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A Measure of Value: FDA in the Age of COVID

An Agency in the Right Place at the Right Time

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Abstract

The US Food and Drug Administration (FDA) is the institutional regulatory gateway through which healthcare business sectors gain access to commercial markets in pharmaceuticals, biologicals, vaccines, medical devices, diagnostic test kits and personal protective equipment. The unfolding of events for the COVID-19 pandemic serve as a case study for understanding, in real time, how FDA has contributed value to the healthcare sector. Federal regulatory agencies, such as FDA, require strong processes to provide fair and consistent outcomes to retain the trust of the stakeholder community. These processes include statutes and regulations, internal manuals of standard operating procedures and policies, guidance documents, external advisory committees and the Office of Inspector General. These processes cover the following activities: product development conditions, regulatory pathways, types of approvals, manufacturing quality, and post marketing safety. Together, the institutional experiences that led to and shaped these processes prepared FDA for the challenges associated with COVID-19. The sum of twelve decades of experience comes down to the following goals that provide value to the degree with which each is successful: 1) The manufacturing process must meet standards of quality and be secured. 2) Medical products must be shown, through scientific evidence and based on evidentiary standards, to be safe and effective for human use. 3) Identified risks must be mitigated, by labeling at a minimum, with additional strategies as necessary. 4) Provisions must exist to address extraordinary circumstances of unmet medical needs and of threats to public health and national security.

Keywords: FDA, economic value, regulatory science, COVID-19

1. Introduction

When we look at the US Food and Drug Administration (FDA) today, we see an agency that stands at the portal of business sectors that develop a staggering array of healthcare products on one side and the extraordinary cornucopia of marketed products on the other side, with FDA as the institutional regulatory gateway through which business sectors gain market access with their products. Thus, a key component of FDA's mission includes protecting the common interests of its stakeholders, keeping the community safe and, where possible, mitigating the risks of harm and exploitation.

This paper describes first, the hierarchical layers and components of the regulatory process and second, approaches to understanding value. These two critical elements serve as vehicles for analyzing representative scenarios of COVID-19 as an overarching case study for demonstrating how the regulatory process creates value.

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2. The Layers and Components of the Regulatory Process

Federal regulatory agencies, such as FDA, require strong processes to provide fair and consistent outcomes to remain credible and retain the trust of the stakeholder community. There are both a) hierarchically layered, inter-connected regulatory processes of decreasing formality and increasing flexibility, and lessening external engagement that translate into a narrowing breadth of impact but that are nonetheless of procedural importance to the efficient conduct of daily activities and decision-making, and b) distinct, unrelated structural processes that support and reinforce the hierarchical layers and provide checks on the content and process dimensions of FDA activities: 1) At the top of the hierarchy are statutes and regulations, the most formal and least flexible processes with the greatest impact that provide the framework for carrying out the agency's mandates. Following a general description, four major categories are discussed in detail. 2) At the next lower rung is the internal manual of standard operating policies and procedures, which is a far less formal and more flexible set of processes with much less breadth of impact that directs much of the daily activities and decision-making. 3) At the next lower rung is the Guidance

document, including Points to Consider, an even less formal and more flexible type of document with far less impact on processes per se but with a significantly greater impact on content, that makes available the agency's best and most current thinking on a given topic of interest. 4) Next is the external Advisory Committee, a formal, separate process with highly consequential impact on the content of approval decisions but which is only periodically convened, that provides solicited advice about major impending regulatory decisions and related issues facing the agency. 5) And finally, there is the Office of Inspector General, a federal, independent assessment function that reviews an agency's internal activities for consistency, fairness, and timeliness. Each is discussed in turn as it applies to FDA.

2.1. Statues and Regulations

FDA's long-term success has depended to a significant degree on its ability to well navigate the constraints of processes set by administrative law. As a nearly invisible infrastructure, administrative law is notable for the following features:

As a branch of public law, regulatory law concerns structural and functional activities of its respective agencies, that is, the organizations, powers, functions, and duties of regulatory authorities that protect public interests with respect to the interests associated with private rights [61]. In the case of FDA, this is expressed in its Mission Statement as protecting the public health, advancing the public health, and contributing to the nation's counterterrorism capability [16]:

- The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.
- FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.
- FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.
- FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Rulemaking is one of the key processes of regulatory agencies, which requires strict adherence to the following process: proposal of a rule in the Federal Register with adequate opportunity to comment by interested parties ("notice and comment"), revision as necessary in response to comments, and publication of a binding Final Rule,[61] again, in the Federal Register. Failure of strict adherence to the process risks a challenge in the courts on procedural grounds alone. This is the primary way that a regulatory agency translates a broadly sweeping congressional statute into narrowly focused and detailed regulations. Such regulations have the full force and effect of the enacting statutes that were passed by the legislature.

