CURING THE DRUG LAG: A PROPOSAL FOR INTERNATIONAL HARMONIZATION OF PHARMACEUTICAL APPROVAL

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I. INTRODUCTION

In 2007, a case came before the United States Court of Appeals for the District of Colombia concerning the urgency to allow terminally ill patients access to experimental drugs.[1] The case revolved around the life of Abigail Burroughs, who died of cancer at the age of twenty-one.[2] Abigail wanted access to the drug Erbitux, which had not yet been approved by the U.S. Food and Drug Administration (FDA).[3] Abigail's oncologist firmly believed that this experimental drug would improve Abigail's chance of surviving the cancer.[4] Unfortunately, Abigail was never granted access to Erbitux, which is now available on the American market. Following her death, the Abigail Alliance was formed in an effort to convince the United States Supreme Court to recognize access to experimental drugs as a constitutional right.[5] Even though access to experimental and unapproved drugs was not found to be a constitutional right, is there a way to grant access to these drugs to terminally ill patients more quickly?

Critics of the FDA agree with the Abigail Alliance that it takes far too long to approve experimental drugs. On average, it can take a new drug application somewhere between nine and twelve years to be approved by the FDA.[6] The costs of drug approval are also very vast. Companies expend approximately U.S. $800 million to get a new drug approved.[7] The 1962 Amendments to the Food, Drug and Cosmetic Act of 1938 may have something to do with the increased cost of drug approval and the "drug lag." The 1962

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1 Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695 (2007).

2 Frank Burroughs, *Our Story*, ABIGAIL ALLIANCE, http://abigail-alliance.org/story.php (last visited Mar. 3, 2014).

3 *Id.*

4 *Id.*

5 *Abigail Alliance for Better Access to Developmental Drugs*, 495 F.3d at 697.

6 Michael Dickson & Jean Paul Gagnon, *The Cost of New Drug Discovery and Development*, DISCOVERY MED. (June 20, 2009), http://www.discoverymedicine.com/Michael-Dickson/2009/06/20/the-cost-of-new-drug-discovery-and-development/ [hereinafter *The Cost of New Drug Discovery*]; *see also* Michael Dickson & Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Discovery and Development*, 3 NATURE REV. DRUG DISCOVERY 417, 417–29 (2004) [hereinafter *Key Factors in the Rising Cost of New Drug Discovery and Development*].

7 *The Cost of New Drug Discovery, supra* note 6.

Amendments added an efficacy requirement to the already stringent safety regulations,[8] although many other countries do not focus as heavily on the efficacy[9] of a drug.

In the past, attempts have been made to harmonize the drug approval processes between nations with similar economies and drug approval systems.[10] In the 1990s, the United States, the European Community (EC), and Japan came together and tried to standardize some of their various pharmaceutical regulations.[11] This was called the International Conference on Harmonization (ICH).[12] Although the ICH did experience some success, especially in the areas of animal and fertility toxicology, the nations failed to synchronize their drug approval standards.[13]

Politically, the United States has made efforts to harmonize with other countries, for example, in 1991, the President's Council of Competitiveness proposed some reforms and procedures to speed up the drug approval process.[14] This gesture was illuminating because it shows the United States' willingness to form reciprocity agreements.[15] However, the United States is reluctant to automatically approve drugs authorized in other countries because of the great differences in regulations and standards.[16]

The United States has synchronized efforts with other nations in the past to solve different global problems. The World Trade Organization (WTO) is a great example of when the United States cooperated with various nations to help solve the global trade problem.[17] Also, to protect itself and other countries from the threats of the Soviet Union, the United States joined the North Atlantic Treaty Organization (NATO).[18] Theoretically, it is possible for the United States to join with other countries in an attempt to harmonize pharmaceutical approval standards as well.

Thus, this note will address what kind of reciprocity agreements can be formed between different countries in the future to harmonize pharmaceutical

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[8] *See Key Factors in the Rising Cost of New Drug Discovery and Development, supra* note 6.

[9] *Efficacy Definition*, MERRIAM-WEBSTER DICTIONARY, http://www.merriam-webster.com/dictionary/efficacy (last visited Feb. 9, 2014).

[10] *See* Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations Among the United States, the European Economic Community, and Japan*, 16 HOUS. J. INT'L L. 665, 667 (1994).

[11] *Id.* at 667–68.

[12] *Id.*

[13] *See id.* at 695.

[14] *See* Julie C. Relihan, Note, *Expediting FDA Approval of AIDS Drugs: An International Approach*, 13 B.U. INT'L L.J. 229, 256 (1995).

[15] *See id.*

[16] *See id.* at 257.

[17] See *Who We Are*, WTO, http://www.wto.org/english/thewto_e/whatis_e/who_we_are_e.htm (last visited Jan. 8, 2014), for information about the WTO.

[18] See *What is NATO?*, NATO, http://www.nato.int/nato-welcome/index.html (last visited Jan. 8, 2014), for information about NATO.

approval standards in the most efficient manner. It will examine the FDA and its current standards for new drug approval. This note will commence with a history of the Food, Drug and Cosmetic Act and why drug regulation is a necessity, but a very costly and slow process. Secondly, this note will describe the current regulations and the process a drug sponsor must go through to gain market approval by the FDA. Thirdly, it will examine the drug approval processes in other countries, such as Great Britain and Japan. Finally, this note will examine other reciprocity agreements that the United States has entered into in the past. Specifically, why would a reciprocity agreement work now when it has failed previously? A reciprocity agreement with foreign nations that has similar pharmaceutical standards would be beneficial to speed up drug approval for terminally ill patients.

II. GOVERNMENTAL REGULATION OF DRUG APPROVAL IN THE UNITED STATES: THE FOOD AND DRUG ADMINISTRATION

A. History

1. Pure Food and Drugs Act of 1906

Prior to 1906, the United States was a "dumping ground for substandard and contaminated drugs" that were shipped from overseas.[19] In response, the first federal drug law was created to provide for laboratory inspections of imported drugs.[20] The law proved futile due to lack of enforcement and political support.[21] Moreover, drug standards varied greatly between the states.[22] After the American Civil War, interstate commerce began to expand and there was a drastic need for change.[23]

The federal government's first attempt to regulate drug distribution and consumption occurred in 1906 when Congress passed the Pure Food and Drugs Act (1906 Act).[24] The 1906 Act protected consumers by requiring manufacturers to label pharmaceuticals with accurate information concerning the identity and ingredients of the drug.[25] However, consumers were not protected from false health claims on drug labels.[26] For example, a drug marketer could claim that a

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[19] Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420, 422 (1981).

[20] *Id.* at 423.

[21] *See id.*

[22] *Id.* at 425.

[23] *See, e.g., id.*

[24] Pure Food and Drugs Act of 1906, ch. 3915, §§ 1–13, Pub. L. No. 59-384, 34 Stat. 768, *repealed by* Federal Food, Drug and Cosmetic Act of 1938, Pub. L. No.75-717, 52 Stat. 1040, 1059 (codified as amended at 21 U.S.C. § 301–99f (1988)).

[25] Janssen, *supra* note 19, at 427.

[26] *Id.*

pharmaceutical cured a disease when, in reality, the drug had no actual effect on that particular disease. Congress responded to the loophole in the law in 1912 by amending the 1906 Act to prohibit false and misleading claims of therapeutic effectiveness.[27] Although the purpose of the amendment was to limit false statements of therapeutic effectiveness, this objective was rarely satisfied because prosecutors had to prove that the drug promoter knowingly and deliberately attempted to defraud the public, which was often impossible to establish.[28]

2. The Food, Drug and Cosmetic Act of 1938

The demand for governmental regulation of drug safety increased in 1937 after the drug Elixir Sulfanilamide, manufactured by a Tennessee drug company, killed more than 100 people in fifteen different states.[29] In June 1938, Congress reacted to the Elixir Sulfanilamide tragedy by implementing the Food, Drug and Cosmetic Act of 1938 (1938 Act).[30] The 1938 Act (which is largely the law still in effect today) required the pharmaceutical company seeking to market its drug to the public to file an application for approval of the new drug.[31] After the FDA received the application, it had the option of testing the drug's safety on human subjects.[32] The FDA then had two months to make a decision about the drug's approval status and "failure to act on the application would theoretically lead to automatic de facto approval of the drug."[33] The overall purpose of the 1938 Act was to address safety concerns for the consumer, and thus, drug efficacy was not a vital consideration for the 1938 Act.[34]

3. The Drug Amendments of 1962

In the 1960s, a pharmaceutical tragedy struck Europe when the drug thalidomide was found to cause birth defects in babies born to mothers who had taken the drug during pregnancy.[35] There was fear that human subjects were

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[27] Sherley Amendment, Pub. L. No. 62-301, 37 Stat. 416, 417 (1912) (repealed 1938).

[28] Janssen, *supra* note 19, at 428.

[29] Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAGAZINE, June 1981.

[30] *Id.*; *see also* Federal Food, Drug and Cosmetic Act of 1938 § 351.

[31] Federal Food, Drug and Cosmetic Act of 1938 § 355.

[32] *Id.*

[33] *Summary of NDA Approvals & Receipts, 1938 to the Present*, FDA, http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm (last updated Jan. 18, 2013).

