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FDA EFFECTIVENESS STANDARDS: HELPFUL OR HARMFUL?

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Abstract
The Kefauver-Harris Drug Amendments of 1962 gave the Food and Drug Administration (FDA) the power to require that new pharmaceuticals be proven effective before they are released. The proof-of-efficacy requirement for new drugs is a large and unnecessary barrier to innovation in the healthcare market. There is evidence that adding this requirement reduced innovation and increased costs to both producers and consumers. Using public choice theory and Austrian economics, this paper argues that the FDA is not the best mechanism for ensuring effectiveness, and it recommends that the FDA remove proof-of-efficacy requirements, allowing market mechanisms to determine which pharmaceuticals are effective.

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Contents

1. Introduction

The FDA currently regulates both the safety and effectiveness of new pharmaceutical products and medical devices. Before 1962, the FDA was purely a safety-regulating agency; it did not regulate for effectiveness until the passage of the Kefauver-Harris Drug Amendments.[i] Passage of the new effectiveness amendments came on the heels of the thalidomide tragedy. The drug thalidomide was sold in Europe in the 1950s as a tranquilizer, but it was prescribed by some doctors to pregnant women for help with morning sickness.[ii] In the late 1950s and early 1960s, it became known that women who had taken thalidomide during their pregnancies were giving birth to babies with severe deformities.[iii] Because thalidomide had not been tested on pregnant animals, its adverse effects on pregnant women were not known.

In the United States, thalidomide had yet to come to market; however, as a result of the tragic stories from Europe regarding thalidomide there was public outcry for raising the standards of the drug approval process.[iv] The Kefauver-Harris Drug Amendments of 1962 were the result of public demands. Senator Estes Kefauver began hearings on increasing the scope and power of the FDA in 1959 because he was concerned about high drug prices and believed that people were being misled by pharmaceutical manufacturers about their products.[v] Because of the public outcry in the early 1960s after the information on the effects of thalidomide was made public, Kefauver's bill was amended to address these concerns, and the bill passed quickly.[vi]

The thalidomide tragedy was not one of ineffectiveness, but rather of safety. It is interesting that the reaction to this tragedy was to increase regulations on a different aspect of pharmaceuticals rather than focus on what went wrong in the case of thalidomide. The Kefauver-Harris Amendments did not even address the problem that is supposed to have prompted this expansion in regulatory power. Thalidomide *was* effective as a sedative. The tragedy should

have made regulators take a closer look at how they regulated safety, not move on to regulate a different area.

The Kefauver-Harris Amendments allowed the FDA to approve only those drugs that had been proven to be effective and required that pharmaceutical companies disclose all potential side effects of their drugs. Along with reviewing all new drug applications with a filter for effectiveness, the law also required that the FDA conduct a retrospective review on all drugs approved between 1938 and 1962 to determine their effectiveness.[vii] The FDA also was given the power to regulate the advertisement of drugs.[viii] Now that it was mandated to determine the effectiveness of new drugs, the FDA had to determine what constituted an effective drug.

2. What Is Effectiveness?

Effectiveness is defined by the FDA as a drug having health benefits over what could be achieved using a placebo or a drug already in existence that was tested in a controlled situation such as a clinical trial.[ix] The drug's effectiveness is only tested for the specific diseases or ailments indicated by the drug manufacturer. Often pharmaceuticals can also be used for off-label purposes, which will be discussed later in this paper.

Since the 1962 amendments requiring the FDA to test for effectiveness were implemented, the standards for proving effectiveness have been debated. The process of clinical trials for Investigational New Drug Applicants occurs in three phases. Phase I, which aims to determine the safety of the new drug, is when the drug is first introduced to human subjects.[x] This is done in a trial with a small sample that aims to determine what the side effects of the drug are, how the drug is removed from the body, and at what level the drug is safe for human use.[xi] The sample tested in Phase I is usually somewhere between 20 and 80 individuals, and can

consist of volunteers or patients who have given consent.[xii] There are some preliminary tests of the effectiveness of the drug, but this phase is mostly used to determine if the interaction between the drug and the human body is safe.