From an historical perspective, the statutes and regulations that govern FDA's activities may be thought of as falling into four large general domains: the domain that established the foundations, the domain that established means to expedite development and approval of new drugs and biologics, the domain that expanded access to investigational drugs for treatment use, and the domain that extended capabilities to emergency use. The origin, evolution and features of each domain are discussed in turn.

Established Foundations: The Biologics Control Act of 1902 [43] was the statutory remedy to the tragic deaths of children who had been treated with tetanus-contaminated products, diphtheria antiserum in one circumstance and smallpox vaccine in another. The Act established licensing processes for the manufacturing site and for individual products, and it also established manufacturing standards for safety, purity, and potency for biological products. While the particulars for these standards have evolved over time, the underlying concepts have remained in place up to the present.

The Pure Food and Drugs Act of 1906 [43] was the statutory remedy to an exposé on patent medicines, The Great American Fraud, published in Collier's Weekly. The Act established definitions and penalties for "misbranding" for the control of fabricated and illicit labeling and for "adulteration" of manufactured products for control of "secret" formulas that would often include one or more of the following: ethyl alcohol, morphine, opium, laudanum or other narcotic agents; and strychnine, mercury, or other heavy metal poisons.

The Drug Amendments of 1962 [43], also known as the Kefauver-Harris Amendments, was the statutory remedy to the thalidomide tragedy, a sedative drug intended to be taken during pregnancy, that resulted in the "flipper limb" birth defect known as phocomelia that was largely averted in the United States [93], though not in Europe. The Amendments added multiple new requirements for manufacturers, including full and free Informed Consent to participate in clinical studies, demonstration of efficacy in addition to safety for NDAs, creation of a new evidentiary standard, "substantial evidence," as a basis of approval, and required reporting of adverse events by manufacturers to FDA after marketing approval.

The Medical Device Amendments Act of 1976 [43] was the statutory remedy to the Cooper Commission that during the conduct of its inquiries collected reports on more than 700 deaths and 10,000 injuries. [76] The Act established a three-tier, risk-based approach to regulation of medical devices and diagnostic test kits.

Together, these five statutes have become foundational laws for establishing standards for manufacturing quality and for documenting safety and efficacy prior to the issuance of marketing approval for drugs and biologics and for establishing stan-

dards for a risk-based approach for medical devices. Experienced regulatory physician and regulatory scientist professionals have a deep understanding of the context in which a manufacturer's new drug/biologic/vaccine/medical device is intended to be used. They are also experienced in the applicable basic sciences and can work with the manufacturer in planning an appropriate development pathway to market. In that process, they assess the benefits and risks drawn from the data obtained from preclinical animal studies, Phase 1 dose-escalation, pharmacokinetic and pharmacodynamic studies, Phase 2 dose comparison studies, and Phase 3 large-scale, randomized, controlled trials. Finally, they can propose strategies to manage identified risks through appropriate labeling, assessment of the need for focused follow-up studies, and the potential for restrictions in use through Risk Evaluation and Mitigation Strategies [27].

Other important foundational statutes: While not essential to the background for the COVID-19 case study, other statutes play foundational roles in addressing important closely related areas of drug development.

The Orphan Drug Act of 1983 [43, 57, 54] was the statutory remedy to the growing awareness and concern about the more than 20 million patients suffering from the approximately 5 thousand rare diseases about which there was little commercial interest in developing drugs. ODA provided incentives to the drug development community, including tax credits, user fee waivers, and 7 years of market exclusivity following approval.

Best Pharmaceuticals for Children Act of 2002 (BPCA) and the Pediatric Research Equity Act of 2003 (PREA)[19] were the statutory remedies to the decades of frustration in the pediatric community to the virtual lack of response by the pharmaceutical industry to broad community encouragement to develop pharmaceutical drugs explicitly for children. BPCA offers financial incentives to voluntarily conduct pediatric studies and PREA requires companies to assess safety and efficacy in pediatric patients. They were made permanent in 2012.