[34] *See* Dale H. Gieringer, *The Safety and Efficacy of New Drug Approval*, 5 CATO J. 177, 178 (1986).

[35] Sam Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. POL. ECON. 1049, 1050 (1973).

being exposed to dangerous drugs during clinical testing.[36] The thalidomide incident contributed to the speedy development of the Drug Amendments of 1962 (1962 Amendments).[37] The 1962 Amendments expanded the requirements for obtaining drug approval by the FDA.[38] Now, drugs have to be proven effective as well as safe.[39] Additionally, experimental drugs became rigorously controlled, a consideration that past drug consumption laws had overlooked.[40]

Under the new 1962 Amendments, a drug sponsor must submit its testing procedures to the FDA for approval.[41] At any time, the FDA can halt clinical testing or order changes to a clinical investigation if a drug is deemed unsafe or ineffective.[42] More notably, a proof of efficacy requirement was added to the proof of safety requirement.[43] This means that a new drug cannot be marketed unless the FDA deems it both safe and effective in its intended use.[44] To be "effective," a drug must meet the manufacturer's claims.[45] The 1962 Amendments to the 1938 Act remain the current law in the United States.

B. The Current Drug Approval Process in the United States

There are two routes through which a new drug can become approved for marketing in the United States. The first route, and beyond the scope of this note, provides that some drugs are exempted from the operation of the 1938 Act through the 1962 Amendments.[46] The second route provides that a new drug can be marketed in the United States if the FDA has approved it under the agency's New Drug Application procedure.[47] There are four stages of the FDA approval process under the New Drug Application procedure: pre-clinical testing; Investigational New Drug stage testing; New Drug Application stage testing; and post-marketing surveillance.

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36 *Id.* at 1050–51.

37 *Id.* at 1051; *see also* Pub. L. No. 87-781, § 102(b), 76 Stat. 780 (codified as amended at 21 U.S.C. § 355(b) (1988)).

38 Peltzman, *supra* note 35, at 1051.

39 Gieringer, *supra* note 34, at 178.

40 *Id.*

41 Peltzman, *supra* note 35, at 1051.

42 *Id.*

43 *Id.*; *see also* Federal Food, Drug and Cosmetic Act of 1938 § 355(b).

44 Peltzman, *supra* note 35, at 1051.

45 *Id.*

46 JAMES R. NIELSEN, HANDBOOK OF FEDERAL DRUG LAW 13 (1986).

47 Federal Food, Drug and Cosmetic Act of 1938 § 355(a)–(b).

1. Pre-Clinical Testing

In the pre-clinical testing stage, the drug sponsor must submit data to the FDA from small-scale clinical studies showing that the drug is reasonably safe.[48] The drug sponsor must also conduct clinical investigations by performing drug testing and analysis on animals.[49] The purpose of the pre-clinical testing stage is to determine whether human testing trials should commence.[50] Beginning with pre-clinical testing and continuing throughout the entire approval process, the primary objective of the FDA is to place the safety and rights of human subjects at the forefront.[51]

2. Investigational New Drug Application

If it is determined at the conclusion of pre-clinical testing that a new drug is safe to test on human subjects and is likely to be effective, the sponsor of the drug files an Investigational New Drug (IND) Application.[52] In this submission, the results of the pre-clinical testing stage, including animal toxicology studies and other human testing studies, are disclosed.[53] An IND goes into effect thirty days after it is filed with the FDA, unless the FDA says otherwise.[54] The IND stage for a previously untested drug includes three phases of clinical investigations.[55] The FDA has the power to terminate the clinical testing at any of the following three phases if the drug sponsor does not meet the specified guidelines.[56]

Phase I finally introduces the new drug to humans subjects.[57] Studies are conducted "to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."[58] Generally, Phase I studies include twenty to eighty subjects.[59]

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48 *Drugs*, U.S. FOOD & DRUG ADMIN. (Feb. 22, 2010), http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm176522.htm [hereinafter *Drugs*].

49 21 C.F.R. § 312.23(a)(8) (1992).

50 *See, e.g., id.* § 312.22.

51 *Id.* § 312.22(a); *see also Drugs*, *supra* note 48.

52 *Drugs*, *supra* note 48.

53 21 C.F.R. § 312.22(c).

54 *Id.* § 312.40(b)(1).

55 *Id.* § 312.21.

56 *Id.* § 312.44 (listing instances where the FDA would have power to terminate IND testing).

57 *Id.* § 312.21(a)(1).

58 21 C.F.R. § 312.21(a)(1).

59 *Id.*

Phase II usually involves no more than several hundred subjects.[60] The subjects of this phase are patients with the disease or condition that the drug is designed to treat.[61] The purpose is "to determine the common short-term side effects and risks associated with the drug."[62]

To enter Phase III of clinical testing, there must be evidence suggesting that the drug is effective.[63] The purpose of this phase is to do a risk-benefit analysis of the drug and then form a satisfactory basis from which labels will be based from that information.[64] There are several hundred to several thousand subjects involved in this phase.[65]

3. New Drug Application

Once the three phases of the IND stage have been successfully completed, the drug sponsor files a New Drug Application (NDA).[66] The NDA "has become the principal regulatory device for the control of drugs in the United States."[67] Basically, a review of all of the compiled information about the drug must show that the drug is both safe and effective.[68]

After filing, the FDA has six months to approve or disapprove the new drug.[69] If the FDA approves the NDA, the drug sponsor must file periodic reports and maintain data concerning clinical experiences with the drug, post-market risk identification, drug safety, and other drug information.[70]

4. Post-Market Surveillance

After the FDA approves a new drug, post-market surveillance monitors instances of adverse or uncommon reactions. The goal of post-marketing surveillance studies is to find out more information about a drug's safety and efficacy.[71] This stage is particularly important because some experts claim that approximately half of all new drugs have unknown side effects that are not

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60 *Id.* § 312.21(b).

61 *Id.*

62 *Id.*

63 21 C.F.R. § 312.21(c).

64 *Id.*

65 *Id.*

66 Federal Food, Drug and Cosmetic Act of 1938 § 355(a)–(b).

67 Neilsen, *supra* note 46, at 15.

68 *Id.*

69 Federal Food, Drug and Cosmetic Act of 1938 § 355(c).

70 *Id.* § 355(k).

71 *See* Marion J. Finkel, *Phase IV Testing: FDA Viewpoint and Expectations*, 33 FOOD DRUG COSM. L.J. 181, 183–84 (1978).

detected until the post-marketing surveillance stage.[72] However, the FDA often lacks the money and staff to provide efficient and effective surveillance of new drugs.[73] Although it is mandatory for drug companies to report when drugs show adverse effects, there are currently major problems with late or non-reporting by drug companies.[74]

C. Criticisms of the Drug Approval Process in the United States

Under current U.S. law, a new pharmaceutical may only be introduced into the public market when the FDA has deemed it "safe and effective."[75] Most commonly, critics claim that the current FDA approval process prohibits potentially life-saving drugs from entering the market quickly enough.[76] Many critics complain of overregulation, and, as a result, the FDA has acquired a reputation for inefficiency and delay.[77] Additionally, the cost of drug approval in the United States has risen drastically and thus has contributed to the "drug lag."[78] Many argue that the cost and delay in drug approval has outweighed the benefits of more safety and efficacy.[79]

Many drugs are approved overseas that are never approved in the United States, and therefore, patients in the United States have limited treatment options.[80] Some studies have shown that approval times in other countries, like Great Britain, are significantly quicker than those in the United States.[81] "Orphan drugs," which are drugs that are not brought to the United States because of the time and cost associated with approving them, are being developed overseas, and as such, Americans do not have access to these drugs.[82]

The 1962 Amendments to the Food, Drug and Cosmetic Act of 1938 shifted the focus of drug approval drastically. The 1938 Act focused almost exclusively on the safety of new drugs that entered into interstate commerce and became available to consumers.[83] When the 1938 Act was amended in 1962, legislators decided that the effectiveness of a new drug was also vital to its approval. [84]

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72 Richard A. Deyo, *Gaps, Tensions, and Conflicts in the FDA Approval Process: Implications for Clinical Practice*, 17 J. AM. BD. FAM. MED. 142, 142–49 (2004).

73 *See id.*

74 *Id.*

75 Gieringer, *supra* note 34, at 177.

76 *See, e.g., id.*

77 *Id.* at 178.

78 *Id.*

79 *See, e.g., id.*

80 Gieringer, *supra* note 34, at 179.

81 *Id.*

82 *Id.*

83 *Id.* at 178.

84 *See id.*

1. The "Drug Lag"

Arguably, the most frequent criticism of the FDA and the current drug approval process is the drug lag experienced by the public and those who are ill. As described in the introduction, the Abigail Alliance argued in 2007 that terminally ill patients in the United States are suffering because they are not given access to experimental drugs quick enough.[85] The Abigail Alliance argued in court that the efficacy requirements of the 1938 Act and 1962 Amendments are unnecessary and prevent terminally ill people from getting their final chance at survival.[86] However, the Court of Appeals for the D.C. Circuit held that there is no fundamental right for terminally ill patients to get access to experimental drugs,[87] and the United States Supreme Court denied certiorari on the issue.[88] The drug that would have saved Abigail's life has since been approved in the United States. United States drug law continues to be a very controversial issue.

