAP, and other stakeholders to pursue other inventions for system change. For several years debates continued between advocates pushing for the inclusion of pediatric research in the technological regulatory system and opponents who argued against. While the FDA supported the views of other system components such as the AAP and public advocates for pediatric drug indications based on clinical research, it lacked the authority to force or mandate the drug industry to conduct studies of their drug products in children. On December 13, 1994, the FDA posted in the Federal Register a regulation called the 1994 Rule, which required manufacturers to survey existing data and determine if the data was sufficient to support additional pediatric use in drug labeling. Yet only a few product surveys were returned to the FDA. Instead, drug manufacturers tried to negotiate a compromise and not take on this added responsibility by requesting that off-labeling use

[194] U.S. Department of Health and Human Services, Food and Drug Administration, "Labeling and prescription drug advertising: content and format of labeling for human prescription drugs," *Federal Register,* 1979, 44:37434-37467.

continue as a viable method, and suggested that to address product labeling the following statement be included.

> "Safety and effectiveness in pediatric patients have not been established."[195]

On November 21, 1997, Congress had enacted The Food and Drug Administration Modernization Act of 1997 (FDAMA), containing provisions to improve the regulation of food, drugs medical products and cosmetics. To help insure that health care professionals have the best information available when making health care decisions and treating patients, one provision of the law was to abolish the long-standing prohibition on manufacturers disseminating information about unapproved uses of drugs and medical devices. Congress took the role of system builder by reducing the functioning of the drug industry via a formal set of rules while also addressing the needs of other social institutions. The Food and Drug Administration Modernization Act helped insure stability and uniformity of the system. As a result, drug firms could circulate peer-reviewed journal articles about an off-label indication provided the company submitted to the FDA a supplemental application with the supportive information. The information needed to be adequate,

[195] U.S. Government Publishing Office, "Federal Register", Wednesday December 2, 1998 Part II Department of Health and Human Services Vol. 63, No 231 Washington, DC.

objective, and scientifically sound.[196] If the information submitted did not comply with regulatory requirements, as deemed by the FDA, additional information or revisions would need to be needed until the regulatory requirements were met. While this approach placed restrictions on drug organizations, it had little impact on drug industry that still financially supported academic research institutes and other outside agencies that publish their own findings of off-label product use.

Congress also included economic incentives for drug sponsors who conduct pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Term Restoration Act. Thus, if drug manufacturers conducted pediatric studies, as requested by the FDA and in accordance with the requirements of FDAMA, they would be entitled to 6 months drug exclusivity or drug patent protection that could result in millions of dollars in earned

[196] Per 21 CFR Part 99 entitled "*Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices*" off-label scientific information which has not been included in the approved FDA prescription insert may be disseminated to health care providers, pharmacy benefit managers and health insurance issuers in the form of peer reviewed journals and referenced publications. U.S. Department of Health and Human Services, Food and Drug Administration (February, 2010, February) *Regulatory Information.* http://www.fda.gov/regulatory information/legislation/federalfooddrugandcosmeti cactfdcact/significantamendmentstothefdcact/fdama/ucm089179.htm *Accessed March 6, 2016.*

revenue.[197] Despite a number of efforts and some help from Congress, the FDA still was unable to change the system to make pediatric drug trials the norm.

5.5 The Pediatric Rule – A Power Struggle Among Horizontal Actors

In 1997, the FDA took a more aggressive stance towards mandating pediatric study requirements by posting a proposal in the August 15, 1997, Federal Register, which became the Pediatric Rule of 1998. This rule required manufacturers of certain new and marketed drugs and biologics to conduct studies to provide adequate labeling for the use of these products in children. The proposal cited reports of injuries and deaths in children that were linked to the absence of pediatric testing and labeling and denying pediatric patients therapeutic advances. Before posting the proposal, the FDA held a daylong public hearing to solicit comments from drug industry, experts in the pediatric community, patient groups and bioethicists on three issues. These comments included questions like when pediatric studies are needed, what types of studies are needed, and comments concerning the special challenges in testing pediatric patients. Comments were received from the American Psychiatric Association and National Institutes of Mental

[197] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule Federal Register: December 2, 1998 (Volume 63, Number 231)[Page 66631-66672]

Health, who argued that certain medications are underutilized in the pediatric population since no pediatric indication is included in product labeling. Opponents for this change argued that the FDA should use encouragement and early discussions with sponsors along with incentives, rather than imposing requirements.[198] In response to the comments received, the FDA released guidance in May 1998 entitled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, which provided to drug developers a description of the kinds of studies that could support effectiveness in supplemental or original applications.[199]

The new rule provoked a backlash from the drug industry. On December 3, 1999, Consumer Alert, The Association of American Physicians and Surgeons (AAPS), and the Competitive Enterprise Institute filed a citizen's Petition requesting that the FDA Commissioner immediately revoke the provisions of the Pediatric Rule. They argued that the FDA should not direct the research efforts of the drug industry and should instead expeditiously approve all drugs that are safe and effective for their intended

[198] U.S. Government Publishing Office, "Federal Register", Wednesday December 2, 1998 Part II Department of Health and Human Services Vol. 63, No 231 Washington, DC.
[199] U.S. Department of Health and Human Services, Food and Drug Administration, "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (1998), *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf* (accessed March 12, 2016).

purposes and leave to doctors the decision of whether any "off-label" use is appropriate. The Competitive Enterprise Institute is a pro-business organization dedicated to the principles of free enterprise and limited government who portrayed regulation as something that interferes with consumer freedom, contesting the FDA's portrayal of regulation as something that protects patients. Rather than invoking their own self-interest in not wanting to pay for additional clinical trials, this organization joined the Association of American Physicians and Surgeons in arguing to the FDA and consumers that the Pediatric Rule would cripple the pediatrics community's ability to treat their patients and the system revision constituted a drastic change in the drug approval process.[200] Furthermore, the Association of American Physicians and Surgeons voiced that this type of system change would result in additional cost coming back to the consumer. Consumer Alert was another pro-business organization aimed at persuading consumers to pursue market approaches, rather than regulatory approaches, to consumer safety.[201] These three organizations argued that the FDA was abusing its

[200] Hans Stotter, "Paediatric Drug Development Historical Background of Regulatory Initiatives" in *Guide to Paediatric Clinical Research, ed.* Klaus Rose and John van den Anker, *(Basel, Switzerland 2011), 27.*

[201] "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients"; *Final Rule Federal Register*: December 2, 1998 (Volume 63, Number 231)[Page 66631-66672].

authority and that the rule was a radical and unauthorized expansion of the FDA's power that would further complicate the drug approval process.[202]

The FDA refused to revoke the provisions of the Pediatric Rule and in December 2000, the three groups brought suit challenging the authority of the FDA to issue the rule. On the other side, a number of groups including the AAP, the Elizabeth Glaser Pediatric AIDS Foundation, and the Pediatric Academic Societies strongly supported the Pediatric Rule and became *amici curiae* in the case. In 2002, the federal district court of the District Of Columbia sided with the plaintiffs and overturned the pediatric rule, but not before considering the view of the public who was not party to the lawsuit but had strong interest in the outcome. While the court sided with the plaintiffs, in the United States District Court Decision it included the following:

> "The Pediatric Rule may well be a better policy tool than the one enacted by Congress; it might reflect the most thoughtful, reasoned, balanced solution to a vexing public health problem. The issue here is not the Rule's wisdom. Indeed, if that were the issue, this court would be a poor arbiter indeed. The issue is the Rule's statutory authority, and it is this that the court finds lacking. For the foregoing reasons, this court finds that the Pediatric Rule exceeds the FDA's statutory authority and is therefore invalid."[203]

---

[202] Ibid.