User Fee Acts [39]: Beginning with the Prescription Drug User Fee Act of 1992, a sea change was taking place in how problems and, importantly, potential problems were to be addressed, that is, instead of waiting until catastrophic events occurred before Congress would react with significant effect, issues were being addressed proactively on a quinquennial basis. The program has continued to be renewed every 5 years and has gradually expanded to include generic drugs, biosimilars, over-the-counter drugs, medical devices, and veterinary drugs.

The Drug Quality and Security Act of 2013, in particular Title II, the Drug Supply Chain Security Act [29], which built on the foundational Biologics Control Act, was the statutory remedy to the tragic deaths of more than 80 patients because of financially motivated adulteration of heparin during the remote, upstream sourcing of raw materials in the manufacturing process. This comprehensive legislation is also intended to address the substantial black market in substandard/spurious/falsely- labelled/falsified/counterfeit (SSFFC) medicinal products [67]. It-'s deeply unfortunate that such a completely unforeseen tragedy occurred. But the still unfinished, nearly decade-long period of scope and depth that this legislation has gradually reflected shows how difficult it would have been to proactively change manufacturing practices through the quinquennial mechanism without an identified "problem" to address.

Expedited Development and Approval: From 1992 to 2016, Congress legislated five mechanisms by which manufacturers could expedite the development of appropriately identified new drugs and biologics [4].

Priority Review, enacted in 1992 [4, 52], reduced the expected time for FDA to complete review of an application from 10 months to 6 months for applications that showed significant improvement in safety or effectiveness.

Accelerated Approval, enacted in 1992 [4, 17], shortened development time for manufacturers by shifting the study endpoints from clinical markers to earlier documentable laboratory surrogate markers for serious or life-threatening illnesses lacking satisfactory treatment, thereby potentially reducing development time by years, leading to substantially earlier access to patients.

Fast Track, enacted in 1997 as part of the FDA Modernization Act [4, 33], established processes for facilitated development and expedited review of new drugs to treat serious diseases that fill an unmet medical need, thus creating new populations of treatable patients.

Breakthrough Therapy, enacted in 2012 as part of the FDA Safety and Innovation Act [4, 21], enabled FDA to accept preliminary clinical evidence indicating that a new drug may demonstrate substantial improvement over available therapies on a clinically meaningful endpoint. It also enabled FDA to utilize features of the Fast Track designation and allowed FDA to provide intensive guidance to sponsors in the development process.

Regenerative Medicine Advanced Therapy, enacted in 2016 as part of the 21st Century Cures Act [15], was an explicit means of identifying cell therapies, therapeutic tissue engineered products, and human cell and tissue products that are "intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition" for which "preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition." Products with this designation would have access to the benefits of Fast Track and Breakthrough Therapy designations.

Together, these five mechanisms provide FDA with tools to respond to nuanced features of new drug and biological products in development to facilitate the most expeditious avenues to market and awaiting patients.

Expanded Access to Investigational Drugs for Treatment Use: Since the 1960's, FDA had made informal processes available to practicing clinicians to request investigational drugs for use in treatment of their desperately ill patients who had no alternatives available to them [11]. Some of the terms used for these circumstances include "compassionate use INDs," "single-patient protocol exceptions," and "large open protocols."

In 1987 [45, 46, 100], in response to AIDS activists who demanded access to experimental drugs during the early years of the worsening AIDS epidemic when there were no available drugs of any sort for the primary HIV infection and no approved drugs for the frequently rapidly fatal secondary op-

portunistic infections, FDA codified these practices under the IND regulations (21 CFR §§312.34, 312.35 and 312.36) by issuing a Final Rule that would make "promising investigational new drugs available to patients with serious and immediately life-threatening diseases for which no comparable or satisfactory alternative drug or other therapies exist... as early in the drug development process as possible."

This regulation was substantially updated in 2009, and has been recently discussed, [31, 41, 70, 71, 72] to recognize 3 general categories of expanded access: 1) for individual patients, including in emergencies; 2) for intermediate-size patient populations; and 3) for expected large populations that were previously identified for Treatment IND or treatment protocol.

In 2018, Right to Try [55, 86] was enacted to provide another "way for patients who have been diagnosed with life-threatening diseases or conditions who have tried all approved treatment options and who are unable to participate in a clinical trial to access certain unapproved treatments."