Phases II and III are when the FDA requires the clinical trial to begin testing the effectiveness of the new drug. Phase II is used to evaluate the effectiveness of the drug and to determine the common short-term side effects and risks associated with the drug.[xiii]This evaluation is usually conducted by comparing the patient's reaction to the new drug with either a placebo or a different drug.[xiv] The sample size in Phase II can be anywhere from 12 to 300 individuals. Once Phase II has enough preliminary data to determine the drug's effectiveness, the testing moves onto Phase III.

Phase III is simply a larger trial of the drug's effectiveness. The sample size is increased to anywhere from a few hundred to a few thousand participants, allowing the FDA to see if the drug is effective on different populations and in modified doses.[xv] Phase III gives the FDA a larger set of data in order to conduct a benefit-risk analysis and decide if the drug is effective enough to be put on the market.[xvi]

The 1962 amendments state that pharmaceutical manufacturers must provide "substantial evidence" of the effectiveness of new drugs.[xvii] Substantial evidence is defined as

> Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the

> effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[xviii]

Although there has been debate over how exactly to obtain this substantial evidence, the FDA has been operating under the direction that two adequate and well-controlled studies (Phase II and III) will fulfill this requirement.[xix]

The reason that the FDA has been using two studies as sufficient evidence is because of the need for independent substantiation of the results.[xx] A single clinical study that determines effectiveness is not considered adequate scientific support. Single studies can be subject to bias, variability in the human biological system, specific factors of where the investigation took place, and occasionally fraud.[xxi] Because of these potential problems, it is deemed necessary by the FDA for there to be at least two independent verifications of effectiveness.

The FDA has issued guidance about the quantity of evidence necessary in three different possible drug-creation situations. The first situation is when the effectiveness of a new drug can be extrapolated from existing studies. The second situation is when effectiveness can be determined by a single well-controlled study, by supplementing that study with evidence from other studies of the same disease or studies of similar diseases. The last situation is when just a single multicenter study can provide sufficient evidence of effectiveness. The FDA acknowledges that this set of three cannot cover all possible scenarios; however, the agency offers these situations as examples, and explains how to determine what amount of data is sufficient to determine effectiveness in each of them.[xxii]

Overall, what amount of evidence is considered sufficient is still somewhat unclear to pharmaceutical manufacturers. Although the FDA has tried to provide some guidance and

information on what it will consider sufficient, the decision is ultimately at the discretion of the FDA official in charge of approving or not approving the specific drug. The three phases of clinical trials attempt to make the process more standardized, but the requirements for each phase still depend on the judgment of the reviewers.

3. Consequences of FDA Effectiveness Requirements

Alexander Schmidt, a former FDA commissioner, once said, "I am unable to find a single instance where a congressional committee investigated the failure of the FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them."[xxiii] This quote provides a glimpse into the incentives facing the FDA; the approval of a drug when it should not have been approved will result in visible consequences. Not approving a drug that should be approved will not result in visible consequences. Because of these incentives, the FDA errs on the side of caution, and this cautious approach increases the barriers facing a drug trying to come to market. The extreme caution of the FDA is not without ramifications.

Decreased Innovation

The first effect that the 1962 amendments had on the pharmaceutical market was to decrease the pace of innovation. In 1973 Sam Peltzman wrote an article identifying the results of the new effectiveness requirement.[xxiv] Peltzman created a statistical model using data on the amount of "New Chemical Entities" (NCEs) from 1948 to 1962.

This model attempts to predict the number of new drug introductions. The most predictive variable in the model is a "lagged variable," the size of the prescription drug market two years earlier. Before 1962, it took approximately two years to introduce a new drug into the

market. In a given year, if the market for drugs was large, a company would be likely to invest in the creation of a new drug. Then two years later, the new drug would appear on the market. In essence the lagged variable predicts the level of investment in new pharmaceuticals based on the previous size of the market. So as the market for new drugs shrank, there was even less investment in the creation of new drugs.