[203] U.S. District Court For the District of Columbia Association of America Physician and Surgeons INC., et al Plaintiffs, V. United States Food and Drug Administration, et al., Defendants

Tommy G. Thompson, former Secretary of the United States (U.S.) Department of Health and Human Services, responded to the court's decision by announcing that his department would push for rapid passage of legislation that would give the FDA authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on drugs.[204]

5.6 A new coalition of system builders: Congress and Pediatric Research Incentives

As a newly active component of the techno-regulatory system, Congress brought the legislative power to provide incentives, research funds, and ultimately, mandates. To encourage drug manufacturers to conduct pediatric drug studies as requested by the FDA, Congress enacted in 2002 the Best Pharmaceuticals for Children Act (BPCA) for drugs still under patent protection. BPCA provided drug manufacturers with 6 months pediatric exclusivity from other competitors and their generic drug equivalent. BPCA also provided a mechanism for studying off-patent drugs, which many manufacturers refused to study following a Written Request by the FDA. BPCA authorized the Foundation of the National Institutes of Health in

---

Civil Action 00-02898.

[204] Hans Stotter, "Paediatric Drug Development Historical Background of Regulatory Initiatives," in Guide to Paediatric Clinical Research, ed. Rose Klause and John Van den Anker, (Washington, D.C./Rotterdam, 2007),*27.*

consultation with the FDA to fund studies when drug sponsors decline written requests for pediatric studies of off-patent drugs.[205] The NIH would then publish a request for contract proposals to conduct pediatric drug studies described in the Written Request and award contracts to qualified universities, Contract Research Organizations, hospitals, federally funded networks (such as the Pediatric Pharmacology Research Unit Network, the Neonatal Network, the Maternal Fetal Medicine Network), and other public or private institutions.[206] Under the BPCA Congress authorized $200 million in fiscal year 2000 and such sums as necessary for each of the five succeeding fiscal years to carry out needed studies when drug companies refused to do so.[207]

In 2003, the House of Representatives passed the Pediatric Research Equity Act (PREA), which was a bill to codify the previously overturned Pediatric Rule and require drug companies to conduct clinical research into pediatric applications for new

[205] Marcia Crosse, *Pediatric Drug Research: The Study and Labeling of Drugs for Pediatric Use under the Best Pharmaceuticals for Children Act (*GAO-07-898T). (Washington DC: U.S. Government Accounting Office, 2007), 1-15, http://www.gao.gov/products/A69826

[206] U.S. Department of Health and Human Services, National Institute of Child Health and Human Development (2003). "*Pediatric Off-Patent Drug Study (PODS) Center – Lorazepam – Status Epilepticus,"* http://grants.nih.gov/grants/guide/notice-files/NOT-HD-03-012.html (accessed March 12, 2016).

[207] Office of Legislative Policy and Analysis (n.d.). 107th Congress: "Best Pharmaceuticals for Children Act", [Weblog], http://olpa.od.nih.gov/legislation/107/publiclaws/1best.asp

drugs.[208] Under the Pediatric Rule, applications submitted to the FDA for changes in active ingredients, age indication, dosage form or route of administration (i.e., subcutaneous to intramuscular injection) were required to include pediatric assessments unless the requirement was waived or deferred by the FDA. Under PREA, Congress provided the FDA with the authority to require pediatric studies and to waive or defer certain studies, if needed. This pediatric study requirement applied to all applications submitted on or after April 1999 and led to mandating pediatric research and labeling.[209] In response to the long back and forth pediatric research and labeling debates, Congress used its authority empowered by society to create and implement the BPCA and the PREA and empower the FDA to mandate pediatric drug research.

Following the passage of the BPCA and the PREA, more appropriate drug and biologic development studies have been conducted in children over the past 10 years than likely conducted over the past five decades. FDA tracks the drug manufacturers pediatric study commitments to ensure that they are being conducted and completed. Where there was once as much

[208] Stotter, "Paediatric Drug Development Historical Background of Regulatory Initiatives," *27.*

[209] U.S. Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry How to comply with the Pediatric Research Equity Act*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079756.pdf

as 80% of the listed medication labeling disclaimed usage or lacked dosing information for children, an estimated 50% of drugs used in children are now studied, and for biologics this study percentage is expected to be much higher.[210,211] Through a complex process of conflict and cooperation between system actors, none of whom had complete authority but each of whom controlled some necessary part of the system, a workable policy finally emerged.

[210] Temeck, "Pediatric Product Development in the U.S."
[211] "BPCA and PREA Reauthorization," Congressional Childhood Cancer Caucus, last modified March 18, 2016, https://childhoodcancer-mccaul.house.gov/issue/bpca-and-prea-reauthorization

Conclusion

I have proposed the concept of a techno-regulatory system to make sense of the dynamics of a highly regulated system with multiple competing yet cooperating actors, such as the development and approval of biologics. This dissertation has identified flaws with Thomas Hughes's Systems Theory that can lead to key pieces of historical information being overlooked. I have suggested, provided and applied to this case study the inclusion of additional system models principles (Actor Network Theory, Organizational Theory, and Collaborative Theory) to address gaps with Hughes LTS Theory and my analytical approach of using these selected models principles to revise Hughes LTS Theory make it robust enough to encompass and explain techno-regulatory systems. By including these other models of investigation to this case study I was better able to understand the deeper developments that led to the shaping of pediatric drug development by system actors and those that are part of the environment.

The techno-regulatory system model helps explain the important role of actors who seem external to the system and would be overlooked by Hughes's system model. For example, Dr. Shirkey was instrumental in the emergence of pediatric drug development by promoting the awareness of the pharmacokinetic and pharmacodynamic differences between adults and children, and advocating for system change of the drug development process. Dr. Shirkey helped spur a social need to have organizations such as FDA, NIH, AAP, and others

devote resources to this challenging technological innovation. As this example shows, actors who make up a techno-regulatory system of drug development are not always part of the system of drug development but instead may be part of the environment and may overlap between two systems. Another example of actors who are not part of the drug development system but are pulled into it for a short period are Vaccine Related Biological Products Advisory Committee (VRBPAC) members. VRPBAC members are often university researchers, private practice physicians and other actors who are part of the environment, not affiliated with drug industry to avoid product bias, and become part of the system of drug development while also being part of the environment. Quite often, when a BLA is close to licensure or there is a significant change in a drug process, a VRBPAC meeting is held and its members, who are viewed as technical experts in their professional field, make determinations and recommendations about product safety and effectiveness to FDA. My model of the techno-regulatory system incorporates the concept of the obligatory passage point from Actor Network Theory to explain how actors who seem outside the system can nonetheless force change within the system.