Why is the drug approval time in the United States so lengthy? There are many regulatory barriers that contribute to global drug lag.[89] A lack of harmonization between countries also contributes to the drug lag.[90] The statutory requirements associated with drug approval have become extremely stringent.[91] The efficacy requirements in the 1962 Amendments greatly expanded the clinical testing necessary for new drugs.[92] Additionally, the FDA lacks the resources and manpower necessary to approve drugs more quickly.[93]

2. The Costs Associated with Drug Approval

The 1962 Amendments to the Food, Drug and Cosmetic Act of 1938 increased the clinical testing requirements for new drug approval and, consequently, the costs associated with drug approval also increased.[94] Recent studies predict the cost of new drug development to be around U.S. $802 million.[95] Because of the high costs associated with developing and approving a

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85 Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007).

86 *See id.* at 703.

87 *Id.* at 697.

88 Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 128 S. Ct. 1069 (2008) (denying certiorari).

89 Harriet Wileman & Arun Mishra, *Drug Lag and Key Regulatory Barriers in the Emerging Markets,* 1 PRESP. CLINICAL. RES. 51–56 (2010), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148610/.

90 *See, e.g., id.*

91 *Key Factors in the Rising Cost of New Drug Discovery and Development, supra* note 6.

92 *Id.*

93 *Id.*

94 *See id.*

95 *The Cost of New Drug Discovery, supra* note 6.

new drug in the United States, many countries are moving their efforts overseas.[96] Theorists speculate that perhaps the FDA has become too close to the industry that it is trying to regulate, and this, in turn, is affecting funding.[97]

3. Politics Within the FDA

Critics of the current United States drug approval process argue that the system lacks an impartial mechanism to address disagreements between the FDA and various pharmaceutical companies.[98] Drug companies are hesitant to challenge decisions by the FDA in a legal environment because they fear that the FDA will retaliate in the future.[99] Critics of the system claim that the FDA delays consideration of new drugs if there is a controversy with the drug manufacturer.[100] Conversely, drugs should be evaluated based on scientific merit, efficacy, and safety concerns.[101]

4. Unqualified Personnel

Some critics have noted that the FDA headquarters in Maryland are in very poor condition: there is inadequate space and poor temperature control.[102] Thus, because of the poor working conditions, the FDA is unable to attract top quality personnel to work on the drug approval process.[103] Some argue that the FDA is unable to keep up with technological and scientific advancements within the industry because they cannot attract the right employees for the job.[104] If the best employees and personnel are not recruited to work with the FDA on the new drug approval process, it is unlikely that new drugs will be able to hit the public market as quickly as possible.

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96 Gieringer, *supra* note 34, at 179.

97 *See, e.g.*, Curt D. Furnberg et al., *The FDA and Drug Safety: A Proposal for Sweeping Changes*, 18 ARCH. INTERN. MED. 166 (2006), *available at* http://archinte.jamanetwork.com.ezproxy2.library.arizona.edu/article.aspx?articleid=411074 (arguing that the FDA is trying to punish pharmaceutical companies and that the drug sponsors are unable to fight the costs and delays associated with producing a new drug because the FDA will treat these "rule breakers" unfavorably).

98 David W. Jordan, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND. J. TRANSNAT'L L. 471, 486 (1992).

99 *Id.*; Furnberg et al., *supra* note 97.

100 Jordan, *supra* note 98, at 486.

101 *See id.*

102 *Id.*

103 *Id.*

104 *Id.*

5. Poor Drug Surveillance During the Market Phase

The FDA's primary source for identifying adverse drug reactions in the post-marketing surveillance stage is through the drug companies themselves.[105] The FDA receives reports from the pharmaceutical companies through the Adverse Event Reporting System.[106] However, major issues arise under this system. The FDA receives approximately 400,000 reports annually primarily from drug companies, but there are also a few reports from doctors and other health care providers.[107] The faults in the system arise because there is a significant amount of underreporting.[108] It has been estimated that only 1% of all adverse drug reactions and only 10% of all serious adverse drug reactions are reported to the FDA.[109] Additionally, pharmaceutical companies tend to report incidents without investigating whether the incident was drug-induced or naturally occurring.[110] Whether a drug company reports an incident is completely subjective.[111] When underreporting is paired with a subjective threshold for reporting, a large portion of the population can be subjected to potential harms as a result of a drug's adverse or reactions.[112]

The FDA can make recommendations to a pharmaceutical company to submit trial information and studies concerning drugs in the post-market surveillance phase.[113] However, the FDA lacks direct legal authority to enforce such recommendations.[114] The FDA rarely seeks assistance from the Department of Justice to take action against a drug company.[115] In the post-marketing surveillance stage, the FDA needs more direct legal authority so the drug companies who offend FDA standards face certain consequences.[116] Critics argue that such consequences should include fines, probation, public embarrassment, or in severe situations, withdrawal of the drug from the public market.[117]

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105 Furnberg et al., *supra* note 97, at 166.

106 *Id.*

107 *Id.*

108 *Id.*

109 *Id.*

110 Furnberg et al., *supra* note 97, at 166.

111 *Id.*

112 *Id.* It was estimated that approximately four million patients were exposed to each of the five different drugs (Bromfenac, Dexfenfluramine, Fenfluramine, Mibefradil, and Terfenadine) that were eventually taken off of the market between September of 1997 and September of 1998. *Id.*

113 *Id.*

114 *Id.*

115 Furnberg et al., *supra* note 97, at 166.

116 *Id.*

117 *Id.*

III. DRUG APPROVAL PROCESSES IN OTHER COUNTRIES[118]

A. Drug Regulation in Great Britain

The Medicines and Healthcare Products Regulatory Agency (MHRA) was created in 2003 to regulate medicines and medical devices in Great Britain.[119] Member states of the European Community also follow the guidance of the European Medicines Agency (EMA or EMEA) whose legislation supersedes the MHRA.[120] The processes employed by the MHRA are based on safety, quality, and efficacy concerns.[121]

Through the guidance of the Medicines Act of 1968, the MHRA seeks to find a stable balance between safety and efficacy.[122] This Act requires that pharmaceuticals first be approved by a licensing authority called the Medicines Division, which is comprised of scientists and other government officials.[123] The central pillar of this regulatory process is the Commission on Human Medicines (CHM), whose advice and guidance is sought for the review of all new drugs.[124]

A license called a "marketing authorization" must be issued by the MHRA before any drug can be used in Great Britain.[125] Similar to the FDA, pharmaceutical companies must apply to the MHRA to test drugs through clinical trials.[126] All results of the clinical trials, including side effects and chemical components of the drugs, are then sent to the MHRA for a detailed assessment.[127]

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[118] This note compares the drug approval process in the United States to that in Great Britain and Japan because of the similarity between the processes and the strength of each nation's economy. The processes employed in Great Britain and Japan each have qualities that could contribute to a more efficient system in the United States or a more harmonized international scheme. *See* discussion *infra* Part III.A–B.

[119] *Medicines & Medical Devices Regulation: What You Need to Know,* THE MEDS. & HEALTHCARE PRODS. REGULATORY AGENCY 2 (2008), http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con2031677.pdf. The MHRA brought together the functions of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). *Id.*

[120] *How We Regulate Medicines,* THE MEDS. & HEALTHCARE PRODS. REGULATORY AGENCY (July 11, 2011), http://www.mhra.gov.uk/Howweregulate/Medicines/index.htm.

[121] *Id.*

[122] *Id.*; *see also* John Abraham & Courtney Davis, *Deficits, Expectations and Paradigms in British and American Drug Safety Assessments: Prising Open the Black Box of Regulatory Science,* 32 SCIENCE, TECH., & HUMAN VALUES 399, 402 (2007), *available at* http://sth.sagepub.com/content/32/4/399.

[123] Abraham & Davis, *supra* note 122, at 403.

[124] *Id.*; *see Medicines & Medical Devices Regulation: What You Need to Know, supra* note 119, at 3 (stating that the CHM was previously called the Committee on Safety of Medicines (CSM) until the name changed in 2005).

[125] *Medicines & Medical Devices Regulation, supra* note 119, at 5.

[126] *Id.*

[127] *Id.*

If the MHRA is satisfied with the safety and efficacy of the new drug, then the marketing authorization is granted.[128]

The drug regulation system adopted by Great Britain is highly comparable to the system employed in the United States.[129] In fact, Great Britain's system is considered more similar to the United States' system than any other nation.[130] There are two major distinguishing features between pharmaceutical regulation in the two nations: pre-market evaluation phase and post-market withdrawal of drugs.[131] Historically, a comparison of the two nations suggests that the United States demands greater assurances in the areas of drug safety and efficacy in the pre-market stage compared to Great Britain.[132] Alternatively, Great Britain emphasizes post-marketing surveillance much more heavily than the United States does.[133]

Post-marketing surveillance in Great Britain involves systematic and mandatory reporting of adverse drug reactions and other studies or new information concerning the newly approved pharmaceutical.[134] By law, manufacturers must report drug defects to the MHRA.[135] Individual patients may also report adverse side effects directly to the MHRA with the "Yellow Card Scheme."[136] The Yellow Card Scheme receives about 20,000 reports of possible side effects each year.[137] On occasion, Great Britain has approved drugs that were too dangerous or ineffective to stay available to consumers.[138] In such instances, speedy market withdrawal procedures are typically performed.[139]

Great Britain does pre-market surveillance on human subjects as well.[140] However, the amount of pre-market clinical testing and other studies is not as

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[128] *Id.*

[129] *See, e.g.*, Claire L. Ahem, *Drug Approval in the United States and England: A Question of Medical Safety or Moral Persuasion? – The RU-486 Example*, 17 SUFFOLK TRANSNAT'L L. REV. 93, 99 (1994) (citing Rosemary P. Wall, *International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation*, 10 RUTGERS COMPUTER & TECH. L.J. 317, 324 (1984)).