Extended Capabilities to Emergency Use: 9/11 brought to the country's attention the importance and need of having a completely new dimension of product development and regulatory pathways that involve medical countermeasures to respond to emergencies and threats to national security. Nine statutes have been enacted since 2001 to address a range of issues. Pertinent to this discussion is BioShield, enacted in 2004, which established the Emergency Use Authorization (EUA) [30] by which the FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN (chemical, biological, radiological, and nuclear) threat agents when certain criteria are met, including the absence of adequate, approved, and available alternatives.

2.2. Policies and Procedures

FDA maintains a public record of its internal policies and procedures: for example, the Center for Biologics Evaluation and Research (CBER) has its Standard Operating Policies and Procedures (SOPP) [20] and Center for Drug Evaluation and Research (CDER) has its Manual of Policies and Procedures (MAPP) [22].

2.3. Guidance Documents

Guidance documents [56], including Points to Consider [47], do not carry specific regulatory weight, in that it is not required that Guidance documents be followed by the industries to which they are addressed. But the guidance does reflect the agency's best, current thinking about a topic, particularly of science or technology, that may be in flux or evolving rapidly, such as in response to the COVID-19 pandemic. A company does have the opportunity to offer alternatives to an applicable guidance when a good scientific or technological case can be made for a different approach or use of other criteria.

Examples of Guidance Documents include the following: COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention; [26] Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests. [51]

Examples of Points to Consider include the following: Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use; [50] Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals.[49]

2.4. Advisory Committees

Advisory Committees are highly regulated, with their own statutes, regulations, and guidance documents, in order to make known the "steps that FDA has taken to enhance decision making, increase transparency, and strengthen public confidence in [the] advisory committee program [18]." FDA Advisory Committees have their roots in the Federal Advisory Committee Act of 1972, which is employed by all agencies in the federal government. It emphasizes 1) transparency through open meetings, 2) conformance with established procedures through chartering, 3) stakeholder involvement through public engagement, and 4) documentation through reporting.

FDA has made use of advisory committees for scientific review of product applications, policy review for use of products, and miscellaneous topics such as communication. All reviewing divisions in CBER, CDER, and CDRH have multiple dedicated advisory committees, including, for example, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) [14].

2.5. Inspector General

The Office of Inspector General (OIG) for the Department of Health and Human Services provides the following description of its functions [83, 62]:

OIG was established by law as an independent and objective oversight unit of the Department to carry out the mission of preventing fraud and abuse and promoting economy, efficiency, and effectiveness of HHS programs and operations. In furtherance of this mission, the organization:

- Conducts and supervises audits, investigations, evaluations, and inspections relating to HHS programs and operations
- Identifies systemic weaknesses giving rise to opportunities for fraud and abuse in HHS programs and operations and makes recommendations to prevent their recurrence
- Leads and coordinates activities to prevent and detect fraud and abuse in HHS programs and operations
- Detects wrongdoers and abusers of HHS programs and beneficiaries so appropriate remedies may be brought to bear, including imposing administrative sanctions against providers of health care under Medicare and Medicaid who commit certain prohibited acts
- Keeps the Secretary of Health and Human Services and Congress fully and currently informed about problems and deficiencies in the administration of HHS programs and operations and about the need for and progress of corrective action.

3. Approaches To Value

Oxford's English Dictionary defines value as "the regard that something is held to deserve; the importance, worth, or usefulness of something." [84] This definition can be reasonably extended to the impact of its "...importance, worth, or usefulness..." Thus, one measure of value for a regulatory agency is the economic output (i.e., the impact) of the business sector(s) over which it has responsibility. For FDA, the following Fact Sheet highlights key contributions to public health [32]:

- FDA is responsible for the oversight of more than $2.8 trillion in consumption of food, medical products, and tobacco.
- FDA-regulated products account for about 20 cents of every dollar spent by U.S. consumers.
- FDA regulates about 78 percent of the U.S. food supply. This includes everything we eat except for meat, poultry, and some egg products.
- There are over 20,000 prescription drug products approved for marketing.
- FDA oversees over 6,500 different medical device product categories.
- There are about 1,600 FDA-approved animal drug products.
- There are about 300 FDA-licensed biologics products.
- FDA oversees over 90,000 tobacco products, not including e-liquids.

The estimated number of regulated products is continually assessed for accuracy and reliability.