The techno-regulatory system model also incorporates insights from Organizational Theory and Collaborative Theory to capture the back and forth collaboration and conflict between system actors. Unlike many of Hughes's system examples, where the system builders had a shared interest in the fortunes of a single corporation or

other large organization, organizations in a techno-regulatory system may have diverse and competing interests but are obliged to work together. Because of regulatory mandates that certain actors work together, a techno-regulatory system has constant back and forth interaction between actors to resolve conflict, and the development of a technology is not linear but much more complex. For example, many different regulatory actors who are assigned to review a drug product make a determination if the technology meets established regulatory guidelines or, if not, communicate their regulatory concerns to the drug sponsor. Until the drug company addresses the regulatory issues or some type of compromise is reached, the drug product will not advance to licensure and the consumer market. This collaborative effort to develop drug technology takes place throughout the lifecycle of the product and involves many different actors. The example of the BSE case study and the passing of the PREA are two examples where conflicts had to be resolved in order for the technology to advance. Organizational Theory and Collaborative Theory help explain how decisions are made concerning a technology and how these decisions may have influenced the outcome.

While the focus of my discussion has been limited to biologics, my revised system model could also apply to other proactively regulated technologies involving drug development (i.e. Drugs) and other techno-regulatory systems beyond this case study. For example, my system model would be appropriate to explore case

studies involving the Federal Communication Commission (FCC), the United States Environmental Protection Agency (EPA) and the United States Nuclear Regulatory Commission (NRC). Each of these systems includes rulemaking, licensing, inspections, regulations, actor conflict and compromise. System actors include the mainstream actors and actors from the environment. For example, the NRC issues rules through a process called "rulemaking" and any member of the public can propose that NRC develop, change, cancel, or rescind the regulation.

From a policy perspective, understanding the unique characteristics and challenges of a techno-regulatory system could potentially produce better guidance, White papers and regulatory policies that play a crucial role in drug development and affect many actors. This new model approach can help to improve written policy and guidance by recognizing both the mainstream system actors and those who are part of the environment (e.g., public and/or patient-advocacy groups) who play an influential role in the techno-regulatory system of drug development. Once these mainstream actors and external actors are identified, a collaborative approach can be used to discuss the proposed policy or drafted guidance and actor concerns identified. The knowledge gained through this early collaborative process can help to iron out differences early in the process and then be applied to revising the draft guidance, and/or policy before implementation. This will result in less revisions, actor conflicts, and cost.

The regulation process has substantially grown since the 1902 Act, and to many this complex system of regulation might be stifling. Today, many actors within an organization are involved in the process of drug development, each with their own agenda and goals. Quite recently, during the 2016 State of the Union Address, President Obama announced the National Cancer Moonshot Initiative to harness the spirit of American innovation to identify new ways to prevent, diagnose, and treat cancer. To accomplish this task, the Obama administration plans to provide 1 billion dollars to jumpstart this program by having the FDA develop a virtual Oncology Center for Excellence. This initiative will leverage the combined skills of regulatory scientists and reviewers with expertise in biologics, drugs, and devices. My improved LTS Theory can greatly help this cancer initiative by identifying the internal organizations and external system actors who are to be involved in this collaborative effort. By exploring the cultural differences between the stakeholders that are to be involved in this National Cancer Moonshot Initiative, one can gain a better understanding of what makes sense to each actor. This understanding can help make decisions, establish rules, avoid potential conflicts and most importantly help to expand the combined skills of system actors to gain needed knowledge and overall success. In response to the 2016 Union Address, the FDA CBER Center Director responded by informing staff to develop this program, the FDA will seek the involvement of all stakeholders. These stakeholders will be from various

organizations and will have diverse and competing interests and cultures. The techno-regulatory system model is a promising approach and no other System Theory approach appears to measure up to tackle this complex challenge.

Appendix A

Phases of Clinical Drug Development

Following animal testing, manufacturers may choose to submit an investigational new drug application (IND) to the FDA for testing of their investigational product in humans. Congressional acts regulating interstate commerce forbid a drug product from crossing state lines without an assigned investigational new drug number or the FDA's approval of the product. Since drug products are often shipped via interstate commerce from the drug manufacturer to the clinical research organization, the sponsor must submit an IND to satisfy this requirement or to request an exemption from this requirement.[212] FDA's role in the development of the investigation drug begins when a drug sponsor requests permission from the FDA to conduct a clinical study using an investigational product. This occurs by submission of an IND application that contains a clinical protocol and summary information of the laboratory testing, and manufacturing.[213] These clinical trials are controlled

[212] U.S. Department of Health and Human Services, Food and Drug Administration, *Investigational New Drug (IND) Application*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm (accessed March 12, 2016).

[213] Norman Baylor and Karen Midthun, "Regulation and Testing of Vaccines," Vaccines 4th Edition, ed. Stanley A. Plotkin, Walter A. Orenstein and Paul A. Offit, (Philadelphia: W.B Saunders Co.,

experiments that have an established clinical outcome.[214] The clinical trial process that takes place for a product to reach licensure is often time-consuming, costly and ranges from $350 million to $500 million.[215] In addition to determining the clinical outcome, drug manufacturers will need to test their product(s) for safety, sterility, purity, and potency prior to licensure. This helps to ensure consistently of a suitable product and subsequently used for testing.[216] The clinical investigation of a novel drug generally goes through three investigative phases before potential licensure. These three stages of clinical trials are in Figure 9.[217]

2004), 1539-1556.

[214] Committee on Strategies for Small-Number-Participant Clinical Research Trials, Board on Health Sciences Policy (2001) *Small Clinical Trials: Issues and Challenges*. Washington, DC: The National Academies Press (p.12). http://www.nap.edu/catalog /10078/small-clinical-trials-issues-and-challenges

[215] Zeke Ashton, The FDA and Clinical Trials: A Short History. The Body: The complete HIV/AIDS Resource, http://www.thebody.com /content/art398.html (accessed March 10, 2016.

[216] Norman Baylor and Karen Midthun, "Regulation and Testing of Vaccines, 1539-1556.

[217] U.S. Department of Health and Human Services, Food and Drug Administration, 21 CFR312.21 CFR – Code of Federal Regulations, Title 21, *Phases of an investigation*. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/ CFRSearch.cfm?FR=312.21 (accessed March 12, 2016).

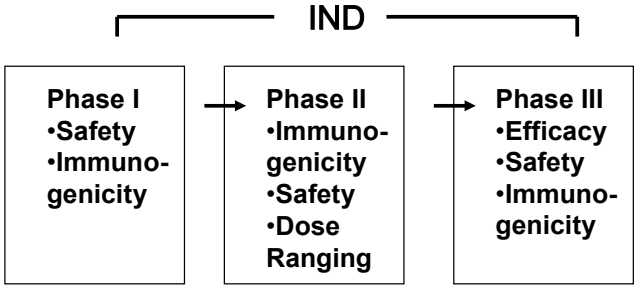

Figure 9: The Three Phases of an IND
This figure illustrates the primary focus of each phase of drug development.