[130] Rosemary P. Wall, *International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation*, 10 RUTGERS COMPUTER & TECH. L.J. 317, 324 (1984).

[131] John Abraham, *Sociology of Pharmaceuticals Development and Regulation: A Realist Empirical Research Programme*, 30 SOCIOLOGY OF HEALTH & ILLNESS 869, 878 (2008).

[132] *See id.*

[133] *See id.* at 878–79.

[134] Wall, *supra* note 130, at 324.

[135] *Medicines & Medical Devices Regulation*, *supra* note 119, at 13.

[136] *Id.* at 12.

[137] *Id.*

[138] Wall, *supra* note 130, at 325.

[139] *Id.* Removing the drug quickly from the open market reduces the risk of continued and dangerous incidences associated with the drugs ingestion by the public. *Id.*

[140] *Id.*

numerous.[141] Because of this focus on post-market surveillance, some studies estimate that new drugs hit the open market in Great Britain about 201 days sooner than in the United States.[142] Proponents of a system more similar to Great Britain believe that such a system is more in touch with "scientific reality"[143] because pre-market clinical testing often shows frequent, yet minor side effects.[144] Post-marketing surveillance, on the other hand, shows more infrequent and severe side effects associated with a drug.[145]

Another vast difference between the system used in Great Britain and the system used in the United States is the management of safety and efficacy requirements.[146] The FDA has direct responsibility for all safety and efficacy concerns while the MHRA is primarily concerned with safety.[147] A medical advisory committee examines therapeutic efficacy.[148] Using these committees isolates approval decisions from political, private, and commercial influences.[149] Consequently, "[a] patient can obtain access to new drugs that have not been authorized for human use, provided a physician prescribes the drug for therapeutic purposes."[150]

Of all new drugs approved around the world between 1999 and 2007, the European Union (EU) approved 314 (78.9%) of them.[151] Drugs of European and American origin were approved at a high rate in both countries.[152] Perhaps the drug approval system in the United States would benefit from some of the aspects used by the MHRA. One persuasive facet of the approval process in Great Britain is that the process "may justifiably be viewed as scientific, rather than political, because it leaves scientific evaluation of new drug uses to the scientists as opposed to vesting this authority in bureaucrats far less suited to the task."[153] As a result of the focus on safety rather than efficacy, the British system is less expensive and less time-consuming than its counterpart in the United States, and many side-effects are caught in the rigorous post-market surveillance stage.[154]

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141 *Id.*

142 Joshua Cohen et al., *Patient Access to Pharmaceuticals: An International Comparison*, 8 THE EUROPEAN J. OF HEALTH ECON. 253, 260 (2008).

143 Wall, *supra* note 130, at 325.

144 *Id.*

145 *Id.*

146 *Id.* at 326.

147 *Id.*

148 Wall, *supra* note 130, at 326.

149 Relihan, *supra* note 14, at 246.

150 *Id.*

151 Kao Tsuji & Kiichiro Tsutani, *Approval of New Drugs 1999-2007: Comparison of the US, the EU, and Japan Situations*, 35 J. OF PHARMACY & THERAPEUTICS 289, 289 (2010).

152 *Id.*

153 Wall, *supra* note 130, at 326.

154 Relihan, *supra* note 14, at 248.

B. Drug Regulation in Japan

Japan is the third largest economy in the world.[155] It also significantly contributes to the development and breakthrough of new drugs and devices in the pharmaceutical and medical device industries.[156] The drug approval process in Japan is very strict and easily comparable to the drug approval process in the United States.[157] Japan has taken steps towards the deregulation of the pharmaceutical industry with the amendment to the Pharmaceutical Affairs Law in July 2002.[158] Now, there is a greater focus on the global drug market and a hope to harmonize with other large global markets such as the United States.[159] The Japanese Ministry of Health and Welfare (Ministry) declared the three purposes of the amendment to the law: (1) to enhance the safety measures taken for medical devices, (2) to enhance regulations for the application of medical products with the advancement of biotechnology and genome technology, and (3) to strengthen post-market surveillance while remembering to take international conformity into account.[160]

The Pharmaceutical Affairs Law controls the distribution of new drugs and pharmaceuticals in Japan.[161] The Ministry regulates drug approval and drug licensing through a series of nine divisions in the Pharmaceutical Affairs Bureau.[162] An investigative board called the Central Pharmaceutical Affairs Council (CPAC) advises the Ministry on new drugs and pharmaceuticals and their scientific effects.[163] Prescription drugs, some over-the-counter medications, cosmetics containing hormones, and medical devices all require approval and licensing.[164] Certain drugs are exempt from Ministry approval if their safety and efficacy have already been established.[165]

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[155] *See GDP (current US$)*, WORLD BANK, http://data.worldbank.org/indicator/NY.GDP.MKTP.CD (last visited Mar. 15, 2014); *World Economic Outlook Database*, INT'L MONETARY FUND (Oct. 2013), http://www.imf.org/external/pubs/ft/weo/2013/02/weodata/index.aspx.

[156] Katherine Neckers, *Harmonization of Drug and Medical Device Development in the U.S. and Japan: Movement Towards International Cooperation in the Post Genomic Era*, 12 NEW ENG. J. INT'L & COMP. L. 295, 295 (2006). Medical devices will not be discussed in this note.

[157] Tsuji & Tsutani, *supra* note 151, at 290.

[158] Neckers, *supra* note 156, at 295–96.

[159] *Id.*

[160] *Id.* at 298 (internal citation omitted).

[161] Kanusky, *supra* note 10, at 683 (citing Pharmaceutical Affairs Law No. 145 of 1960, *translated in* Standards and Certification Systems Concerning Drugs in Japan (1985)).

[162] *Id.* at 684.

[163] *Id.* (internal citation omitted).

[164] *Id.* (internal citation omitted).

[165] *Id.* (internal citation omitted). These drug exemptions will not be discussed in this note.

In Japan, drugs are classified as prescription or nonprescription.[166] The classification affects how long the approval process will take.[167] If a drug is classified as a prescription, it will need to be further classified to identify the various scientific stages and testing it will need to endure.[168]

The drug approval process in Japan involves research, pre-clinical testing, evaluation of such trials, and finally, clinical trials.[169] Applications for drug approval must contain information concerning pre-clinical testing results, including details of development, use in foreign countries, chemical and physical characteristics, and the way the drug was tested and what those results were.[170] Based on this information, the drug applications are divided between the committees of CPAC.[171] Once the clinical trials are over and the information from such trials has been compiled, the drug company submits a New Drug Application to the Ministry.[172] The Ministry then requests a recommendation concerning the drug from CPAC, and after that, a decision about that drug's approval status can be made.[173]

In Japan, drugs must be licensed as well as approved by the Ministry.[174] Licensing of drugs for import and sale involves an examination of the manufacturer to ensure that the manufacturing process complies with certain standards.[175] However, there is a list of reasons why a drug company may become disqualified from licensing as well.[176]

The post-market surveillance stage of the Japanese drug approval process has received the most criticism. Although pharmaceuticals are obviously tested for side effects in the pre-clinical and clinical testing phases, post-market surveillance examines adverse effects once the drug has been distributed in the community.[177] Japan has tried to strengthen their post-market surveillance phase over the past couple of years.[178]

The major regulatory facets of Japanese post-market surveillance include adverse drug reaction and infection reporting, re-examination, and re-evaluation.[179] The adverse drug reaction reporting portion is very similar to that

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166 Kanusky, *supra* note 10, at 685 (internal citation omitted).

167 *See id.* A drug that is labeled "prescription" will have a greater approval time than a drug that is labeled "nonprescription" because prescription drugs must be further classified. *See id.*

168 *Id.*

169 Neckers, *supra* note 156, at 299.

170 Kanusky, *supra* note 10, at 685 (internal citation omitted).

171 *Id.* (internal citation omitted).

172 Neckers, *supra* note 156, at 299.

173 *Id.*

174 *Id.* at 300.

175 *Id.*

176 *Id.*

177 Neckers, *supra* note 156, at 300.

178 *See id.* at 306.

