

# Food and Drug Administration Oversight: Origins and Contribution to the National Covid Response

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## ABSTRACT

The Food and Drug Administration (FDA) has been a key actor in the USA's response to the Covid-19 pandemic. The extensive use of Emergency Use Authorizations (EUAs) during the pandemic as part of its broader strategy to protect the health of the country has raised this federal agency to the public psyche. The FDA's response has been guided by its position within the national governing framework as well as its own unique history. A review of this framework and the FDA's history can be illuminating in understanding this agency's response during a national crisis.

**Key Words:** Emergency Use Authorizations (EUAs), Administrative Law, Covid-19

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## 1. Introduction

The Covid-19 pandemic and the United States' response thrust the Food and Drug Administration (FDA) into the public psyche. Not unlike prior important moments in FDA history, a national tragedy prompted its action. While some may be familiar with the FDA and its actions in the national response to the pandemic, they may not be familiar with how the FDA fits into the federal government's framework. A more complete understanding of the FDA and its location within the US regulatory structure as well as processes it uses to allow products to enter commerce help support an appreciation of the Emergency Use Authorizations that have been used extensively during the pandemic.

## 2. Administrative Law Primer

The FDA is a government agency. While differences exist in defining an agency, a common understanding for the purposes of

this paper will be a government organization created for a specific purpose. Agencies fall under the broad area of law known as administrative law. Using this baseline, hundreds of government agencies exist on the federal level (*Agency Index*, n.d.). However, that number fails to include the thousands of agencies that exist on other levels of government, including those on a state and local level. Arguably, citizens interact with agencies more frequently than with any other part of the government. Not many individuals are going to interact with members of Congress, and most would like to stay out of court but whether it is the renewal of license plate tags through the Department of Motor Vehicles, or figuring out our taxes every April, citizens regularly interact with government agencies. For those practicing medicine in the United States, a state agency issues your medical license (*Texas Medical Board*, n.d.).

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Agencies are generally considered to be part of the executive branch (Strauss, 1984). Broadly speaking, the president can direct government agencies to their administration's goals by appointing leadership. Under the Budget and Account Act of 1921, the president submits an annual budget to Congress and through this mechanism can impact agency functions (Dearborn, 2019).

The judiciary branch has significant interactions with government agencies. More than just a forum for litigation, the courts impact agencies through their decisions. Stare decisis, or precedent, is an important concept underpinning legal decisions. Within the judiciary, the United States Supreme Court is the final word on legal issues and provides a uniform national standard. The court in 1984 provided in *Chevron, U.S.A. v. Natural Resources Defense Council, Inc.* what has come to be called the "most important doctrine in administrative law" (*Kavanaugh And The "Chevron Doctrine" Hoover Institution Kavanaugh And The "Chevron Doctrine,"* n.d.). In this doctrine, now known as the Chevron Doctrine, courts are instructed to provide great deference to agency regulations. So long as the agency's decision is based on "permissible construction of the statute," and Congress has not spoken directly on an issue, the agency's decision is to be generally respected. Thus, in an appreciable way, courts in the United States back up agency decisions.

The legislative branch provides the foundation and rationale for much of the power granted to agencies. This is due to the relationship between statutory code and administrative regulations. In the US, a legislative body, Congress, creates laws that are broadly referred to as statutes listed within the United States Code (USC), which is the official consolidation and codification of federal law. These laws can be directly

applied to matters within the US, but they also often direct agencies to establish regulations. Regulations are the rules that agencies create that often flesh out federal statutes. It is unrealistic for legislators to be experts on every piece of legislation and agencies contain the experts who can help implement the broad goals of legislation. An example of this is the Clean Water Act (CWA), originally established in 1972, which sets forth the structure of governing pollutants in US waters (*Summary of the Clean Water Act*, n.d.). A legislator is unlikely to know how many parts per million of mercury should be allowed to exist in drinking water. The Environmental Protection Agency, relying on the CWA, has established that water for public drinking systems should contain no more than 15 micrograms of mercury per liter (*National Primary Drinking Water Regulations*, n.d.).

The process an agency takes of fleshing out Congressional mandates, referred to as rulemaking, is so vital to the function of the federal government that Congress passed the Administrative Procedure Act in 1946 to direct this process (Garvey, 2017). Simplified, Congress passes a law that requires an agency to promulgate regulations. The agency develops a "proposed rule" which is given to the Office of Management and Budget (OMB) which is then published and passes through period of public notice and comment before an agency creates a "final rule." This final rule is then published in the Federal Register and goes into effect.

Combined, the three branches of the federal government are key to the function of administrative law within the US. Rather than discuss the arguments for or against agencies, this paper will next discuss one such agency, the FDA, and how its response to Covid fits within the broader administrative law context.