With these descriptive statistics, the measures of value are simple and easily understood, and they point to the breadth of responsibility and the impact that FDA has in the consumer marketplace. However, these statistics are only snapshots-in-time of the *outcomes*, and they do not show the *process* by which there is value creation and value destruction. To gain an understanding of how the process affects value, the COVID-19 pandemic may serve as a useful, current, overarching case study with the following features: The pandemic in its present guise is an event that last occurred on this scale a century ago, and is deeply affecting virtually every aspect of society, including the economy, healthcare, politics, and culture. As a distinct temporal event unencumbered by the impact of other pandemics that occurred remotely to COVID-19, it's possible to analyze how the many scenarios that involve healthcare products, including personal protective equipment, diagnostic test kits, medical devices, drugs, biologics, and vaccines, can shed light on how value is created.

The following are proposed chronological events about the COVID-19 pandemic that may serve as useful reference points for gaining insight through a regulatory lens into the ways that value has been created:

- On January 9, 2020, W.H.O. issues a statement regarding cluster of pneumonia cases in Wuhan, China [99].
- On January 11/12, 2020, Chinese scientists shares the full sequence of 2019-nCoV with the global scientific communities [88].
- By June, 2020, ten companies have candidate vaccines in clinical development [82].
- On December 11 & 18, 2020, FDA issues Emergency Use Authorizations to two companies for vaccines based on a previously untested mRNA platform that showed 95% efficacy [38, 44].
- By December 14, 2020, first doses of vaccines are administered to the public. The rollout has led to rapid, early vaccination with at least one dose of 53% of the population, with 45% fully vaccinated, as of June 19, 2021 [68].
- Beginning in early June, 2021, there is a steady, if uneven, opening up of social venues and a substantial return to commerce [9].
- Beginning in late June, 2021, the Delta variant started to gain dominance in the U.S. New data emerged that it is more contagious and causes more severe disease, leading to a 4th wave of infection across the United States borne primarily by those who are unvaccinated [7].

This stands as a most remarkable, even unprecedented, historical achievement in regulatory science. How was this possible? In the face of a rapidly developing pandemic with so many scientific unknowns and so much surrounding political uncertainty, how was it possible for a regulatory agency to manage the science, technology, manufacturing, labeling, advertising, promotion, logistics, and politics to bring all of the many working parts together to facilitate the commercial marketing of desperately needed vaccines? The underlying set of statutes and regulations that forms the basis for structuring the overall development processes for medicinal products provides the key to understanding the historical backdrop that prepared FDA to anticipate and to respond to circumstances of catastrophic or lethal potential.

4. COVID-19 as a Case Study

With these brief descriptions of the hierarchical layers and components of the regulatory process in place, critical representative scenarios that occurred during the first year and a half of the pandemic can serve as touch points to highlight the structures in place that were able to support and facilitate responses to the respective issues.

4.1. PPE, Diagnostic Test Kits, and Ventilators

Almost immediately after the first cases of COVID-19 were being identified in the United States, including New York City which became the epicenter of the initial wave of infections, there was the worrisome awareness that there would likely be a dramatic shortage of "protective clothing, gloves, masks, helmets, shields, goggles, respirators and other equipment designed to protect the wearer from injury or spread of infection [48]." FDA responded by issuing EUAs as quickly as applications were being received. Similarly, diagnostic test kit requests were being submitted to FDA and were being given EUAs just as quickly. (See next paragraph for further comments.) Circumstances turned particularly dire when, within weeks of the lockdown, it became evident that hospitals were facing an imminent, critical shortage of ventilators. FDA took several, innovative regulatory steps [60]: 1) Publication of an Enforcement Policy for ventilators and accessories. 2) Issuance of "umbrella" EUAs for the use of certain ventilators, anesthesia gas machines modified for use as ventilators and positive pressure breathing devices also modified for use as ventilators. and 3) Working directly with ventilator manufacturers to add models to "umbrella" EUAs and issuance of 510(k)s for new and modified ventilators, routinely within days of requests by manufacturers.

Another of FDA's decisions concerning diagnostic test kits became problematic. [90] In the first week after COVID-19 was declared a pandemic, FDA published a guidance that enabled developers of serological test kits to market their tests without an EUA, contingent upon validation, FDA notification, and disclaimer of limitations. Within weeks, government officials were promoting the test's potential to support reopening of the economy. Misuse of the tests followed, and by early May, FDA changed its policy to require FDA's review of all test kits.