Figure 1

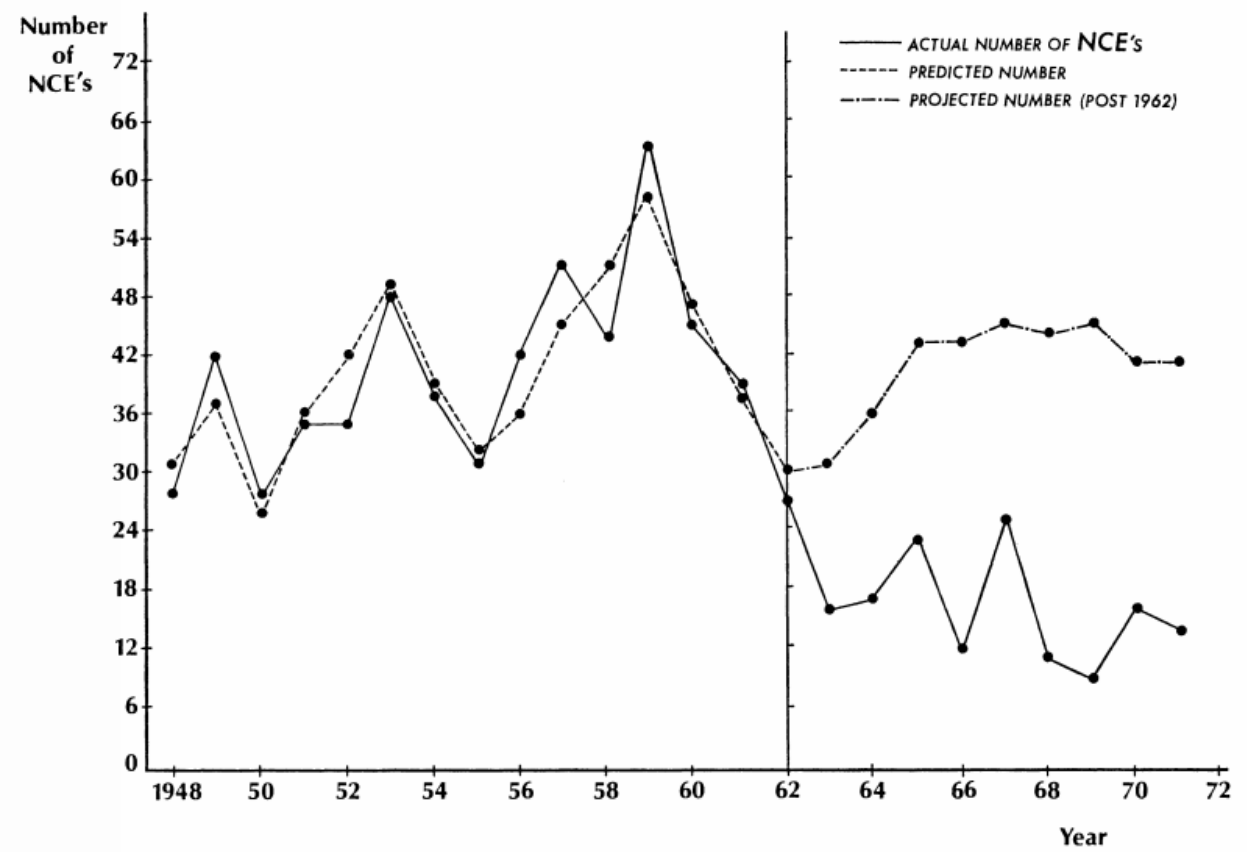

FIG. 1.—New chemical entities, 1948–71

The estimates that the Peltzman model produces for the number of new drugs introduced before 1962 track very close to the actual data, as is shown in figure 1. Therefore, it is reasonable to assume that the model would have continued to fairly accurately predict the market in the absence of the new effectiveness amendments. But we can see that, after the new regulations in

1962, the number of new drugs dropped considerably below what we would estimate from the lagged size of the market.[xxv]

Peltzman also analyzes whether the new amendments were truly reducing the number of ineffective drugs that were on the market. Even though the amendments were costly in that they decreased the number of new drugs introduced, if they were accomplishing the goal of reducing the number of ineffective drugs released then perhaps the amendments were helpfully correcting a market failure. But Peltzman finds little evidence to support the claim that the amendments were truly causing a decline in the number of ineffective drugs released to the market.[xxvi] Based on Peltzman's paper, the amendments seem to impose a heavy cost on innovation without producing any benefit.