When a product goes through IND phases, the drug manufacturers often submit publications about the progress of the clinical trials to solicit stakeholder interests. Typically, substantial progress in a particular drug occurs in increments over time and advances build on each other. From peer review articles about the progress of the investigational product to the stirring of the collaborative research ecosystem, this process consists of industry, academia, government and other actors. With this sharing of information, other groups such as advocacy groups show interest in the product and push for further development of the investigational product. Based on the results of animal testing of a product, an investigator (e.g., the drug manufacturer) may pursue further development of the investigative new drug by deciding to study the investigational drug product in humans in a Phase 1 trial. To do this they submit an investigational drug application to the FDA that includes a study protocol outlining inclusion and exclusion

criteria, study purpose, informed consent documents, an investigator brochure and other key information. These same documents are submitted to an Institutional Review Boards (IRB). When designing the clinical trial the drug study design must be in alignment with established regulations enforced by the IRB and the FDA or the clinical evaluation of the investigational drug product halted.

Phase I trials assess the safety and immunogenicity in a small, highly controlled population of 20-80 subjects. The studies themselves are designed to determine the metabolism and pharmacologic actions of the drug product being investigated in study participants.[218] For example, when assessing the management and prevention of a disease, a thorough understanding of the factors that influence a response in humans when being exposed to a drug is paramount. Typically, Phase 1 trials are conducted in adults and later evaluated in lower age ranges as more information is gathered. Phase 2 trials are clinical trials that are conducted to assess the safety and effectiveness of the drug for a particular indication. These closely monitored trials usually include a study population of several hundred subjects

[218] U.S. Department of Health and Human Services, Food and Drug Administration, (2014). 21 CFR312.21 CFR – Code of Federal Regulations, Title 21, *Phases of an investigation*, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.21

and include the assessment of dose-ranging to determine the lowest dose that can be given to establish a response. An established response may include stimulating immunity following vaccine administration, or the prevention or treatment of disease. If the close monitoring of subjects identifies no safety concerns, sponsors may request from the FDA an End-Of-Phase-2 meeting to discuss any outstanding issues, clinical endpoints, safety concerns and clinical drug protocol proposals for Phase 3 trials to show efficacy needed for licensure. Phase 3 studies include study populations of several hundred to several thousands and need to demonstrate safety as well as efficacy (or effectiveness).[219]

Throughout the IND and biologics licensing application (BLA) process, drug manufacturers are in constant communication with the FDA via teleconferences, face-to-face meetings, submission of annual progress reports, and safety reports. It is only after completion of these pre-market studies under IND that the manufacturer may choose to submit to the FDA a BLA. Based on review of the submitted IND study data and product manufacturer testing information, the FDA may communicate to the drug manufacturer that the IND may move forward to the licensure process. (Figure 10)[220]

---

[219] Ibid.

[220] Martin S. Lipsky and Lisa K. Sharp, "From Idea to Market: The

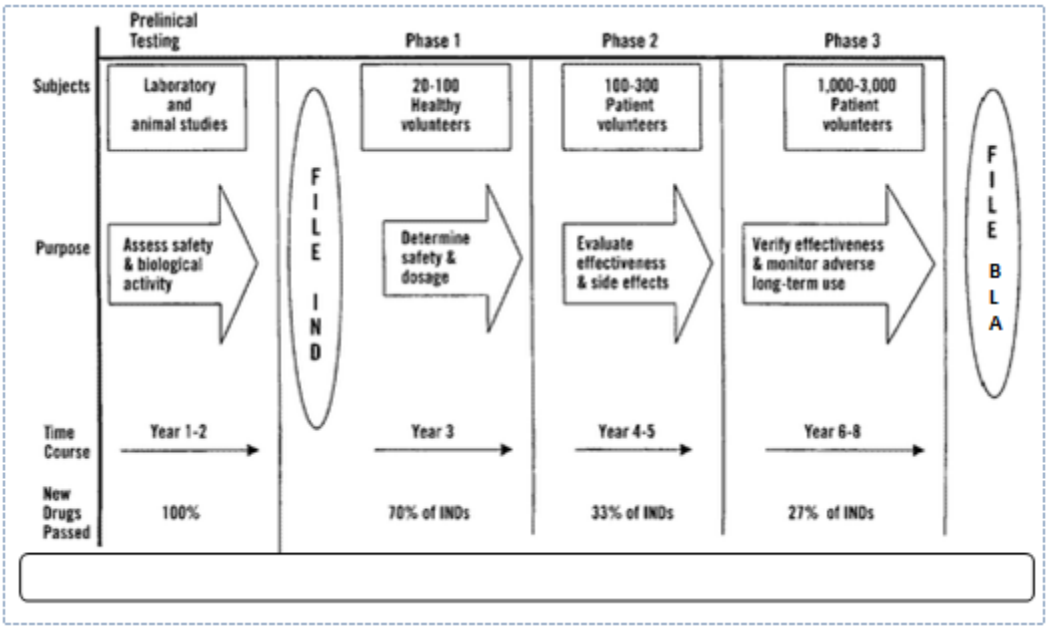

Figure 10 [Fair Use]: Study Phases
This figure illustrates the study phases of drug development, the average time needed to complete a study phase, the number of study subjects needed for clinical phase of drug development, and the percentage of drugs that make it through each phase of development.

After the FDA receives the drug submission requesting licensure, the review team with concurrence from the division director will designate the application as priority or standard per the FDA's Prescription Drug User Fee Act performance goals.[221] The designation establishes the milestones and goal

---

Drug Approval Process", Journal of American Family Medicine, 2001;14(5), http://www.medscape.com/

[221] U.S. Department of Health and Human Services, Food and Drug Administration, *Manual Policies and Procedures Center For Drug Evaluation and Research Policies and Procedures Office of New Drugs Review Designation Policy: Priority (P) and Standard (S) MAPP 6020.3 Rev. 2 (2013).* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf

date by which the application needs to be reviewed. Applications may be designated as "priority' if they are for drugs that treat serious conditions and provide significant improvements over existing therapies. Priority review applications have a set 6-month goal date for the FDA to take action. Standard review designation submissions have a 10-month standard review time to either approve the submission or halt review of the submission by issuing a complete response letter.[222] During this 6-month or 10-month review time, the FDA reviewers assess chemistry, manufacturing, and control information and the clinical results to evaluate safety, efficacy, and statistical information, including the proposed prescribing information. Information requests are often communicated to the sponsor to request additional information or clarifications. If the FDA identifies significant deficiencies when reviewing the submission, the FDA may issue a Complete Response letter that lists the significant deficiencies and halts the drug approval process until the sponsor provides the information to address the deficiencies and start the review clock. Deficiencies identified may include established endpoints concerns, missing data, manufacturing compliance issues, drug substance concerns, and/or identified safety concerns. Once a drug sponsor submits the complete

[222] Ibid.

response information to the FDA for review, the FDA has 6 months to review clinical related issues/or 4 months to review non-clinical review issues (chemistry, manufacturing) and make a determination to either approve the licensing application or issue another complete response letter if the sponsor's response information is not adequate. When complete response letters are issued all deficiencies are to be included in the letter. During the review of the drug licensing application, the drug manufacturer and the FDA often agree to postmarketing commitments (PMCs) or Phase 4 studies. Additionally, many manufacturers also take their own initiative to conduct studies for other indications such as younger or older age groups. The process described above occurs in the development of biologics such as vaccines and for new drug development.