Created value: It was the 9/11 crisis that led directly to enactment of the BioShield legislation in 2004 and establishment of the Emergency Use Authorization process. Its most frequent use has been for medical devices, and its most urgent use was in the early days of the pandemic when unprecedented demand rapidly overwhelmed available supply, and every day that was saved until supplies were replenished resulted in saved lives.

The serological test kit experience that reflected good intensions overtaken by political forces which were quickly recognized and corrected provided valuable lessons learned, first among them, "the importance of authorizing medical products independently..." [90] The experience was of limited immediate consequence, but it clearly showed the potential for unforeseen consequences when even small degrees of increased flexibility were exercised.

4.2. Vaccine INDs

An NIH-funded Phase 1 study was conducted at Kaiser Permanente Washington Health Research Institute in Seattle, Washington, and Emory University School of Medicine in Atlanta, Georgia. It was an open-label, dose-escalation Phase 1 study that enrolled 45 healthy adults between 18 and 55 years of age over approximately 6 weeks, beginning on March 16, 2020. Preliminary findings were published July 14 [69]. The study was done under an IND, there was an Institutional Review Board, and there were procedures for obtaining Informed Consent, establishing oversight by a safety monitoring committee, developing a statistical analysis plan, and creating a committee to write up the results.

Moderna submitted its own application for an IND on April 27, 2020 [81, 8], for a Phase 2 randomized, blinded, placebo-controlled study to evaluate safety, reactogenicity and immunogenicity of two different dose amounts, each dose regimen given as a 2-dose vaccination schedule of its mRNA vaccine, given 28 days apart, in 600 healthy participants in two cohorts, aged 18-55 years (300), and older than 55 years of age (300). "The protocol was approved by regulatory and institutional committees." There were procedures for obtaining Informed Consent, establishing oversight by a safety monitoring committee, instructing participants in use of electronic diaries, developing a statistical analysis plan, and creating a writing committee. The same degree of attention was paid to the Phase 3 trial [2]

A parallel program was carried out by Pfizer and BioNTech, beginning with approval of a Phase 1/2 clinical trial in Germany by the Paul-Ehrlich-Institut, [5] and continuing on to the phase 3 trial. [85]

Created value: It's essential to appreciate that the statement in [8], "...The protocol was approved by regulatory and institutional committees..." refers to FDA and covers all of the activities that are needed to conduct the study and to provide the necessary governance. This is all done under the company's IND, which has its roots in the Food Drug and Cosmetic Act of 1938, as amended.

4.3. Expedited Development and Approval

One of the little appreciated aspects of the expedited development and approval designations is the opportunity for a sponsor to work with FDA to arrange for documents completed by the company to be provided to FDA in a "rolling submission." For COVID-19-related applications, a given sponsor and FDA professional staff communicate frequently on an informal, documented basis by telephone, email, and videoconferencing about progress of studies, availability of new data, and outstanding issues. They develop timetables for submission of individual components of regulatory documents rather than waiting until there are complete sets of documents to submit, thus contributing to the overall efficient use of resources and expedited timing of the review process.

Created value: The use of expedited mechanisms for development and regulatory review began in the early HIV/AIDS era and expanded to address issues in orphan drugs, cancer and infectious diseases and were well developed in terms of available SOPPs/MAPPs and Guidance documents / Points to Consider by the time of the COVID-19 pandemic. Thus, FDA was able to seamlessly transition to working with manufacturers to develop expedited pathways for vaccine products and drug products.

4.4. Expanded Access

Of the panoply of statutes and regulations available to FDA, only the Expanded Access regulations have found limited use

in this pandemic and it would be difficult to speculate about the circumstances in which it could be applicable.

4.5. Advisory Committees

Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session on October 22, 2020, to discuss, in general, without specific applications to consider, "the development, authorization and/or licensure of vaccines to prevent COVID-19." [13, 14] VRBPAC convened a second time in open session on December 10, 2020, to discuss data in the Pfizer-BioNTech EUA to support use in individuals 16 years of age and older for the prevention of COVID-19. [14] VRBPAC convened a third time one week later, on December 17, 2020, to discuss data in the Moderna EUA to support use in individuals 18 years of age and older for the prevention of COVID-19. These well-organized meetings included background materials from the sponsors and FDA that were also made available to the public [14].

Created value: Across the federal government, outside subject matter experts have been able to contribute their knowledge and perspectives at advisory committees (AC) since the Federal Advisory Committee Act became law in 1972. [18] ACs have evolved over the decades through carefully structured statutes, regulations, and guidance documents to standardize the process, minimize the risk for conflicts of interest, and enhance the transparency of their activities.