In another study, Steven Wiggins uses a slightly longer span of data, but finds results similar to Peltzman's. The model that Wiggins uses indicates that the regulations imposed by the 1962 amendments reduced the rate of introduction of new drugs by about 60 percent.[xxvii] The results of Wiggins's study again show that there is a tradeoff between allowing the FDA to regulate effectiveness and the rate of drug introductions.[xxviii]

Another study, which surveys the literature concerning the 1962 amendments, finds that the decline in the introduction of new drugs was not concentrated in the reduction of ineffective drugs.[xxix] This suggests that increasing the scope of the FDA resulted in fewer total drugs reaching the market, but not necessarily more effective drugs reaching the market.

Increased Costs

A second effect that the 1962 effectiveness amendments had was that they dramatically increased the time and cost of bringing a drug to market. Before the implementation of the

effectiveness requirement, it took about two years to get a drug to market.[xxx] With the addition of effectiveness testing, which is conducted in both Phase II and Phase III clinical trials, it can take anywhere from 11 to 14 years to get a drug through the required process and approved.[xxxi] Phase II and Phase III testing lasts 25.7 and 30.5 months respectively.[xxxii] The additional time added is in how long it takes the FDA to approve the methodology and New Drug Application. This approval process can add years to the timeline.

During this time, American consumers are suffering significant unseen costs. People are not able to access drugs that have been deemed safe, and this can cost lives. In light of the evidence that the FDA is not efficient at removing ineffective drugs, this wait seems even more costly. The FDA has implemented a fast-track option, in which certain drugs that are deemed to be of high priority are able to get through the process faster, but the evidence shows that the fast track is only marginally faster than the regular approval method.[xxxiii]

The cost of bringing a drug to market also increased dramatically with the addition of effectiveness testing. Since Phase II and III are both effectiveness phases, it can be seen how costly the creation of a new drug is just by looking at the expense for those two phases. One study estimates that the average costs for pharmaceutical manufacturers of Phase II and Phase III testing a drug are about $23.4 million and $86.5 million respectively, while another study by the Manhattan Institute points to Phase III as the main cost driver in the clinical-trial process.[xxxiv] This study looks at the development of drugs in four different areas of medicine. The data reveal that in most cases companies spent more than 90 percent of their development money per drug on Phase III testing.[xxxv] Higher costs to the companies are passed on to the consumers in the form of higher prices. Ironically, this is the opposite of the effect that Kefauver had in mind when he created the amendments.

Importantly, this process is not only costly to firms, but each delay of the release of a drug means that more lives are being lost while the drugs are held up in effectiveness testing. Although it is difficult to estimate how many lives are being lost as a result of these restrictions, it is obvious that there are lives at stake.

The FDA has an expanded-access, or "compassionate use" pathway for patients to have access to experimental drugs, but many feel this pathway is not enough.[xxxvi] States have been working on creating "Right to Try" legislation in order to circumvent the FDA approval process and allow terminally ill patients access to experimental drugs.[xxxvii] Seventeen states have passed Right to Try legislation and 22 states have legislation pending, but these laws do not automatically secure patients access to potentially life-saving care. Many pharmaceutical companies are still reluctant to allow these terminally ill patients to try their experimental treatments for fear of how it may affect their FDA approval process.[xxxviii]

Right to Try policies are an attempt by the states to increase access, but they have not been able to create a widespread increase in access. The addition of user fees, which are fees paid by pharmaceutical companies seeking drug approval, has helped to speed up the process some through increased FDA funding, but effectiveness testing is still an extremely long process.[xxxix] The next question that needs to be asked is whether there is evidence that drugs can be as effective on average without the FDA's approval.

4. Economic Theory behind Removal of FDA Effectiveness Standards

Would the market be better able to determine effectiveness standards for drugs than the FDA is? This is a difficult question to answer in absolute terms. There is evidence from pre-1962 data to show that the market was operating and determining effectiveness without the FDA. But

there is no way to know for sure what would happen today if the FDA removed itself from this process. However, economic theory can provide insight into the efficiency of FDA regulation of effectiveness and the efficiency of a possible market alternative.