The above-described phases of drug development are typical for many biologics. However, at times, based on the seriousness of the condition or perhaps a shortage of drug product an accelerated approval licensure pathway may be used. An accelerated approval licensure pathway allows for an earlier approval of drugs for the treatment of serious conditions or to fulfill an unmet medical need based on a marker, such as a laboratory measure that is thought to predict clinical benefit,

but is not itself a measure of clinical benefit.[223,224] Under an accelerated approval pathway, the FDA approves the product to allow earlier public access to the drug product, but it requires post-marketing studies be performed to confirm the product's clinical benefit. This pathway differs from a traditional approval pathway in that traditional product approval often takes longer to determine the clinical outcome since the clinical benefit is determined first followed by product approval or licensure.[225] Because of the longer time needed under a traditionally approval pathway, marketing access to the drug takes longer.

Following fulfillment of the regulatory requirements for accelerated approval, the drug sponsor is then required to perform adequate and well-controlled postmarketing studies to assess the clinical benefit of the product. If the confirmatory trial shows that the drug actually provides a clinical benefit,

---

[223] U.S. Department of Health and Human Services, Food and Drug Administration, (2014) 21 CFR601.41 CFR – Code of Federal Regulations Title 21, http://www.accessdata.fda .gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=601.41

[224] U.S. Department of Health and Human Services, Food and Drug Administration, (2014) 21 CFR314.510 CFR – Code of Federal Regulations Title 21. *Retrieved from* http://www.accessdata. fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&show FR=1&subpartNode=21:5.0.1.1.4.8

[225] Shane FitzMaurice, Transforming the Regulatory Environment to Accelerated Access to Treatment (TREAT) Act Introduced. *Policy and Medicine,* February 23, 2012, http://www.policymed.com/2012 /02/transforming-the-regulatory-environment-to-accelerate-access-to-treatments-treat-act-introduced.html

then the FDA grants traditional approval for the drug. If the confirmatory trial fails to show that the drug provides clinical benefit, the FDA has the regulatory authority and procedures under 21 CFR 601.43 to withdraw product approval, resulting in the removal of the drug product from the market.

References

Abbate, Janet. "From control to coordination: new governance models for information networks and other large technical systems." in *The Governance of Large Technical Systems*, edited by Olivier Coutard, London: Routledge, 1999.

Abrams, William B. "*Rescuing the Therapeutic Orphan: The Potential of Pediatric Pharmacology Realized." American Society for Clinical Pharmacology and Therapeutics.* http://www.ascpt.org/About-ASCPT/Awards/ASCPT-FDA-William-B-Abrams-Award-Lecture/2010-William-B-Abrams-Lecture

Anderson, Juliana DeCarvalho. "Elixir Sulfanilamide." *Toxipedia (2013).* http://www.toxipedia.org/display/toxipedia/Elixir+Sulfanilamide

Ashton, Zeke. "The FDA and Clinical Trials: A Short History." The Body: The complete HIV/AIDS Resource. http://www.thebody.com/content/art398.html (accessed March 10, 2016.

Ballentine, Carol. "Sulfanilamide Disaster: Taste of Rasberries, Taste of Death. The 1937 Elixir Sulfanilamide incident." *FDA Consumer Magazine,* 1981. http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm

Baylor, Norman and Karen Midthun. "Regulation and Testing of Vaccines." Vaccines 4th Edition, editors. Stanley A. Plotkin, Walter A. Orenstein and Paul A. Offit, (Philadelphia: W.B Saunders Co., 2004), 1539-1556.

Blumer, Jeffrey. "Origins of the PPRU - Therapeutic Orphans." *Pediatric Pharmacology Research Units (PPRU*). http://www.Ppru.org/reports.aspx

"BPCA and PREA Reauthorization." Congressional Childhood Cancer Caucus. Last modified March 18, 2016. https://childhoodcancer-mccaul.house.gov/issue/bpca-and-prea-reauthorization

Carpenter, Daniel P. "Pure Food and Drug Act (1906)." Major Acts of Congress. 2004. *Encyclopedia.com.* http://www.encyclopedia.com/doc/1G2-3407400257.html

Cavers, David F. "*The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions." Law and Contemporary Problems, no 6 1939:39. http://scholarship. law.duke.edu/cgi/viewcontent.cgi?article=1937&context=lcp*
Centers for Disease Control and Prevention "Strategic National Stockpile (SNS). "http://www.cdc.gov/phpr/stockpile/ stockpile.htm.

Collazo-Custodio, Carmen. "Summary Basis of Regulatory Action (SBRA)." U.S. Department of Health and Human Services, Food and Drug Administration. http://www.fda.gov/downloads/Biol ogicsBloodVaccines/Vaccines/ApprovedProducts/UCM379624.pdf

Committee on Strategies for Small-Number-Participant Clinical Research Trials, Board on Health Sciences Policy (2001) *Small Clinical Trials: Issues and Challenges*. Washington, DC: The National Academies Press (p.12). Retrieved from http://www.nap.edu/catalog/10078/small-clinical-trials-issues-and-challenges

Cook, Thomas J. "Differences in Clinical Drug Development in Europe, Japan, and the United States: A Biostatistician's Perspective." *Therapeutic Innovation & Regulatory Science* 29 (1995)4. http://dij.sagepub.com/content/29/4/1345. (accessed March 22, 2016) Fair Use determination attached.

Crosse, Marcia. *Pediatric Drug Research: The Study and Labeling of Drugs for Pediatric Use under the Best Pharmaceuticals for Children Act (*GAO-07-898T). Washington DC: U.S. Government Accounting Office, 2007. http://www.gao.gov/products/A69826

Drugs.com, *Fluzone,* http://www.drugs.com/pro/fluzone.html (accesed March 22, 2016) Fair Use determination attached.

Epstein, Steven. "*Histories of the Human Subject." Inclusion.* Chicago: The University of Chicago Press, 2007

Epstein, Steven. *Inclusion: The Politics of Difference in Medical Research.* Chicago: University of Chicago Press, 1989, 43-45.

Epstein, Steven. "The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials." Science, Technology, & Human Values 20, No. 4, 1995:408-437. http://ambounds.org/docs/716/Steven %20Epstein.pdf

Federal Register: Electronic Code of Federal Regulations. "CFRs are general and permanent rules of the Federal Government developed by federal departments and agencies which are published in the Federal Register. Within the Federal Register are public notices of rulemaking, proposed rules, final rules and other types of public interests" http://www.ecfr.gov/cgi-bin/text-idx?rgn=div5&node=14:1.0.1.1.1

Field, Marilyn J. and Richard E. Behrman. "The Necessity and Challenges of Clinical Research Involving Children." in *Institute of Medicine (US) Committee on Clinical Research Involving Children*. Washington DC: National Academies Press, 2004.