### 3. The Food and Drug Administration

The Food and Drug Administration (FDA), through its origin the Bureau of Chemistry, is the oldest consumer protection office in the US (Kennedy, 2006). Created through the Pure Food and Drugs Act of 1906, the FDA was formed in response to public outcry for more safety around food and medication. Three major events were in the national awareness that spurred the federal government to establish the FDA.

One of these national tragedies was the death of thirteen children in 1901 around St. Louis, Missouri (DeHovitz, 2014). Discovered in the 1880s, diphtheria bacterium was established as the cause of ‘the strangling angel of children,’ a major killer of children (Byard, 2013). Shortly after the etiology was discovered, antitoxin was developed in Germany for treatment. The method for obtaining the antitoxin was to inject a horse with large doses of diphtheria toxin. This toxin would not impact the horse, but the horse’s immune system would produce vast amounts of antitoxin that was then harvested in order to be given as treatment. In the US, one horse that produced over 7.5 gallons of antitoxin over his life, Jim, became infected with tetanus. After this discovery, Jim was euthanized but due to some labeling issues, tetanus was given to 13 children in addition to the diphtheria antitoxin, which led to the death of these children.

Another tragedy had to occur before laws were changed to combat contaminated medical products. Also in 1901, nine children died after receiving smallpox vaccination, which was contaminated with tetanus around Camden, New Jersey (DeHovitz, 2014). Combined, these events prompted the Biologics Control Act of 1902, which a few years later would ultimately be rolled into the FDA’s purview, to prevent similar issues from arising. This act was supported by the public and many manufacturers, who hoped

it would reestablish trust by the public in medical manufacturers.

In addition to the events in infectious disease, the public was also becoming outraged about the safety of their food. A major catalyst for this outcry was *The Jungle* by Upton Sinclair. Sinclair’s purpose was to improve working conditions for immigrants in the meat industry, but the public became fixated on health issues around their food. The public outcry became so intense that the US president, Theodore Roosevelt, someone who had described Sinclair as a “crackpot” sent an investigative team to look at the conditions in the meat packing industry (Meredith Francis, n.d.). This led to the Neill-Reynolds Report, which was so damning that it was not released to the public but instead given directly to Congress. This report combined with public outcry led to the Meat Inspection Act of 1906.

The push for better oversight of drugs and food led to the passage of the Pure Food and Drug Act of 1906. These issues were put under the control of a single agency because they both related to oversight of the consumer product marketplace.

Since its inception, the FDA has grown to be a major player in the US economy. The FDA today regulates approximately 20% of the US economy (*Fact Sheet: FDA at a Glance*, n.d.). The FDA regulates five categories of goods: food, drugs, devices, supplements, and cosmetics.

Acknowledging the existence of these other important categories, this paper will focus on drug regulation in the US, with some reference to medical devices, as the two can sometimes overlap.

#### 4. Drug Regulation in the United States

One way to look at regulation of drugs in commerce in the US is to place goods in one of three categories based on how they have been permitted to enter the stream of commerce. These three categories can be recognized as the traditional pathway for goods to receive “approval,” expedited processes that also end with a drug receiving “approval,” and a third category of drugs that have not been granted “approval” but are in use within the US.

Approval is a significant term that has meaning in use by the FDA. FDA approval is granted for drugs, and class three medical devices, and allows for them to be introduced into interstate commerce or marketing. Approval is granted for specific uses or indications, but approval does not necessarily mean something may not be used for other purposes. Off-label use of drugs, especially in pediatrics, may be highly efficacious when using an approved drug but for a non-approved purpose. Thus, approval is a regulatory definition, not a determination of scientific usefulness. As will be discussed later, approval is different than authorization.

The ‘traditional’ pathway has been used since the Pure Food and Drug Act but has been updated and changed over the course of its existence (Federal, Food, Drug, and Cosmetic Act, n.d.). Today, for a drug to be granted FDA approval, it must demonstrate that it is both safe and effective. In 1937, a preparation of elixir sulfanilamide using diethylene glycol as a solvent, a poison to humans, was being sold in the US and has been linked to the deaths of more than 100 people. In response, in 1938 The Federal Food, Drug, and Cosmetic Act of 1938 gave broad authority to the FDA to oversee the safety of products regulated by the FDA.

In 1962, the Federal Food, Drug, and Cosmetic Act was amended through the Kefauver-Harris amendments, also known as the drug efficacy amendments (Drug Amendments of 1962, 1962). This legislation introduced the second element, effectiveness, a requirement that must be met, for drug approval. Once again, passage of this legislation was preceded by a tragedy in the public awareness. The thalidomide tragedy, a medication taken by expectant mothers for morning sickness, led to the birth defects of thousands of children around the world but notably, the FDA had not approved the drug for use in the US and so birth defects in the US were largely avoided. However, samples of the drug had been distributed to physicians in the US, and 17 birth defects were reported due to the drug in the US. This undermined the previous policy of allowing physicians to determine efficacy and the amendments strengthened the FDA’s responsibility in drug approval to expand to include effectiveness in addition to safety.