Public-Choice Analysis of the FDA

It is important to note that the FDA is a large bureaucracy, and is subject to the same pitfalls as any bureaucracy. Public choice theory can help us understand the incentives facing a bureaucratic agency and the problems with bureaucratic management systems. In particular, bureaucracies are incentivized to maximize budgets, engage in expansion both in size and responsibility, and resist technological innovation.

Maximizing Budgets

Government agencies are naturally budget-maximizing entities.[xl] If an agency fails to use all of the funds allotted to it in the federal budget, then the following year its budget could potentially be smaller. An agency would not want to have fewer resources for the following fiscal year, and so it will seek to maximize its use of its budget each year. The FDA is no exception to this rule. In the recent budget proposal for FY 2016 the FDA estimates a need of $4.9 billion, a 9 percent increase from FY 2015.[xli] For medical product safety specifically, the FDA has asked for a 3 percent increase in its budget.[xlii] If the FDA is always seeking to maximize its budget, then where is the incentive to control costs?

An agency often has the upper hand over Congress in negotiating budgets. Because the agency is a monopoly, it can make "take-it-or-leave-it" proposals.[xliii] In particular, the public views the FDA as the only thing standing between them and unsafe pharmaceuticals. If Congress chose not to fulfill the budgetary requirements proposed by a high-profile agency such as the

FDA, it could incur public disapproval. Because of this, the FDA is able to continue to increase its budget, without proof that these budget increases are resulting in higher quality or more efficient outputs.

Expanding in Size and Responsibility

Another incentive facing the FDA is the need to expand, whether in the number of employees or in the fields the agency controls. Because profit is not a motivating factor for bureaucracies, power becomes what bureaucrats seek. In theory, a bureaucrat's success is measured by his or her power.[xliv] There are two main ways in which an increase in power can be achieved: Parkinson's Law and mission creep. Parkinson's Law is the economic theory that bureaucrats are rewarded based on how many jobs they create and how many employees they supervise.[xlv] For instance, the addition of Prescription Drug User Fees was supposed to help increase the FDA budget so that it could hire more individuals to decrease a drug's time to market.[xlvi]

An even more pressing issue with the FDA is mission creep. Mission creep theorizes that another way to increase power is to increase the scope of regulatory power given to an agency. This can easily be seen in any agency where a new product or idea comes out and the question of whose jurisdiction it falls under to regulate the entity immediately appears. In 1962, Congress allowed the FDA to expand its power into regulating drug effectiveness. The FDA continues to expand its role in the regulation of innovative medical technology under the umbrella of its existing regulatory responsibilities. With every new medical innovation, the FDA is right there to either regulate it or issue guidance about it.

Resisting Technological Innovation

Introducing new technologies into the pipeline of communication in a bureaucracy can reduce miscommunication and therefore waste. But the introduction of technology could also remove individuals from jobs in the bureaucracy. As number of employees supervised and job creation are important in the public sector, adding new information technology would be contrary to the incentives facing bureaucrats. Gordon Tullock believes that this implies that bureaucracies are as efficient as they can be, because they will reject technology that can increase efficiency at the expense of jobs.[xlvii]

Bureaucracy's output is not a specific product or unit, but rather an activity. Because of this, it is very difficult to monitor whether or not a given bureaucracy is efficiently and effectively accomplishing its responsibilities. So those attempting to analyze bureaucracies create proxy measures to help track the agencies' performance. In the case of the FDA, which is tasked with keeping the public safe from harmful pharmaceuticals and determining their effectiveness, the output measured is the number of drugs approved, the number of drugs recalled, and the time in the approval process. Although these proxies can give an idea about how efficient the agency is being, using them does not guarantee accurate monitoring.