FitzMaurice, Shane. "Transforming the Regulatory Environment to Accelerated Access to Treatment (TREAT) Act Introduced." *Policy and Medicine.* February 23, 2012. http://www.policymed.com/2012/02/transforming-the-regulatory-environment-to-accelerate-access-to-treatments-treat-act-introduced.html

"Global 2000: The Biggest Drug Companies of 2014," *Forbes,* www.forbes.com/pictures/eedh45fhhmf/no-1-pfizer

Gobburu, Joga "*Learn-Apply Paradigm: Re-Configuring Drug Development Goals,"* U.S. Department of Health and Human Services, Food and Drug Administration. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM209136.pdf.

Harkness, Richard. "Mercury-free flu shot vaccine is an option," *Union Tribune San Diego*, October 24, 2006, http://www.utsandiego.com/uniontrib/20061024/news_lz1c24qanda.html

Hughes, Thomas P. *American Genesis: A Century of Invention and Technological Enthusiasm 1870-1970* Chicago: University of Chicago Press, 2004.

Hughes, Thomas P. "Designing, Developing, and Reforming Systems." in *Daedalus, Cambridge: MIT Press, 1998.*

Hughes, Thomas P. "Managing a Military – Industrial Complex: Atlas." *Rescuing Prometheus* NY: Random House, 1998.

Hughes, Thomas P. "Reverse Salients and Critical Problems." in *Networks of Power: Electrification in Western Society, 1880-1930".* Baltimore: The John Hopkins University Press,1993.

Hughes, Thomas P. "The Evolution of Large Technological Systems." in *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology. edited Wiebe* Bijker and Thomas P. *Hughes* Cambridge MA: MIT Press, 1987.

Joerges, Bernward. "Large Technical System: Concepts and Issues." in *The Development of Large Technical Systems,* Renate Mayntz and Thomas P. Hughes Boulder: Westview Press, 1988.

Jones, Gareth. *Organizational Theory: Text and Cases* **B**oston: Addison-Wesley Publishing Company, 1995.

Kessel, Mark. "Restoring the pharmaceutical industry's reputation." Nature Biotechnology 32. 2014:983-990. http://www.nature.com/nbt/journal/v32/n10/full/nbt.3036.html

Kingham, Richard, Gabriela Klasa and Krista Hessler Carver, "Key Regulatory Guidelines for the Development of Biological in the United States and Europe" In *Biological Drug Products: Development and Strategies*, ed. Wei Wang and Manmohan Singh. (John Wiley & Sons, Inc. Hoboken, New Jersey), 75.

Kline, Ronald and Trevor Pinch. "*The Social Construction of the Automobile in the Rural United States," Technology and Culture* 37, (1996): 763-795. doi: 10.2307/3107097

LaPalombara Joseph. "Power and Politics in Organizations: Public and Private Sector Comparisons," in Dierkes, M., Berthoin Antal, A., Child, J., and Nonka, (Eds.), *The Handbook of Organizational Learning and Knowledge.* New York: Oxford University Press, 2001.

Levin, Myron. "Merck Misled on Vaccines, Some say," *Los Angeles Times,* March 7, 2007, http://articles.latimes.com/2005/mar/07/business/fi-merck7

Lipsky, Martin S. and Lisa K. Sharp, "From Idea to Market: The Drug Approval Process", Journal of American Family Medicine, 2001;14(5), http://www.jabfm.org/content/14/5/362.full.pdf+html (Accessed March 22, 2016) Fiar Use determination attached.

Lorenzetti, Laura. "Is it time for the FDA to consider cost when it comes to new drugs?" *Fortune, February 4, 2015.* http://fortune.com/2015/02/04/is-it-time-for-the-fda-to-consider-cost-when-it-comes-to-new-drugs/(2015, February)

Luck, Jo. "You think you have problems with your research

participants? My research subjects don't have a pulse!" Faculty of Informatics & Communication, Central Queenland University. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.214.6491&rep=rep1&type=pdf

Makwana, Sagar, Biswajit Basu, Yogita Makasana and Abhay, Dharamsi. "Prefilled syringes: An innovation in parenteral packaging" *International Journal of Pharmaceutical Investigation*, 4 2011. accessed March 2, 2016, doi: http://dx.doi.org/10.4103%2F2230-973X.93004

Martin, Darlene. "A Comparison of the Food and Drug Regulations That Provide the Framework for How Probiotics are Regulated in the United States. Unpublished Master's Thesis Hood College, Maryland, 2014.

Martinez, Joel. "An Overview of the Drug Approval Process." *The Body: The Complete HIV/AIDS Resource Center for Aids* (2002). http://www.thebody.com/content/art16845.

Mayntz Renate and Thomas P. Hughes, editors. *The Development of Large Technical Systems.* Frankfurt am Main: Campus Verlag 1988 http://hdl.handle.net/2027/heb.01147.0001.001

Miller, Henry. "Failed FDA Reform." *Regulation* 21 (1998)(3). http://object.cato.org/sites/cato.org/files/serials/files/regulation/1998/7/v21n3-ftr2.pdf

"Miscellaneous News: Electric Lighting in the Metropolis." in *The Journal of Gas Lighting, Water Supply & Sanitary Improvement* London: Walter King, 1889.

"Notice to Readers: Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the U.S. Public Health Service." *CDC Morbidity and Mortality Weekly Report (MMWR)*,(July 9, 1999). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4826a3.htm

Olsson, Mats-Olov, and Gunnar Sjostedt. "Large Technical Systems a Multidisciplinary Research Tradition." in *System Approaches and Their Application Examples from Sweden* Berlin: Springer Science & Business Media, 2004.

Groger, Julia. "*Studiengang, Master of Drug Regulatory Affairs Master Thesis Comparison of the Pediatric Drug Legislation between US and EU Food and Drug Administration safety and Innovation Act (Title V) versus EU Paediatric Regulation (EC) NO*

*1901/2006.” M*aster’s theses, Kooperation Universitabonn, 2014. http://dgra.de/deutsch/studiengang/master-thesis/2014-Julia-Gr%C3%B6ger-Comparison-of-the-Pediatric-Drug-Legislation-between-US-and-EU-F?nav=studiengang

Gruber, Marion. “OVRR Office Director’s MEMORANDUM.” U.S. Department of Health and Human Services, Food and Drug Administration. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM378662.pdf.

Hans Stotter, “Paediatric Drug Development Historical Background of Regulatory Initiatives” in *Guide to Paediatric Clinical Research, ed.* Klaus Rose and John van den Anker, *(Basel, Switzerland 2011), 27.*

Janssen, Wallace F. “The Story of the Laws Behind the Labels.” U.S. Department of Health and Human Services, Food and Drug Administration. http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm

Karst, Kurt R. “Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry.” *American University Law Review* 49 2000(3),739-772.