179 *Id.* at 307.

in the United States.[180] It includes reports by healthcare providers and drug companies about whether they have observed patients and customers experience adverse side effects from the drugs.[181] Japan has encouraged pharmaceutical companies and healthcare providers to report any incidences to ensure drug safety; however, reports of such incidences have not increased substantially.[182]

To promote drug safety and efficacy, Japan has suggested that foreign data from the post-marketing surveillance stage of other counties be available and used globally.[183] Additionally, Japan wants to hear from society as a whole: they wish to hear from the patients that are actually suffering from adverse side effects.[184] When making a final determination as to whether a new drug is safe for the public, Japan believes the decision should be objective and include all points of view and available information.[185]

Overall, the post-marketing surveillance stage in Japan appears to be more precautionary than in the United States.[186] While the United States primarily makes drug observations and determinations based on reports by the pharmaceutical industry, Japan tries to focus on the consumer, pharmacists, and physicians.[187] Drug companies are also required to complete early phase post-marketing vigilance and surveillance.[188]

Despite efforts to slightly deregulate the drug approval process in Japan, the drug approval time in the country is strikingly long and delayed. The *Journal of Clinical Pharmacy and Therapeutics* found that between the United States, European Union, and Japan, the drug approval process in Japan was the slowest and experienced the most "drug lag."[189] Additionally, the study found that Japan had the most stringent drug approval standards comparatively.[190]

Of the 398 new drugs approved globally between the years of 1999 and 2007, Japan only approved 220 (55.3%).[191] Drugs of United States or EU origin were only approved in Japan at a rate of approximately 43.6% and 51.6%, respectively.[192] However, Japan approved drugs that originated within the country at a rate of 94.5%.[193] It has been conjectured that the reason for the drug lag of non-Japanese drugs is because of late NDAs; in other words, foreign pharmaceutical companies are not seeking approval in Japan immediately.[194] The

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180 *Id.*
181 *Id.*
182 Neckers, *supra* note 156, at 307.
183 *Id.* at 308.
184 *Id.*
185 *See id.*
186 *Id.*
187 Neckers, *supra* note 156, at 308.
188 *Id.*
189 Tsuji & Tsutani, *supra* note 151, at 299.
190 *Id.* at 300.
191 *Id.* at 289.
192 *Id.*
193 *Id.*
194 *See* Tsuji & Tsutani, *supra* note 151, at 300.

approval process within Japan has also been criticized as extremely slow because they prefer to have clinical trials conducted exclusively on Japanese subjects.[195] This contributes to the high drug approval lag time. Until the 1990s, Japan required that foreign drug companies conduct all their clinical trials in Japan and on Japanese subjects, but now foreign companies can test on other subjects as well.[196] Japan's preference for using Japanese subjects in pre-clinical and clinical trials in Japan has increased the cost of drug approval and contributed to the drug lag.[197]

Incorporating patients and consumers in the post-market surveillance stage, as Japan wishes to do, could be very beneficial to the drug approval process in the United States. Since this stage is arguably one of the weakest facets of the American approval process, trying a new approach may increase adverse reaction reporting. Japan is interested in pursuing a regulatory relationship with other nations such as the United States,[198] and this openness to change may improve the likelihood that an international approval scheme could be achieved.

IV. GRASPING AT HARMONY: VARIOUS ATTEMPTS AT INTERNATIONAL CONFORMITY

A more harmonized system of pharmaceutical regulation internationally would benefit all of the countries involved.[199] Duplicative testing requirements for private pharmaceutical companies increase the cost of drug development and manufacturing, delay the introduction of the new drug into the consumer market, and make some drugs unavailable in certain countries, although available in others.[200] Countries, such as the United States, have the goals of safety and efficacy and do not want those objectives to be compromised.[201] However, various countries also do not want their regulations to be too restrictive.[202] How can such an intermediate result be reached? An attempt to harmonize globally may be one step in the right direction.

A globalized approach to drug regulation is crucial for a few different reasons. First, there are numerous multinational pharmaceutical companies that

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195 *Id.*

196 *Id.*

197 *Id.*

198 *See* Neckers, *supra* note 156, at 295–96.

199 A harmonized regulatory drug approval system between the United States, Great Britain, and Japan would be beneficial financially and be in the interest of increased drug approval times. This note, however, focuses on the benefits to the United States and does not seek to theorize how other countries would benefit by a more global regulatory system.

200 Ileana Dominguez-Urban, *Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally*, 30 CORNELL INT'L L.J. 245, 245 (1997).

201 *See id.*

202 *See id.*

are operating in many countries all over the world.[203] When a multinational drug company must overcome stringent drug regulations in every country in which it operates, the cost of drug production and the time for drug approval increases. Second, there are worldwide drug problems such as the HIV/AIDS epidemic that would benefit from a more harmonized system of combat.[204] Third, disease often spreads in countries with severe drug shortages.[205] Third-world countries do not have adequate access to drugs readily available in countries, such as the United States, and therefore do not get the proper dosages.[206] Health is a global concern, and when bacteria are not treated in underdeveloped countries, the disease can spread throughout the world.[207]

This section will address different attempts that have been made to harmonize and globalize the drug approval process worldwide. Despite these attempts, none have fully succeeded. This section will also examine reasons why such a global system could be successful in the future by examining other times nations have come together to reach a common goal.

A. The International Conference on Harmonization

One of the FDA's first attempts at achieving harmonization occurred in November of 1991.[208] At that time, the United States, the European Community, and Japan came together for the International Conference on Harmonization.[209] After the first major conference in 1991, another three occurred in 1993, 1995, and 1997.[210] Throughout the 1990s, the ICH developed standardized guidelines for toxicology and other safety requirements using expert working groups (EWGs).[211] EWGs were comprised of scientists from various industries and regulatory agencies that sought to determine the most efficient and safe regulations.[212] The reason that these particular nations came together to form a more global drug market was because the United States, the EC, and Japan accounted for 75% of the world's production of pharmaceutical products.[213]

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203 *See id.* at 247.

204 *Id.*

205 Dominguez-Urban, *supra* note 200, at 249.

206 *Id.* Shortages of needed drugs are a serious issue in the world, but this note does not theorize how this issue would be accomplished for countries uninvolved in the proposed reciprocity agreement.

207 *See id.*

208 Jordan, *supra* note 98, at 491–92.

209 *Id.* at 492.

210 John Abraham & Tim Reed, *Progress, Innovation and Regulatory Science in Drug Development: The Politics of International Standard-Setting*, 32 SOC. STUDIES OF SCI. 337, 342 (2002).

211 *Id.*

212 *See id.*

213 Jordan, *supra* note 98, at 492. The United States, EU, and Japan are the three largest pharmaceutical markets in the world. Abraham & Reed, *supra* note 210, at 342.

Those nations also accounted for 90% of the world's production of pharmaceutical research and development activities.[214]

When a new pharmaceutical is created, drug sponsors want it to cross international boundaries.[215] However, each country's unique legislation and regulations slow down that process significantly.[216] A new drug must be evaluated, tested, and approved in each country where approval is sought.[217] When two nation's regulations are inconsistent, it increases the cost of the pharmaceutical for the drug company and the consumer.[218] The speed at which the drug is introduced to the public also slows down.[219]

In order to harmonize the technical standards for drug testing between the United States, the EC, and Japan, groups of EWGs had to review the differences between the participants in the various technical areas.[220] The EWGs would then try to reconcile those differences with something that all the participants could agree upon.[221] The key objective of the ICH was to reach an agreement to limit high costs and delays associated with drug development in addition to minimizing human and animal testing.[222] These nations had a common goal: "[T]o put safe and effective drugs in the hands of consumers without undue delay."[223]

It is important to recognize that high drug approval costs and long delays due to drug lag are not limited to the countries present at the ICH.[224] However, the possibility that complete harmonization among all nations would occur is very remote.[225] The recommendation of many experts is that harmonization should be attempted regionally or among smaller groups of nations for the immediate future.[226]

1. Major Accomplishments of the ICH

The ICH has made some accomplishments in its journey to reach a more global system of pharmaceutical regulation.[227] Specifically, "[p]articipants in ICH 'technical workshops' attempted to streamline the type of data pharmaceutical

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214 Jordan, *supra* note 98, at 492.

215 *See* Kanusky, *supra* note 10, at 667.

216 *Id.*

217 *Id.*

218 *Id.*

219 *See id.*

220 Abraham & Reed, *supra* note 210, at 344.

221 *Id.*

222 Dominguez-Urban, *supra* note 200, at 252.

223 *Id.*

224 *Id.*

225 *See id.* (explaining that every country has its own standards and regulations that would need to be adapted and if a few countries could harmonize regionally, more success could be sought in the future).

226 *Id.*

227 *See, e.g.*, Jordan, *supra* note 98, at 492–96.

companies must report in seeking approval for new drugs."[228] Participants of the ICH determined that among their nations, they all differed in goals of quality, safety, and efficacy.[229] The participants negotiated some agreements in hopes of eventually reducing the cost of drug approval up to 50% among the nations that were involved in the conference.[230]

As part of the ICH's technical advancements, the participants adopted a "minimum data blueprint" defining conditions acceptable among all of the participants.[231] For laboratory testing, the United States, the EC, and Japan had no common testing conditions, so they negotiated and agreed on a few.[232] The participants agreed to laboratory control conditions such as humidity and temperature.[233] In addition to specifying some control conditions, the participants made exact definitions of laboratory terms such as "room temperature," so no confusion could exist between the participating nations.[234] The positive outcome of the "minimum data blueprint" is that a pharmaceutical company can file the same data package in every participating nation.[235] After filing, each nation can still evaluate the new drug by its own standards, but the drug sponsor will benefit from avoiding repetitive testing because all the participants accept the same tests.[236]

The United States, the EC, and Japan also participated in a Quality Workshop in which the participants sought out inconsistencies between quality assurance regulations and looked for alternatives that they could agree upon.[237] This workshop produced some procedures now known as "stability testing."[238] Stability testing created a set of harmonized procedures for determining the shelf life of new drugs.[239] The expected outcome of stability testing was that a new drug sponsor would save money and costs associated with the development stage of a new drug and at the reexamination stage of a drug's lifetime.[240]

The ICH made some major accomplishments in the area of reproductive toxicology studies as well.[241] Before the ICH, the participants each utilized different and unique testing procedures to determine if a new pharmaceutical

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228 *Id.* at 492.