The traditional pathway for approval is costly and lengthy, with an average of 15 years before a new chemical entity, the term used for a molecule, which may eventually become a new medication, is granted approval, and comes to market. This delay in potential treatments came sharply into the public’s view during the 1980s amid the AIDS epidemic. Organizations such as the AIDS Coalition to Unleash Power (ACT UP) organized in powerful demonstrations that forced government officials to consider ways for drugs to receive quicker approval (Douglas Crimp, 2011). Public pressure led to the creation of a nine-member presidential advisory committee to review the process. The committee published a report that concluded the FDA’s drug approval process likely cost the lives of thousands of Americans each year due to delays in delivery of the necessary therapies for either

cancer or AIDS leading to the creation of four different expedited review processes: Accelerated Approval, Priority Review, Fast Track, and Breakthrough Therapy (*Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, 2018).

All four of these pathways require that the drug treats or prevents a ‘serious’ disease and it fulfills an ‘unmet medical need.’ In general, a serious disease is one that is lethal, one that significantly impacts quality of life, or one which left untreated can become serious. In the event a drug qualifies for one of these designations, it can rely on a surrogate end point, fast review, and/or extra FDA guidance through the approval process. A surrogate end point is one which can be used instead of a clinical outcome or clinical benefit that would be demonstrated through a longer study. An example might be to monitor lipid levels in the blood instead of requiring data on cardiovascular disease outcomes. Gaining fast review cuts the maximum time the FDA is allowed to review documents submitted by the drug sponsor. Finally, extra FDA guidance allows for the FDA to review and approve portions of the sponsor’s application as they arrive, aka rolling review, and allows for additional meetings between the sponsor and the FDA to make sure the drug application process is efficient.

Accelerated approval is the easiest of these fast tracks for a drug to qualify into. It requires the minimum standard all the tracks require, the drug treats or prevents a ‘serious’ disease and it fulfills an ‘unmet medical need.’ The benefit of getting accelerated approval is significant because it allows the drug sponsor to use surrogate end points.

Priority review like all other expedited tracks has the basic requirements but also requires that the drug offer significant improvements

or effectiveness when compared to standard treatments. If a drug qualifies, it can receive fast review; however, it does not receive the option for a surrogate end point.

Fast track has the benefits of both accelerated approval and priority review, in that the sponsor can use surrogate end points and it can receive faster review by the FDA. To qualify, the sponsor must request designation by the FDA. Once again, the drug must demonstrate superior effectiveness or have less serious side effects, improve the diagnosis of a serious condition, and address an emerging or anticipated public health need.

Breakthrough therapy is the accelerated approval track with the most benefits, but also the highest requirements. The benefits include the ability to use a surrogate end point, fast review, and extra FDA guidance. To qualify, in addition to the baseline requirements, a drug must demonstrate substantial improvement over existing therapies. This designation may be requested by a drug sponsor or the FDA may propose it after seeing early data from drug trials.

The significance of these designations lies in the expedited approval of drugs by the FDA. The streamlined processes involved in these designations lead to shorter timelines for approval, setting them apart from the traditional pathway. However, unlike the third category yet to be discussed, drugs with these designations still undergo the gold standard FDA approval process. Other pathways exist for drugs to enter commerce in the United States without obtaining approval from the FDA. While some of these processes have multiple names, two noteworthy pathways are expanded access and emergency use authorizations.

Expanded access, sometimes also called “Compassionate Use”, allows for use of a non-FDA approved drug (*Expanded Access*, 2022). To qualify, the patient must have a life-threatening condition or serious disease or condition for which they are is no comparable or satisfactory alternative therapy options and the potential benefits outweigh the potential risks. The drug itself must have a sponsor which is pursuing FDA approval, i.e. is at some stage of clinical trials. The patient qualifies for use of an investigational medical product, including drugs, biologics, or medical devices. The final requirement is that the drug sponsor be willing to provide the drug to the patient. This can be complicated in cases where the available inventory of the drug is limited or costly, or where the sponsor may be concerned that the patient’s response to the drug could negatively impact the public’s perception of the drug.

## 5. Emergency Use Authorizations

Another major non-approval pathway is through an Emergency Use Authorization (EUA) (*Emergency Use Authorization*, 2023). Of the ways for drugs to enter commerce, it is the newest. While it uses statutory authority from as early as 1938, it only came into existence in the 21<sup>st</sup> century. Once again spurred by the tragedy, this time the events of September 11<sup>th</sup> and concerns generated after the episodes of anthrax being mailed, Congress passed the Project Bioshield Act of 2004. Part of this act requested the FDA to review ways to expedite new drugs and medical devices use in the United States. During a tragedy the typical pathways were simply too long. Taking this direction into account, the FDA worked on creating the process that would become the EUA pathway.