VRBPAC added its positive scientific assessment to FDA's favorable review of each company's EUA application, which led to authorization on the following day for each manufacturer's vaccine, providing strong evidence of internal FDA alignment, coordination, and collaboration.

Advisory committees have also given temperature readings to FDA on the scientific, medical, and patient stakeholder communities. For example, the most surprising response in recent years occurred in early 2021 when three members of the Peripheral and Central Nervous System Drugs Advisory Committee resigned after FDA approved aducanumab, a drug for Alzheimer's disease, after the AC strongly advised against its approval because of lack of evidence supporting efficacy. [78] The degree of value creation is less clear in this situation because of countering influences. There is the prospect of financial benefits that accrue to the drug's manufacturer, that is potentially discounted by the weak evidence of clinical benefit and the risk of potential harm of adverse drug reactions to the substantial number of affected patients who are likely to be prescribed the new drug [36]; and there is the patient stakeholder community that strongly favored having this option available that is countered by an academic stakeholder community that is deeply skeptical about the basis of the regulatory decision, concerned about the integrity of the regulatory process, and wary about participation in the future.[1] FDA leadership has requested a review by Department of Health and Human Services' Office of Inspector General [3]. It is notable that after one quarter of marketing, there has been exceedingly slow uptake of aducanumab, and the manufacturer is expecting continued poor performance [87].

4.6. Emergency Use Authorization

Once the Secretary, Health and Human Services, declares that circumstances exist for a public health emergency, the Commissioner of Food and Drugs has the authority to evaluate requests for use of the Emergency Use Authorization against four criteria that are necessary to support issuance of an EUA, namely that: (1) there is a serious or life-threatening illness/condition caused by the identified agent(s); (2) there is reasonable belief that the product may be effective in preventing, diagnosing, or treating a serious or life-threatening disease or condition caused by the agent(s); (3) the known or potential benefits outweigh the known or potential risks; and (4) there is no adequate, approved, and available alternative to the product [80]. The Commissioner issued EUAs to Pfizer-BioNTech on December 11, 2020 [38], and to Moderna on December 18, 2020 [44], in each case, the Commissioner acted one day after VRBPAC gave a positive assessment of the company materials in its EUA application. Tran and Witek [96] provide a fuller discussion on the use of EUAs during the COVID-19 pandemic.

Altogether, these activities transpired as a seamless process of an almost invisible infrastructure that sets the requirements for what is needed to develop a medical product for human use and ultimately to provide a pathway to patient access via the EUA and eventually to approval. The last piece of the puzzle, described in the next section on VAERS, harkens back to one of the key features of the Kefauver-Harris Amendments of 1962: the requirement to report adverse events after marketing [43], and then as amended by the National Childhood Vaccine Injury Act of 1986 for injuries associated with the use of vaccines [59].

Created value: As with PPE, diagnostic test kits and ventilators, FDA was able to issue EUAs for vaccines because of regulatory infrastructure based on responses to 9/11. But the EUA is still a relatively novel process that's going to require a great deal more experience before the full implications of its use are appreciated in the user community. Upgrading the mRNA vaccine EUAs to full FDA approvals is a case in point.

On July 1, 2021, Topol [95] called for FDA to fully approve the mRNA vaccines, citing the nearly four months of use under the EUAs and the two additional months since filing the companies' Biological License Applications. He emphasizes the strong data from the clinical trials and the extensive experience in marketed use. This was quickly followed by a response from the Director of FDA's Center for Biologics Evaluation and Research, noting that full approval requires "review and verification of data at the level of individual subjects enrolled in clinical trials" which is essential to provide "the public with trust and confidence in the quality, safety, and effectiveness of any vaccine that the agency approves." [79] The Pfizer-BioNTech COVID-19 vaccine [23] was approved on August 23, 2021. Approval has been identified as a potential "turning point" in vaccine uptake [98], thus, highlighting an inherent and not well-recognized limitation of EUAs.