Kent, Alastair. Cor Oosterwijk, Tsveta Schyns and Ysbrand Poortman. “Paediatric Medicine: A View from Patient Organizations.” in *Guide to Paediatric Clinical Research,* edited Klaus Rose and John Van den Anker. *Switzerland: S Karger AG, 2007.*

“ICH Harmonization for Better Health, History,” accessed March 6, 2016. http://www.ich.org/about/history.html

“ICH Harmonization for Better Health, M4: The Common Technical Document.” http://www.ich.org/about/history.html

Lang, Michelle. "Pervasis drug candidate gets EU orphan drug status." Mass High Tech. http://www.bizjournals.com/boston/blog/mass-high-tech/2011/03/pervasis-drug-candidate-gets-eu-orphan-drug.html

MacLoed, Stuart. “Therapeutic drug monitoring in pediatrics: how do children differ?" *Therapeutic Drug Monitoring* 32 no. 3, 2010.

Marks, Harry M. *Cambridge History of Medicine, The Progress of*

Experiment Science and Therapeutic Reform in the United States, 1900-1990. Cambridge MA: Cambridge University Press, 2000.

Nickell, Joe. "Peddling Snake Oil". The Committee For Skeptical Inquiry. http://www.csicop.org/sb/show/peddling_snake_oil/
Kondratas, Ramunas. "*Biologics Control Act of 1902". In The Early Years of Federal Food and Drug Control.* Madison, Wis.: American Institute of the History of Pharmacy, 1982.

Office of Legislative Policy and Analysis (n.d.). 107th Congress: "Best Pharmaceuticals for Children Act", [Weblog], http://olpa.od.nih.gov/legislation/107/public laws/1best.asp

Office of The Press Secretary, "FACT SHEET: Investing in the National Cancer Moonshot, (February 1, 2016) https://www.whitehouse.gov/the-press-office/2016/02/01/fact-sheet-investing-national-cancer-moonshot

Off-label use is when a licensed physician prescribes a drug to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling. FDA does not have the authority to regulate health care providers' use of prescribed drugs for other than what the package insert indicates. Frader, Dresser, R. "Off-Label Prescribing: A Call for Heightened Professionals and Government Oversight." *Journal of Law, Medicine and Ethics*, 37(3), 2009.

Ourso, Andre "Can the FDA Improve Oversight of Foreign Trials?: Closing the Information Gap and Moving Towards a Globalized Regulatory Scheme." *Annual of Health Law* 21 (2012): 2. http://lawecommons.luc.edu/cgi/viewcontent.cgi?article=1008&context=annals

Per 21 CFR Part 99 entitled *Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices* off-label scientific information which has not been included in the approved FDA prescription insert may be disseminated to health care providers, pharmacy benefit managers and health insurance issuers in the form of peer reviewed journals and referenced publications. U.S. Department of Health and Human Services, Food and Drug Administration (2010, February) *Regulatory Information,* http://www.fda.gov/regulatory information/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdama/ucm089179.htm *accessed March 6, 2016.*

Ravesteijn, William, Leon Hermans, and Erik van der Vleuten. "Participation and Globalization in Water System Building." *Knowledge, Technology, & Policy*, 14(4), 2002. http://ocw.tudelft.nl/courses/sustainable-development/technology-dynamics-and-transition-management/readings/

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; *Final Rule Federal Register.* December 2, 1998 (Volume 63, Number 231)[Page 66631-66672].

Rip, Arie "Citation for Thomas P. Hughes, 1990 Bernal Prize Recipient*". Science, Technology & Human Values*, 16 (1991).

Root, George N. "Differences Between Horizontal & Vertical Organizations." *Chron Small Business.* http://smallbusiness.chron.com/differences-between-horizontal-vertical-organizations-20335.html

Shirkey, Harry, C. "The Package Insert Dilemma," *The Journal of Pediatrics.* 79 (1971)4:691-693.

Shirkey, Harry C. "Pediatric Pharmacology and Therapeutics: Drug Administration." *The Journal of Pediatrics.* 66 1965 5:909-917.

Swann, John, P. "FDA's Origin," U.S. Department of Health and Human Services, Food and Drug Administration. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm

Stotter, Hans. "Paediatric Drug Development Historical Background of Regulatory Initiatives." in Guide to Paediatric Clinical Research, edited. Rose Klause and John Van den Anker, (Washington, D.C./Rotterdam, 2007).

Temeck, Jean. "Pediatric Product Development in the U.S." Slides presented at the symposium conducted at the FDA Seminar, Copenhagen, November 2010. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM262309.pdf

Thaul, Susan. "*FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective." Congressional Research Service website. http:www.*fas.org/sgp/crs/misc/RL33986.pdf

The American Academy of Pediatrics. "*AAP History."* https://www.aap.org/en-us/about-the-aap/Pediatric-History-Center/Pages/AAP-History.aspx

The American Academy of Pediatrics. "About the AAP." https://www.aap.org/en-us/about-the-aap/Pages/About-the-AAP.aspx

The American Medical Association. "AMA Mission & Guiding Principles." http://www.ama-assn.org/ama/pub/about-ama.page?

The Free *Dictionary by Farlex. Package Insert.* Accessed May 9, 2015. http//medical-dictionary,thefreedictionary.com /package+insert.

The World Health Organization. "Handbook For Good Clinical Research Practice Guidance for Implementation 2002." www.who.int/medicines/areas/quality_safety/safety_efficacy /gcp1.pdf

Tsai, Wendy and Stanford Erickson. "Early-Stage Biotech Companies: Strategies for Survival and Growth." *Biotechnology Healthcare* 3, no. 3 2006. http://www.ncbi.nlm.nih. gov/pmc/articles/PMC3571061/

University of Pennsylvania, "Thomas P. Hughes," https://hss. sas.upenn.edu/people/hughes

U.S. Department of Health and Human Services, Food and Drug Administration, *Biologics License Application (BLA) Process (CBER)* Last Modified November 5, 2015, http://www.fda.gov /BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLice nseApplicationsBLAProcess/default.htm.downloads/Biologics BloodVaccines/InternationalActivities/UCM273206.pdf.

U.S. Department of Health and Human Services. Food and Drug Administration, Center For Biologics Evaluation and Research *SOPP 8412: Review of Product Labeling,* http://www.fda.gov /downloads/BiologicsBloodVaccines/GuidanceCompliance RegulatoryInformation/ProceduresSOPPs/UCM277726.pdf

U.S. Department of Health and Human Services, Food and Drug Administration. *FDA Approves First U.S. Vaccine for Human Against the Avian Influenza Virus H5N1.* http://www.fda.gov /NewsEvents/Newsroom/PressAnnouncements/2007/ucm108892.htm

U.S. Department of Health and Human Services, Food and Drug Administration. *FDA Transparency Initiative: Draft Proposals for Public Comments Regarding Disclosure Policies of the U.S. Food and Drug Administration,* (1978) http://www.fda.gov/down loads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsa

ndAbbreviations/UCM212110.pdf

U.S. Department of Health and Human Services, Food and Drug Administration. *Guidance and Regulation.* http://www.fda.gov/Food/GuidanceRegulation/

U.S. Department of Health and Human Services, Food and Drug Administration. *Guidance for Industry: General Considerations for the Clinical Evaluation of Drugs in Infants and Children,* September 1977. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071687.pdf

U.S. Department of Health and Human Services, Food and Drug Administration, Guidance for Industry: How to comply with the Pediatric Research Equity Act, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079756

U.S. Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998), *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf (accessed March 12, 2016).*

U.S. Department of Health and Human Services, Food and Drug Administration. *Institutional Review Boards Frequently Asked Questions – Information Sheet.* http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm.