Bureaucracies, Monopolies, and Information

Bureaucracies are monopolistic, which means that they are not subject to the competitive pressures that make profit-seeking entities efficient. Another outcome of the FDA being a monopoly is that it denies the public and Congress any alternative source of information, meaning that there is no way to gauge if the methods or information being released are as accurate as possible. This monitoring problem happens in all bureaucracies, but is especially problematic when the bureau is a monopoly such as the FDA.[xlviii]

Are there some tasks that are just too complex for a large bureaucracy to handle?[xlix] Tullock uses Hayek's concept of the knowledge problem to shed light on how impossible it would be for an agency to possess all the knowledge required to make a regulatory decision. The problem being pointed out here is that the amount of external knowledge and internal coordination necessary to accomplish the task may be larger than is possible to achieve in an agency. The task given to the FDA is to determine the safety and effectiveness of every drug, medical device, and medical innovation being used. Is it possible that this is too large a task to be undertaken by just one agency? Would it be better if many different entities were able to determine effectiveness on a more individual basis?

Michael Polanyi's theory of polycentricity can provide insight into whether or not the current FDA structure can accomplish its stated goal. Polycentricity is a social system where there are many decision centers all operating under an overarching set of rules.[l] Polanyi believed that science is so successful because individual researchers have the freedom to make individual contributions to their profession and structure their research in the way that they believe will yield the best results.[li] If an authority figure attempts to impose a structure that does not allow for this trial-and-error style, then the research will fail because it will no longer evolve with the best practices.

The FDA structure is exactly what Polanyi warned against. The FDA has the power to set regulations for the research and creation of new pharmaceuticals. There is a specified set of rules to create a clinical study, and this set of rules does not allow room for individual researchers and producers to add anything that may improve the process. Pharmaceutical research is incredibly centralized, in the sense that there is no room for individual decision-making on what should be

tested or needs to be examined—this has all been predetermined by the FDA and has not been allowed to adapt to the changing technological landscape.

Market Mechanisms for Effectiveness Standards

Another important point to consider when discussing publicly provided services is the lack of feedback mechanisms. Ludwig von Mises points to the profit-and-loss function of the market as the method by which a firm can determine if its services are valuable and of a high-enough quality for consumers.[lii] When there is no profit mechanism for an agency, it cannot determine if it is efficiently and effectively meeting the needs of its consumers. The FDA is even more prone to this problem because it has two distinct consumers of its "services." Pharmaceutical companies consume FDA services in the form of receiving drug approval, but the ultimate consumers of the FDA product are the general public.

Who is most able to determine if a drug is effective? It is important to consider Hayek's knowledge problem. Hayek posits that it is difficult, if not impossible, to aggregate the "dispersed bits of incomplete and frequently contradictory knowledge which all the separate individuals possess."[liii] Each pharmaceutical product affects different individuals differently, and could potentially be used for different purposes for each individual. Perhaps the best way for effectiveness to be determined is on the individual level, using doctors, pharmacists, and medical experts.

When the FDA first stepped in to regulate effectiveness for the pharmaceutical market, perhaps it was filling a need. In 1960, accessing relevant and necessary information about a particular drug would have been an exceedingly difficult and time-consuming process. The FDA was able to step in and make it easier for individuals to obtain the information, or to remain

rationally ignorant because they had a regulatory body working on this issue for them. While this solution came at the cost of lost innovation and rising drug prices, individuals at that time were facing a level of asymmetric information that seemed insurmountable.

Asymmetric information is a problem that is faced all the time in market interactions, and the question becomes whether government should intervene to solve this problem or whether private mechanisms should be allowed to work to overcome asymmetric information.[liv] In the pharmaceutical industry, companies have much more information about the uses and side effects of the drugs they are creating than consumers can know and even understand. This fact alone is reason enough for many for the FDA to exist—to help eliminate some of this gap in knowledge.

Israel Kirzner observed that the lack of equilibrium created through asymmetric information allows for a profit opportunity.[lv] Knowledge about the pharmaceutical industry and experimental drugs is difficult for consumers to understand on their own, which presents an opportunity for entrepreneurs to fill the knowledge gap. A private, or nonprofit, organization that could help people determine the effectiveness of drugs would be highly valuable to consumers. However, Peter Boettke and Mark Steckbeck explain that regulators are often blind to "the dynamism of markets and the incentive mechanism driving entrepreneurs to discover ways to ameliorate problems associated with market exchange."[lvi]

It is costly to gather all of the information necessary to decide on a drug. One individual consumer could seek to gather all of the information required to determine whether or not a drug will be effective for them, but this would be incredibly time-consuming and difficult. This is where Internet tools can help to solve medical asymmetric information problems. The Internet is able to communicate more information to consumers about products and services than could ever be conveyed before.[lvii] There are a variety of search engines and monitoring tools that could help

educate consumers about any and all pharmaceuticals. Health choices have high costs and benefits associated with them, meaning individuals have a much higher incentive, higher than in many other markets, to conduct research to be sure they are choosing the correct product. And search engines or other Internet knowledge bases that provide useful information to consumers will gain a positive reputation and thus reap the financial rewards in user fees or advertising dollars.