The EUA pathway, in addition to being the newest drug use pathway in the US is also the

most rapid. Rather than waiting years, the process can occur within weeks. Developed during the mid-2000s, the process has been thrust into the national conversation of the past few years due to the disruption caused by the pandemic.

The requirements for issuance of a EUA are minimal when compared to that required for approval. The first requirement for issuance of an EUA is a determination by the Secretary of Homeland Security, the Secretary of Defense, or the Secretary of Health and Human Services that a public health emergency exists that has a significant potential to affect national security or the health and security of United States citizens. This declaration allows the FDA to then review submissions to deal with this issue through the EUA process.

The EUA review process revolves around three elements. The term element used in a legal context indicates that the condition must be met to comply with the law. The first element in the EUA review process is that the product may be effective in diagnosing, treating, or preventing a condition or disease that is serious or life-threatening. Second, that the known and potential benefits of the product must outweigh the known and potential risks of the product. Third, there is no adequate, approved, and available alternative to fulfill this need for the condition (Authorization for Medical Products for Use in Emergencies, 2017). Once these three elements are met, the FDA issues a letter of authorization to the sponsor, the person or company that filed the EUA application. Included in this letter are additional instructions that the FDA may require of the sponsor for use of the EUA. Finally, the EUA will allow for the product in commerce until either the FDA revokes it or the declaration by the Secretary that permitted the use of this pathway is revoked.

The EUA pathway was first put into use for concerns of inhalation anthrax. The declaration of a public health emergency occurred on January 27, 2005. The declaration led to the granting of a EUA for vaccination of individuals at high risk, often members of the armed forces, to inhalation anthrax. The story of EUAs related to anthrax is more complicated than will be addressed in this paper; however, it should be noted that some have terminated, and another process exists, Emergency Use Instructions (EUI), that impacts their use. EUAs in relation to anthrax are raised here because this was the first time a public health emergency declaration led to the issuance of EUAs with their termination at the conclusion of the emergency.

The next use of EUAs occurred during the 2009 H1N1 Swine Flu outbreak and the declaration of a public health emergency on April 26, 2009. This time there was much more use of this pathway, as Peramivir, Tamiflu, Relenza, and eight tests for diagnostics passed through EUA before termination on June 21, 2010, with subsequent discontinuation of these products on June 23, 2010.

Other declarations of emergency were made over the next decade that would occasionally rise to public awareness. Some of these included EUAs for Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Zika virus, and Ebola virus. For these emergencies, EUAs were issued in relatively small numbers, with the MERS virus only receiving two.

In early 2020, the public became acutely aware of EUAs as they became key to the national response to Covid. On February 4, 2020, the Secretary of Health and Human Services issued a declaration that the novel

coronavirus represented a significant potential risk to national security and the health and security of US citizens. In this initial declaration, the EUA pathway was opened for in vitro diagnostics for detection and/or diagnosis of the novel coronavirus. That same day, the FDA issued the first EUA to enable use of the Centers for Disease Control and Prevention's (CDC) 2019-nCoV Real-Time RT-PCR Diagnostic Panel at any CDC-qualified lab across the country. Following this initial issuance, the FDA rapidly became inundated by EUA requests. The declaration to use the EUA pathway would be expanded to drugs and biologics on March 27, 2020.

In response to the early stages of the pandemic, two noteworthy observations emerged. Firstly, revisions were required on the FDA's website as the original Emergency Use Authorization (EUA) webpage failed to effectively communicate the rapidly increasing number of EUAs being issued. Subsequent updates were made to enhance the clarity of the FDA's actions. Secondly, the national media frequently interchanged the terms "authorized" and "approved" when reporting on the agency, highlighting a need for better understanding and accuracy in media coverage.

Hundreds of EUAs were issued for the response to Covid. The volume of EUAs far exceeded that seen in previous emergencies that also used the EUA pathway. The declaration that these EUAs relied on 90 day renewals of the public health declaration, which came to an end on May 11, 2023. While the declaration has ended, the Department of Health and Human Services (HHS) is providing a transition period to allow some authorizations to continue past the termination date and facilitate a smoother return to normal.

## 6. Conclusion

The national response to the Covid pandemic once again thrust the FDA into the public eye. These authors pose the question of whether the heavy use of the EUA pathway will ultimately lead to changes of the pathway itself or modify future responses to public health emergencies. With remarkable speed, the US was able to expand testing for the pathogen as well as provide the opportunity for vaccination and treatment for the disease. However, reliance on a process with fewer requirements may have contributed to the undermining of trust in public health institutions. As it has shown in previous health tragedies, the FDA will need to evolve based on feedback it receives from the public, government, and scientific community.

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