U.S. Department of Health and Human Services, Food and Drug Administration, *Investigational New Drug (IND) Application*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm (accessed March 12, 2016).

U.S. Department of Health and Human Services, Food and Drug Administration. "Labeling and prescription drug advertising: content and format of labeling for human prescription drugs." *Federal Register,* 1979, 44:37434-37467

U.S. Department of Health and Human Services, Food and Drug Administration, *Manual Policies and Procedures Center For Drug Evaluation and Research Policies and Procedures Office of New Drugs Review Designation Policy: Priority (P) and Standard (S) MAPP 6020.3 Rev. 2 (2013).* http://www.fda.gov/downloads

/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf

U.S. Department of Health and Human Services, Food and Drug Administration. "*Office of the Center Director: Resolution of Disputes: Roles of Reviewers, Supervisors, and Management Documenting Views and Findings and Resolving Differences, Manual of Policies and Procedures MAPP 4151.1.*" http://otrans.3cdn.net/8eaee20f2088e70485_38m6iyd3k.pdf

U.S. Department of Health and Human Services, Food and Drug Administration. *Orphan Drug Act.* http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm.

U.S. Department of Health and Human Services, Food and Drug Administration. *Overview of the Office of Vaccines Research and Review*, http://www.fda.gov/

U.S. Department of Health and Human Services, Food and Drug Administration. *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex – Guidance for Industry and Food and Drug Administration Staff. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm342872.pdf*

U.S. Department of Health and Human Services, Food and Drug Administration."Recommendations for the Use of Vaccines Manufactured with Bovine-Derived Materials Transcript of 27 July 2000, Joint Meeting of the Transmissible Spongiform Encephalopathy and Vaccines Related Biologicals Advisory Committees." http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm111476.htm accessed March 23, 2016.

U.S. Department of Health and Human Services, Food and Drug Administration. *The FDA Announces New Prescription Drug Information Format.* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm188665.htm

U.S. Department of Health and Human Services, Food and Drug Administration, "Thimerosal in Vaccines," http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228 accessed March 22, 2016.

U.S. Department of Health and Human Services, Food and Drug Administration, *21 CFR 312.21 CFR – Code of Federal Regulations,*

Title 21, Phases of an investigation http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.21

U.S. Department of Health and Human Services, Food and Drug Administration, (2014) *21 CFR314.510 CFR – Code of Federal Regulations Title 21 Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses,* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8

U.S. Department of Health and Human Services, Food and Drug Administration, (2014) *21 CFR601.41 CFR – Code of Federal Regulations Title 21 Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.* http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=601.41

U.S. Department of Health and Human Services, National Institute of Allergy and Infectious Diseases. *RSV Vaccine Workshop National Institute of Allergy and Infectious Diseases.* https://respond.niaid.nih.gov/conferences/RSVWorkshop/Pages/Logistics.aspx.

U.S. Department of Health and Human Services, National Institute of Child Health and Human Development (2003). *Pediatric Off-Patent Drug Study (PODS) Center – Lorazepam – Status Epilepticus,* http://grants.nih.gov/grants/guide/notice-files/NOT-HD-03-012.html.

U.S. Department of Health and Human Services, National Institutes of Health. "*The Need for Awareness of Clinical Research."* http://www.nih.gov/health-information/nih-clinical-research-trials-you/need-awareness-clinical-research.

U.S. Department of Health and Human Services, National Institutes of Health. "Turning Discovery into Health." http://www.nih.gov/about/

U.S. District Court For the District of Columbia Association of America Physician and Surgeons INC., et al Plaintiffs, V. United States Food and Drug Administration, et al., Defendants Civil Action 00-02898.

U.S. Government Publishing Office (n.d.) "ABOUT FEDERAL REGISTER". [Weblog], http://www.gpo.gov/help/about federalregister.htm

U.S. Government Publishing Office, *Federal Register,* Wednesday December 2, 1998 Part II Department of Health and Human Services Vol. 63, No 231 Washington, DC.

U.S. Nuclear Regulatory Commission, "Rulemaking", http://www.nrc.gov/
U.S. Public Health Service Syphilis Study at Tuskegee, "The Tuskegee Timeline" Centers for Disease Control and Prevention http://www.cdc.gov/tuskegee/timeline.htm, February 19, 2016.

"Vaccine Resistance Movement," http://vaccineresistance movement.org/?page_id=7452 (accessed March 22, 2016,) Fair use determination attached.

Van der Vleuten Erik. "Infrastructures and Societal Change: A View from the Large Technical Systems Field." *Technology Analysis & Strategic Management*, 16, (2004). accessed February 22, 2016, doi:10.1080/0953732042000251160.

Van der Vleuten, Erik. "Large Technical Systems". In Olsen, J.K.B, Pedersen, S.A & Hendricks, V.F (Eds), *A Companion to the Philosophy of Technology.* Blackwell Publishing Ltd, 2009
Mayntz, Renate and Thomas P. Hughes."The Development of Large Technical Systems." *The Business History Review*, 65, 1991.

Vander Stichele, Robert H. "*Impact of written drug information in patient package inserts: Acceptance and benefit/risk perception.*" *Doctoral dissertation., Ghent University*, 2004. https://books.google.com/books?isbn=9038206186

Wheatley, George. "Pediatrics in Transition," *Journal of the American Medical Association, 168, (1958):856*

Wittich, Christopher M., Christopher M. Burkle and William Lanier, "Ten Common Questions (and Their Answers) About Off-label Drug Use." *Mayo Clinic Proceedings. 87 2012:* 982-990, http://doi.org/10.1016/j.mayocp.2012.04.017

Woodland, Rebecca and Michael S. Hutton, "Evaluating Organizational Collaborations: Suggested Entry Points and Strategies." *American Journal of Evaluation* 33 2012:366-383.

Wright, Tiffany. "Principles of Organizational Theory." Small Business *Chron*. http://smallbusiness.chron.com/principles-

Yaffe, Sumner J. and Jacob V. Aranda. "Introduction and Historical Perspective." in *Neonatal and Pediatric Pharmacology*

Therapeutic Principles in Practice, editors. Sumner J. Yaffe, and Jacob V. Aranda. Philadelphia, PA: Lippincott Williams & Wilkins, 2010.

Yaffe, Sumner J., Harry C. Shirkey, Arnold P. Cold, Frederick M. Kenny, Mary Ellen Avery, Harris D. Riley, Jr., Irwin Schafer, Leo Stern, Henry L. Barnett, Alfred M. Bongiovanni, Robert J. Haggerty, American Academy of Pediatrics Committee on Drugs Statement of Purpose, Scope and Functions." *Pediatrics* 41 (1968):534. http://pediatrics.aappublications.org/content/pediatrics/41/2/534.full.pdf

Zachary, G. Pascal. "Remembering Thomas P. Hughes," *The New Atlantis 42 published by Center for the Study of Technology and Society, 2014*.

"Zyrtec Product Information." UCB Pharma. https://gp2u.com.au/static/pdf/Z/ZYRTEC-PI.pdf