This approach has been used for many other industries with asymmetric information problems. *Consumer Reports*, Angie's List, and Yelp, just to name a few, gather the relevant information on products and services. The information gathered by many of these third-party sites relies heavily on reputational feedback mechanisms. When a consumer has a bad experience with a product or service, that information is available instantaneously to consumers all across the world. Reputation mechanisms used to function only on word of mouth and the centralized media; now, any consumer can openly discuss his or her bad experiences.[lviii] Especially in health care, where a mistake can have enormous repercussions, the reputation-feedback mechanism would work swiftly to reward good pharmaceutical companies and punish bad ones.

Consumers, though, do not have to be left completely on their own in interpreting the information they learn on the Internet. Doctors and pharmacists would be able to help consumers digest and understand much of the information. Today more and more people are doing research on their ailments prior to going to see a doctor, so it is not a stretch to think people could research their drug options.[lix] If people review and research restaurants before they go to them, why would they not do the same for pharmaceuticals? The Internet opens up new and exciting ways to provide information, and the FDA does not need to be a part of this process.

As a final avenue to be sure that pharmaceutical companies are producing effective drugs, there are always contracts and torts as an ex post solution to any ineffective drugs that make it through to the market. These legal remedies do not place an unnecessary burden on innovation and often are able to work in tandem with many of the market solutions proposed above.[lx] Legal ramifications also provide credible threats to individuals or companies who seek to release ineffective or harmful drugs onto the market. In combination with information available through the Internet, this could be a very powerful way to monitor effectiveness.

5. Empirical Evidence of Effectiveness Determination without the FDA

Economic theory can provide useful insight into the problems of the FDA's involvement in effectiveness testing and potential market solutions, but there is already evidence that the FDA does not need to be a part of determining the effectiveness of drugs. Both the Drug Efficacy Study called for by the Kefauver-Harris Amendments and current off-label uses for pharmaceuticals show that ensuring effectiveness does not require government regulation.

Drug Efficacy Study Implementation (DESI)

The first example of the market working to determine effectiveness comes from the program implemented by the 1962 amendments. One of the additions was the retrospective review of drugs that were approved from 1938 to 1962 to determine their effectiveness. The program, the Drug Efficacy Study Implementation (DESI), was conducted by the National Research Council's Division of Medical Sciences.[lxi] To conduct the review, the National Research Council put together 30 expert panels that were to review over 3,000 drugs that had been approved only on safety and not on effectiveness.[lxii] By 1984 the review process had found that of 3,443 drugs reviewed, 2,225 were effective and 1,051 were ineffective (167 were still

under review).[lxiii] Those that were found to be ineffective were removed from the market along with any generic drugs of a similar chemical makeup.

These results mean that two-thirds of the drugs that were put on the market in the 24 years that the DESI experts reviewed were effective even though their makers had not been required by the FDA to prove them effective. The other one-third were ineffective, but still safe. It would be interesting to see how often the drugs deemed ineffective were still being used by the public, or if the market had determined they were ineffective and had already begun to eliminate them.

Off-Label Uses

One other consideration is that the "ineffective" drugs may have been ineffective for their original use, but may have also had "off-label" uses. When the FDA approves a new drug and tests for effectiveness, it is testing the drug for a specified use, and that use is the on-label use. When the drug is prescribed for a use that was not part of the original effectiveness test, this is an off-label use.[lxiv] It has become common practice for doctors to prescribe drugs for off-label uses as they see fit. This practice does not go against FDA regulations. The FDA's position on off-label use is, "If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."[lxv] Thus, the FDA gives doctors discretion to use approved drugs as they see fit for the best practice of medicine.