229 *Id.* at 493.

230 *Id.*

231 *Id.*

232 Jordan, *supra* note 98, at 493.

233 *Id.*

234 *Id.*

235 *Id.*

236 *Id.*

237 Jordan, *supra* note 98, at 493.

238 *Id.*

239 *Id.* Shelf life means the length of time that a substance remains usable and fit for consumption. *Shelf Life Definition*, MERRIAM-WEBSTER DICTIONARY, http://www.merriam-webster.com/dictionary/shelf%20life (last visited Feb. 9, 2014).

240 Jordan, *supra* note 98, at 493.

241 *See id.* at 494.

caused birth defects or affected fertility.[242] The ICH sought to agree on which test would be used to determine reproductive toxicology.[243] The participants agreed to accept data from those in the ICH concerning a new drug's effects on fertility.[244]

Another area where the United States, the EC, and Japan differed in the realm of drug approval was the use of animals in testing.[245] The ICH agreed to discontinue the LD 50 test; a test the agencies used to determine the lethal dose of a new drug.[246] The ICH discontinued this method because it involved administering a drug to animals at increasing doses until the dosage killed 50% of the laboratory animals.[247] Additionally, the ICH agreed to reduce the length of time that toxicology studies are to be performed on canines and rodents.[248] The length of time was reduced from one year to six months.[249] This was a great achievement because it should reduce the cost of laboratory animals over time in addition to saving the lives of many animals.[250]

The most over-arching and significant accomplishment of the ICH was political.[251] There were many supporters of harmonization, but others feared that too many cultural differences existed.[252] There was a concern that the FDA favored isolation from the rest of the world when it came to drug administration.[253] However, it became apparent that the United States and other nations seeking harmonization are capable of coming together with one common goal.[254] The United States, the EC, and Japan were able to come together and compromise on these various regulatory issues. With continued participation and cooperation, the future of the pharmaceutical approval process may be expedited to reach all of these common goals.

B. Recognizing Foreign Drug Approvals

In 1991, the United States President's Council of Competitiveness (President's Council) proposed a series of procedures and reforms to accelerate the drug approval process.[255] The President's Council proposed that the FDA give automatic approval to drugs that have been approved by foreign countries that

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242 *Id.*
243 *Id.*
244 *Id.*
245 Jordan, *supra* note 98, at 494.
246 *Id.*
247 *Id.*
248 *Id.*
249 *Id.*
250 *See* Jordan *supra* note 98, at 494.
251 *See, e.g., id.* at 494–95.
252 *See id.* at 495.
253 *Id.*
254 *See, e.g., id.*
255 Relihan, *supra* note 14, at 256.

have a reciprocity agreement with the United States.[256] It emphasized that only those countries with very similar standards to the FDA would be accepted[257] and that such agreements would be negotiated on a country-by-country basis.[258] This agreement has not happened, however.[259]

The FDA has stricter standards than most other nations, which likely prevents the creation of a reciprocity agreement.[260] Many safeguards would need to be put into place to ensure that the safety and efficacy of new drugs would not be compromised.[261] The FDA seeks to protect the public and ensure everyone's safety and therefore wants countries involved in a reciprocity agreement to have similar quality assurances.[262]

The proposal of the President's Council provided an outline of the types of procedures that would be used to ensure that the public would still be safe.[263] For example, the FDA would be given the opportunity to evaluate the other country's clinical testing practices, validity of studies, and safety and efficacy standards.[264] Additionally, the FDA would be able to assess the quality of the foreign studies even after a reciprocity agreement was entered into.[265]

The FDA began the process to attempt some form of reciprocity agreement by entering into mutual agreements with other countries.[266] Such mutual agreements are called Memorandums of Understanding (MOUs).[267] MOUs "allow for an exchange of clinical information and give the FDA legal authority to rely on foreign inspections of pre-clinical laboratories and manufacturing plants."[268] The FDA also has the power to send their own inspectors to various manufacturing plants in other countries.[269] The FDA has executed numerous MOUs with various countries around the world, like China, Japan, and Canada.[270]

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256 *Id.*

257 *Id.* at 256–57.

258 *Id.*

259 *See id.*

260 *See* Relihan, *supra* note 14, at 257.

261 *Id.*

262 *See id.*

263 *Id.*

264 *Id.*

265 Relihan, *supra* note 14, at 257.

266 *See id.* at 257–58.

267 *Id.*; *see also FDA Memorandum of Understanding*, U.S. FOOD & DRUG ADMIN. (June 26, 2012), http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/default.htm.

268 Relihan, *supra* note 14, at 257.

269 *Id.*

270 *See id.*; *see also International Programs,* U.S. FOOD & DRUG ADMIN. (Nov. 19, 2013), http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm.

MOUs are a great initial attempt at harmonization; however, there still have been no attempts at actual reciprocity agreements.[271] "In other words, while there have been mutual agreements between and among countries to exchange inspection reports regarding pre-clinical laboratory and manufacturing plant practices, there has been no agreement to exchange clinical reports or data."[272]

C. Other International Agreements

1. The World Trade Organization

The World Trade Organization is relevant to the proposal of this note because it is a successful international agreement that incorporates many different countries and each country's various trade standards. The WTO formed to help lower the barriers between foreign nations to engage in trade and commerce.[273] "The system's overriding purpose is to help trade flow as freely as possible – as long as there are no undesirable side effects – because this is important for economic development and well-being."[274] If the WTO can unite many countries around the globe for the common goal of more free trade, there is a compelling argument that the FDA can unite with other nations like Great Britain and Japan for drug approval synchronization.

According to the WTO's website, 159 countries are members of the organization as of March 2, 2013.[275] The WTO was created in 1995 as a result of the Uruguay Round Negotiations.[276] Now, the headquarters are located in Geneva, Switzerland.[277] The functions of the WTO are to administer agreements to participating nations, monitor trade negotiations and disputes, monitor national trade policies, assist in training for developing countries, and cooperate with other international organizations.[278]

The theory behind the formation of the WTO is an interesting one for the purposes of this note. Statistical data shows a definite link between freer trade and economic growth.[279] According to this theory, countries thrive the most when they trade ideas and products with other countries that excel in different areas.[280]

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271 Relihan, *supra* note 14, at 257.

272 *Id.*

273 *Who We Are*, *supra* note 17.

274 *Id.*

275 *Id.* The United States, Japan, and Great Britain are among the countries that are represented by the WTO. *Id.*

276 *Id.* (explaining that the Uruguay Round probably had the largest number of trade negotiations).

277 *Id.*

278 *Who We Are*, *supra* note 17.

279 *The Case for Open Trade*, WTO, http://www.wto.org/english/thewto_e/whatis_e/tif_e/fact3_e.htm (last visited Jan. 8, 2014).

280 *Id.*

The WTO believes that a freer trade market will "sharpen competition, motivate innovation, and breed success."[281] A main principle behind the WTO is non-discrimination: if you do not discriminate between trading partners, everyone will be better off.[282]

The road to the creation of the WTO was a rocky one. In fact, it took seven and a half years from its inception for the WTO to be born.[283] Modernly, the WTO has set up a system of regulations and principles for the benefit of all countries involved.[284] There is a long list of about sixty agreements, annexes, decisions, and understandings.[285] The agreements fall into three different areas of trade: goods, services, and intellectual property.[286]

The WTO has been very successful in the realm of global economics.[287] There is an abundance of evidence demonstrating about 120% of additional world trade is a result of the agreements and negotiations.[288] The WTO has been called "the single most effective international agency."[289]

There are two significant costs associated with dispute resolution in the WTO.[290] The first cost is the stigma associated with failing to comply with dispute settlement resolutions provided by the WTO.[291] For example, if a member country decides not to utilize the dispute methods laid out by the WTO, other member countries may not wish to do business with that country any longer, affecting its economy in the long term.[292] Therefore, there is an incentive for member countries of the WTO to utilize the dispute resolution remedies that are provided.[293]

The second cost a country can suffer for failing to conform to WTO standards is the cost of a dispute settlement for a guilty defendant and possible retaliation by a member country.[294] The WTO's success may be attributed to this possible retaliation by other member countries,[295] which is commonly achieved by

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281 *Id.*

282 *Principles of the Trading System*, WTO, http://www.wto.org/english/thewto_e/whatis_e/tif_e/fact2_e.htm (last visited Jan. 8, 2014).

283 *Who We Are*, *supra* note 17.

284 *See id.*

285 *Overview: A Navigational Guide*, WTO, http://www.wto.org/english/thewto_e/whatis_e/tif_e/ agrm1_e.htm (last visited Jan. 28, 2014).

286 *Id.*

287 *See, e.g.*, Arvind Subramanian & Shang-Jin Wei, *The WTO Promotes Trade, Strongly but Unevenly*, 71 J. INT'L ECON. 151, 151 (2007).

288 *Id.*

289 William A. Niskanen, *Building the WTO's Success*, 19 CATO J. 459, 459 (2000).

290 Chad P. Brown, *On the Economic Success of GATT/WTO Dispute Settlement*, 86 REV. ECON. & STATS. 811, 813–14 (2006).

291 *Id.* at 814.

292 *See id.*

293 *See id.*

294 *Id.*

295 *See* Brown, *supra* note 290, at 822.

raising tariffs.[296] Retaliation is something that the WTO can authorize.[297] When a country wishes to retaliate against another non-complying country, the WTO authorizes this action by allowing the retaliating country to raise trade barriers.[298] Some critics of the WTO retaliation system claim that it is inherently risky.[299] If retaliation authorized by the WTO induces compliance with WTO regulations, then the system has achieved its goals.[300] However, there is fear that the retaliation system will be counterproductive if it actually encourages retaliation rather than deters violations.[301]

Critics of the retaliation system fear that such a system may foster protectionism.[302] Overall, it appears that compliance by the member countries of the WTO is achieved by the self-interested behavior of the entities involved.[303] The WTO's supervisory methods are successful because they encourage "compliance by cultivating technocratic and more politicized forms of legitimization, providing mechanisms for institutional laundering, and allocating resources."[304]

There was initial apprehension that such a large international organization would fail. Many entities feared that the WTO would be inefficient, ineffective, or that the countries involved would be unaccountable like other bureaucracies.[305] The WTO has become a success, and this note seeks to prove that perhaps a similar system or organization could be set up in the realm of pharmaceutical law making. However, some have argued that the WTO really is not such a success.[306] Some theorists believe that there is little evidence that nations involved with the WTO/GATT have any more trade success than non-member nations.[307] As previously noted, however, other theorists believe that the WTO has increased trade production by 120%.[308]

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296 *See id.* at 1.

297 *Id.* at 814.

298 *See* ROBERT Z. LAWRENCE, CRIMES & PUNISHMENTS? 4 (2003).

299 *Id.* at 4.

300 *Id.*

301 *Id.*

302 LAWRENCE, *supra* note 298, at 4.

303 Jose E. Alvarez, *The WTO as Linkage Machine,* 96 AM. J. INT'L L. 146, 148 (2002).

304 *Id.*

305 *See id.* at 150; *see also* Michael N. Barnett & Martha Finnemore, *The Politics, Power and Pathologies of International Organizations*, 53 INT'L ORG. 699 (1999) (addressing the inefficiency, ineffectiveness, repressiveness, and unaccountability of international organizations in general).

306 *See, e.g.*, Subramanian & Wei, *supra* note 287 (discussing that many scholars and theorists do not believe the WTO is truly very effective and reconciling the inconsistent views between scholars and theorists).

307 Andrew K. Rose, *Do We Really Know that the WTO Increases Trade?*, (Nat'l Bureau of Econ. Research, Working Paper No. 9273, 2002).

308 Subramanian & Wei, *supra* note 287, at 151.

Some positive facets of the WTO are definitely apparent, despite the debate between scholars as to whether the WTO is successful at achieving its objectives. First, the WTO has acknowledged that different countries excel in different areas.[309] The WTO has an open-minded policy: no discrimination.[310] Second, the WTO has set up an efficient system that provides incentives to follow the rules[311] and also provides punishment for those that violate the rules.[312] These positive aspects of the WTO could be incorporated in a potential regulatory model for the pharmaceutical industry.

Researchers and economists may not agree on whether the WTO is truly an effective and efficient international agency. However, most researchers agree that an international agreement in the world of pharmaceuticals is lacking. Perhaps an international agreement can begin on a very small scale and involve only a few select countries. An international system of pharmaceutical law-making, regulation, and enforcement could ultimately increase the speed with which new pharmaceuticals could be approved and decrease the cost of producing, marketing, and testing the drugs if the nations involved focused on the goals illuminated by the WTO: economic efficiency and free flow of goods.

2. The North Atlantic Treaty Organization

The North Atlantic Treaty Organization is a unity of twenty-eight member countries from North America and Europe.[313] The primary purpose of the organization is to protect the security and freedom of the member countries.[314] Under the principle of collective defense, NATO views an attack against one member nation as an attack against all.[315]

The organization began its formation in 1949 when twelve nations, including the United States, signed the North Atlantic Treaty in response to ideological clashes between the East and West.[316] The Soviet Union was seeking control of various parts of Western Europe and the objective of the NATO alliance was to assist in the defense of an attack by the Soviet Union.[317] Since

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309 *See The Case for Open Trade*, *supra* note 279.

310 *Principles of the Trading System*, *supra* note 282.

311 *The Case for Open Trade*, *supra* note 279. Incentives include the ability to trade freely and foster economic growth. *Id.* Countries will also benefit from being able to trade with countries they did not trade with before. *Id.*

312 *Id.* Punishments include removal from the WTO, retaliation by member-countries, and decreased economic benefits. *Id.*

313 *What is NATO?*, *supra* note 18.

314 *Id.*

315 *Id.*

316 *Washington Treaty*, NATO, http://www.nato.int/cps/en/natolive/topics_67656.htm (last visited Feb. 9, 2014).

317 *Id.*

then, NATO has continued pursuing three core tasks: collective defense, crisis management, and cooperative security through partnerships.[318]

One of the main reasons that NATO has been so successful, even though so many different nations are involved, is that there is complete cooperation. The North Atlantic Council (NAC) is the decision-making unit.[319] The NAC meets weekly and even more frequently if needed.[320] Within the NATO headquarters, located in Brussels, each member nation has a permanent representative.[321] NATO's decision-making process is based on unanimous consent to ensure that every country is respected and that each decision made by the organization is fully supported.[322]

Modernly, NATO has continued to operate well into the 21st century.[323] Today, just under 100,000 military personnel are engaged in various on-going missions and operations.[324] NATO is pursuing peace-support operations and crisis management in Afghanistan and the Balkans.[325] NATO is currently working on a counter-terrorist operation in the Mediterranean.[326] Among other things, NATO is also performing a support mission for the African Union including a counter-piracy operation.[327]

NATO has been persistent even after the decline of the Soviet threat.[328] Naturally, many organizations, such as NATO, may cease to exist after the mutual threat has dissolved. However, NATO has continued to be a vital defense organization in the North Atlantic to this day.[329] Even after the Cold War, NATO has not only survived, but has continued on to new endeavors.[330] NATO's longevity may partially be attributed to the way the "allies have updated their common strategic concept, maintained NATO's integrated military structure, and continue to engage in joint military planning, training, and exercises."[331]

There are many reasons why NATO continues to be such a success. First, external threats by non-member nations help preserve the alliance.[332] Second,

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318 *See, e.g.*, *What is NATO?*, *supra* note 18.

319 *Id.*

320 *Id.*

321 *Id.*

322 *Id.*

323 *What is NATO?*, *supra* note 18.

324 *NATO Operations and Missions*, NATO, http://www.nato.int/cps/en/natolive/topics_52060.htm (last updated Oct. 18, 2013).

325 *Id.*

326 *Id.*

327 *Id.*

328 John S. Duffield, *NATO's Functions after the Cold War*, 109 POLI. SCI. QUART. 763, 764 (1994).

329 *See, e.g.*, *NATO Operations and Missions*, *supra* note 324.

330 *See id.*

331 Duffield, *supra* note 328, at 765.

332 *Id.* at 766. Examples of such threats include threats posed by Russian military power. *Id.*

NATO has a great capacity for institutional adaptation.[333] This has been achieved because NATO plays a significant role in controlling military conflicts between Central and Eastern Europe.[334] Third, there are other compelling reasons for staying neutral with the member countries, like foreign investment and use of imports/exports.[335]

The North Atlantic Treaty Organization is a model of a successful unity between many different nations. Threats to the homeland are so serious that it is natural to unify with stronger countries with different talents. NATO has been so successful because protection is something that every country needs. Mutual respect and cooperation has led NATO to be a real international accomplishment.

The North Atlantic Treaty Organization also has some positive aspects that a global pharmaceutical industry could mirror. First, NATO has qualified representatives from every participating country that are permanently placed at NATO headquarters.[336] This placement of representatives helps ensure that every participating country is able to express its opinions and ideas.[337] Mutual fears by member countries help ensure that the alliance will continue as well.[338] Also, other outside rationales keep the entities together; member countries want to stay on positive terms with the other member countries for economic benefits.[339]

V. WHY A GLOBAL REGULATORY SCHEME WILL WORK

A. The "Psychology" Behind International Cooperation

Generally, national governments want to keep their legal sovereignty.[340] Governments enjoy having the sole authority to evaluate their own policies and regulate internationally.[341] Typically, government entities enter into international agreements with skepticism and are reluctant to designate a supranational body to make decisions.[342] Therefore, international relations theorists are puzzled because so many different nations are entering into international agreements modernly.[343]

Scholars have theorized various rationales for why so many international agreements are being entered into by national governments. First, there is a

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333 *Id.*

334 *Id.*

335 *Id.*

336 *What is NATO?*, *supra* note 18.