Off-label prescriptions are the result of doctors trying to meet patients' needs, either because the drug is known to be effective for an off-label use or because a patient has been

unresponsive to all known treatment and requires an innovative approach. Because the process to approve a drug for new uses is time-consuming and expensive, it is much more efficient for doctors to try off-label uses.[lxvi] There are numerous examples of off-label uses. Two of the most common are for amoxicillin and aspirin. In 1982 it was discovered that the cause of stomach ulcers is bacteria, not diet and excessive stress. So to treat ulcers, doctors began prescribing amoxicillin, and it is still prescribed for ulcers to this day, even though this is an off-label use.[lxvii] Aspirin is used to relieve headaches, but it can also ameliorate heart attacks when taken in low doses consistently. This is also an off-label use that has become common practice.[lxviii]

Off-label prescriptions can increase the speed with which medical innovation is delivered to patients by lowering the cost of medical innovation. A study conducted by the General Accounting Office found that off-label prescription for treatment of cancer patients is widespread.[lxix] Another study found that off-label uses appear in well-respected medical journals two and a half years faster than they are recognized by the FDA.[lxx] Understandably, there are concerns about the lack of testing that occurs before an off-label prescription is written, but there are also benefits. One such benefit is that by allowing the doctors to determine the uses for approved drugs, knowledge can be gained that might not have been thought of by one panel of experts.[lxxi] Web databases have even begun to emerge to collect the data from patients that are using drugs for off-label uses. A website called PatientsLikeMe collects patient-reported outcomes about the drugs that they are using and can provide a valuable resource for secondary uses.[lxxii] The data collected could even be used to create a systematic evaluation of the secondary use for a drug.

Based on the information compiled in this paper, it is clear that the FDA should review the proof-of-effectiveness requirement. Action can be taken by policymakers to remedy the lack of innovation in the drug market and turn the decisions over to the consumers.

6. Policy Recommendations

Policy recommendations to remedy the current barriers to innovation caused by the 1962 amendments are as follows:

1. Remove the proof-of-effectiveness requirement and regulate only the safety of new drugs. Removing this requirement would decrease the cost of clinical trials dramatically, and lead to a decrease in the price of drugs. People would have access to new and potentially life-saving drugs much faster. The removal of this one clause could save lives every year. With the removal of the effectiveness clause, market mechanisms would step in to ensure that the drugs were effective. Doctors and pharmacists would be a source of knowledge and consultation before the use of any drugs. Organizations that compile reviews and reports for consumers would emerge to meet the demand for knowledge. Torts would also be a way to ensure that if a drug were sold under false pretenses; the consumer could penalize the producer for their wrongdoing.
2. The FDA should play an informational role only. The FDA would simply provide information to consumers, doctors, and pharmacies regarding the uses and effectiveness of drugs. There would still be a large demand for knowledge regarding the use and effectiveness of each drug, and the FDA could fill that role without limiting consumer choices. The FDA would then be in competition with other organizations providing pharmaceutical information, which would increase the quality of the information

provided to consumers. If the FDA failed to provide adequate information, consumers would look to other organizations to gather the requisite knowledge.

3. The FDA could serve as an entity for certification. Instead of being a licensing entity, the FDA would serve as a certification body. This would provide a signal to consumers, while not allowing the FDA a monopoly on approval. The FDA could be in competition with other certification sources, which would require them to improve the quality and efficiency of approvals.

7. Conclusion

Overall, the evidence suggests that requiring proof-of-effectiveness testing is detrimental to human health and medical innovation. The FDA should remove the requirement for proof of effectiveness and allow market mechanisms to regulate the production and consumption of pharmaceuticals. How the market will react is unknown—it may continue to take an extended period of time to release new drugs, or the process may speed up. What is important is that the market offers the flexibility to adjust to the research process required for each drug in a new way, which the FDA is unable to do. Certainly, the resulting drugs would not be effective 100 percent of the time, but the FDA's process does not ensure 100 percent effective medicines either. It would be beneficial to put the choice into the hands of the consumers and the medical professionals that serve them.

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