337 *Id.*

338 Duffield, *supra* note 328, at 766.

339 *Id.*

340 Beth A. Simmons, *Compliance with International Agreements*, 1 ANNUAL REV. OF POLI. SCI. 75, 75–77 (1998), *available at* http://www.annualreviews.org/doi/full/10.1146/annurev.polisci.1.1.75.

341 *Id.*

342 *Id.* at 80.

343 *See id.* at 81.

functional need for international agreements because of the rising level of interdependence between different nations.[344] For example, our world is more interconnected than ever due to the speed which information can be disseminated through the internet. Countries communicate more efficiently than ever before and are always seeking to expand. Second, theorists believe that countries have a greater desire for predictability and regularity in international relations because of the vast nature of the potential consequences.[345] Third, and perhaps most important, national governments often wish to enter into international agreements to change and gain influence over the policies of other nations.[346]

The common problem with international agreements is compliance and enforceability.[347] Including "design elements" in an agreement helps to ensure enforceability and compliance.[348] Design elements include making an agreement formal rather than informal, creating mandatory dispute resolution procedures, and establishing a central unit to monitor and enforce that agreement's terms.[349] Such design elements increase the cost associated with a compliance violation and therefore decrease the likelihood of defiance by a country participating in the agreement.[350]

Most scholars agree that the enforceability of international agreements is essential for the agreement to be successful.[351] Some theorists believe that the agreement must be enforceable itself, and dispute resolution should not just be left to a central governing body.[352] Forming non-legal agreements, such as memoranda of understanding or nonbinding resolutions, is often unenforceable in the long run.[353]

A persuasive argument could be made that the above components would help to create an international agreement concerning pharmaceutical regulation. The agreement would have to be legal and binding to ensure compliance by the member countries. Additionally, in the realm of drug law, it would be especially

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[344] *Id.* at 77 (construing KEOHANE, AFTER HEGEMONY: COOPERATION AND DISCORD IN THE WORLD POLITICAL ECONOMY 290 (1984)).

[345] Simmons, *supra* note 340 (citing J.L. BRIERLY, THE LAW OF NATIONS 442 (1963)). Potential consequences of an international agreement could vary widely. However, when the consequences could be as severe as war, predictability of international relations is crucial. *Id.*

[346] *Id.* (construing R.O. KEOHANE, *supra* note 344, at 91–107).

[347] Andrew T. Guzman, *The Design of International Agreements*, 16 EUR. J. INT'L L. 579, 579–612 (2005), *available at* http://ejil.oxfordjournals.org/content/16/4/579.full.

[348] *Id.*

[349] *Id.*

[350] *Id.*

[351] *See* Barbara Koremenos, *If Only Half of International Agreements Have Dispute Resolution Provisions, Which Half Needs Explaining?*, 36 J. LEGAL STUDIES (2007), *available at* http://www.jstor.org/stable/10.1086/509275.

[352] *Id.*

[353] *See generally* Jack L. Goldsmith & Eric A. Posner, *International Agreements: A Rational Choice Approach*, 44 VA. J. INT'L L. 113, 114 (2003).

important that compliance is achieved to ensure the safety of all the citizens of the nations bound by the agreement.

B. A Proposal for International Harmonization of Pharmaceutical Approval

After examining many of the criticisms of the drug approval process in the United States, this note proposes an international regulatory drug approval scheme with Great Britain and Japan. The time and money expended to approve a new drug is astronomical.[354] Arguably, the United States is not utilizing their best resources and manpower to get the job done.[355] Since the United States does not want to compromise the safety standards of drug approval, perhaps more regulations could be put into place in the post-market surveillance stage, putting less emphasis on the efficacy of a drug.

Both Great Britain and Japan have strengths and weaknesses in their respective drug approval processes. Great Britain does the majority of their drug research in the post-market surveillance stage.[356] The clinical analysis in Great Britain, before the pharmaceutical is released to the open market, is shorter than that done in the United States.[357] The reporting system is also mandatory.[358] Many dangerous side effects of new drugs are not found until the drug has been released on the open market, so a mandatory reporting system done by others than the manufacturer would be beneficial to the safety of the consumer.[359] Great Britain also differs on safety and efficacy requirements.[360] More focus on safety and less on efficacy will allow terminally ill patients to have access to the drug sooner.[361]

Japan has the third largest economy in the world and plays a large role in the development and breakthrough of new pharmaceuticals.[362] Although Japan's drug regulations are somewhat lengthy and costly, the nation has taken steps to deregulate.[363] Japan would like to incorporate more feedback from patients and consumers in the post-market surveillance stage[364] to strengthen their ability to remove harmful drugs from the market quicker. Japan is seeking to harmonize with other nations in the realm of drug regulation and consequently the Japanese system deserves a second look from the United States.[365]

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354 *See The Cost of New Drug Discovery, supra* note 6.
355 *See* discussion *supra* Part II.C.3–4.
356 Wall, *supra* note 130, at 325.
357 *Id.*
358 *Id.*
359 *See id.*
360 *Id.* at 326.
361 Wall, *supra* note 130, at 326.
362 *See* Neckers, *supra* note 156, at 295.
363 *See id.*
364 *See id.* at 308.
365 *See id.*

To solve some of the issues with the system in the United States, the FDA should place less emphasis on efficacy and focus primarily on the safety of a new drug. This targeted ideology would likely help decrease the drug lag and the cost associated with approval. In turn, pharmaceutical companies may no longer do their business primarily overseas. The FDA could also incorporate a more impartial mechanism to approve drugs, like Great Britain does with the CMH.[366] Consequently, there would be less "politics" within the FDA. The FDA should also increase the reporting requirements in the post-market surveillance stage. Unsafe drugs could be taken off of the market more quickly and the reporting process could also include an efficacy evaluation during this stage, rather than during the testing stages before approval.

As evidenced by the ICH, the United States, Japan, and members of the Economic Community have considered the possibility of a more uniform system of pharmaceutical laws.[367] Although the accomplishments of the ICH were limited, the progress showed the nations' willingness to unify as opposed to becoming isolated from an international scheme. The President's Council also made a suggestion for successful international regulation: allowing the FDA to evaluate the clinical and testing procedures that each participating nation currently uses for drug approval.[368] Since the United States has very stringent safety standards, perhaps allowing the FDA to examine facilities, research, studies, and other clinical processes more thoroughly would give the agency some comfort that safety considerations are fully emphasized.

The United States has historically participated in international agreements when a situation calls for change. In response to a global trade crisis, the WTO was formed.[369] NATO was organized to protect the security of the member-nations during a time of hostility.[370] Although those organizations are unrelated to pharmaceutical approval, each employs techniques and procedures that could translate to a successful drug approval process.

First, a central decision-making body is crucial. A representative from each participating nation, the United States, Great Britain, and Japan, would gather at a headquarter. If there is a feeling of centrality and community, actions by the regulatory authority could probably be expedited and less costly. Second, a non-discriminatory policy would be beneficial. Each participant has different strengths. For example, Great Britain has a very successful reporting rate in the post-market surveillance stage. This international regulatory authority would be wise to follow Great Britain's drug regulations in that particular area. Alternatively, the United States' strength lies with the ability to implement strict safety standards. Third, the decisions made by the regulatory authority must be enforceable. Perhaps the best method to enforce decisions would be as the WTO

366 *See* Abraham & Davis, *supra* note 122, at 403.
367 *See* discussion *supra* Part IV.A–A.1.
368 *See* Relihan, *supra* note 14, at 257.
369 *Who We Are*, *supra* note 17.
370 *What is NATO?*, *supra* note 18.

did: with sophisticated incentive and punishment procedures.[371] As demonstrated in this note, international agreements are more successful when they are enforceable.[372] The proposed drug approval agreement would need to incorporate strict regulations so that each participating nation is aware of the consequences. All regulations implemented by the proposed regulatory authority should be legal and binding, to ensure the safety of each nation's citizens.

Researchers have been curious about why so many nations are eager to enter into international agreements.[373] International agreements have many positive aspects associated with them. Nations are more dependent on each other and want to experience the benefits that other nations can offer them.[374] Various nations also wish to influence or change the policies of other nations.[375] Here, the United States could benefit from the regulatory techniques of Great Britain and Japan. The United States may also be able to influence international policy by harmonizing with these other nations. The United States, EU, and Japan are the three largest pharmaceutical markets in the world and with international cooperation, the drug approval process would surely be expedited.[376]

VI. CONCLUSION

Coming around full circle, this note began with a discussion of the recent case about Abigail Burroughs and Abigail Alliance's efforts to convince the U.S. Supreme Court that access to experimental drugs is a constitutional right. Although the Supreme Court denied certiorari and therefore indirectly was unwilling to find such access a constitutional right, accelerating the drug approval process is still a possibility.

A reciprocity agreement between a small number of nations could be an effective way to minimize the criticisms of the FDA and give people like Abigail Burroughs the opportunity to access live-saving medication. The United States, Great Britain, and Japan could all mutually benefit from a more harmonized pharmaceutical regulatory regime by incorporating aspects of successful international agreements and making the overarching focus keeping citizens safe while decreasing the immense cost and time expended on drug approval.

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371 *See The Case for Open Trade*, *supra* note 279.

372 *See* discussion *supra* Part IV.A.

373 *See* Simmons, *supra* note 340.

374 *See id.*

375 *See id.*

376 *See* Abraham & Reed, *supra* note 210, at 342.