4.7. Vaccine Adverse Event Reporting System (VAERS)

The rare development of immune thrombotic thrombocytopenia associated with antibodies against Platelet Factor-4 [63]

was identified after more than 82 million doses of 4 different vaccines against COVID-19 had been distributed in the European Union. Detailed analysis implicated ChAdOx1 nCov-19 (Oxford /AstraZeneca). In the US, physicians at FDA identified a similar syndromic picture of 6 case reports of cerebral venous sinus thrombosis with thrombocytopenia following vaccination with approximately 7 million doses of Ad26.COV2.S COVID-19 vaccine (Janssen/Johnson & Johnson) and reported to VAERS [89]. These findings prompted FDA and CDC to advise doctors to "pause" the J&J vaccine on April 13, 2021, while the extremely rare blood clots were being investigated [42]. FDA and CDC subsequently lifted the pause 10 days later on April 23, 2021 [35].

Created value: While it may appear counterintuitive that value creation can follow from the identification and announcement of adverse drug reactions that have occurred in association with the use of a specific vaccine, a more patient-centered perspective shows that an emphasis on transparency, particularly regarding adverse drug reactions, heightens confidence in the use of vaccines, especially when reaching out to those who are hesitant about or resistant to the use of vaccines, or who may be inclined to harbor conspiracy theories.

4.8. Manufacturing

As in all other areas of pharmaceutical regulation, manufacturing has made quantum changes since the Biologics Control Act of 1902. Today's state-of-the-art innovations at FDA concern quality-by-design [53, 101]. Multiple failures to meet QbD principles were clearly behind the rejection of 75 million doses-worth of bulk COVID-19 active pharmaceutical ingredient of the Ad26.COV2.S COVID-19 vaccine [35] because of cross-contamination [74, 70, 71, 72]. An ongoing, serious threat to manufacturing integrity is the substantial global black market in substandard/spurious/falsely-labelled/falsified/ counterfeit medicinal products, which has recently touched a COVID-19 vaccine [66].

Created value: The Biologics Control Act of 1902 is, in fact, a founding statute of what was to become the FDA, even though the Pure Food and Drugs Act of 1906 is the marker for its centennial because Harvey Wiley, MD, became FDA's first commissioner on January 1, 1907. [24] Outside of the U.S., the greatest threats to the integrity of pharmaceutical products are counterfeit products. [67] The Drug Quality and Security Act of 2013, specifically Title II, the Drug Supply Chain Security Act, put in place the most far-reaching changes in manufacturing in the last century [29]. The Act requires that key stakeholders in the supply chain (manufacturers, wholesaler drug distributors, repackagers, and dispensers [pharmacies]) perform essential functions to maintain the integrity of pharmaceutical products, including product identification, tracing, verification, detection and response, and notification of regulatory authorities.

5. Discussion

5.1. An Agency Under Unprecedented Pressures and Stress

From the COVID-19 case study, it would appear that FDA has been flawless in the execution of its many responsibilities. But as with any new challenge to the status quo, especially an external challenge, it's well recognized that pressure testing can often reveal weaknesses in the overall system that would not otherwise be evident during routine performance. In looking at FDA under pressure testing, it's helpful to consider issues from the perspective of structure and function.

5.2. Structure

As an organization, FDA is bureaucratic, in that it's hierarchical, with multiple components performing narrowly prescribed activities. At its head is the Commissioner of Food and Drugs, a position that until 1969 had been a non-partisan, presidential appointment. [24] Then-Secretary of Health Education and Welfare, Robert Finch, brought in a physician with management expertise and connections to the consulting industry to address apparent deficiencies in managing high profile issues, including cyclamates. [77] Over the ensuing decades, political influence was gradually brought to bear (Patel, 2020) on a key function (transferring oversight for rule-making to the Office of Management and Budget, 1981), [58] reporting structure (converting the status to a PAS position, that is, a presidential appointment requiring senate confirmation, 1988) [34] and decision-making (slowing approval of mifepristone, also known as RU-486, and blocking regulation of food additives and nutritional supplements, 1990s), [28] leading to gradually diminished agency autonomy. The topic of FDA as an independent agency has been discussed by seven former FDA commissioners. [6]

5.3. Function

Political influence has also been evident with COVID-19. Diamond and Toosi [12] reported in March, 2020, that the White House encouraged FDA to issue an EUA for favipiravir (Avigan®), an antiviral agent used to treat influenza in Japan and manufactured by Fujifilm. In April, 2020, the White House similarly encouraged use of chloroquine and hydroxychloroquine, two anti-malarial drugs. [92] The EUAs for chloroquine and hydroxychloroquine were subsequently withdrawn after clinical evidence showed lack of effect. [25]

Beyond the COVID-19 case study, FDA has in recent times made controversial approval decisions that have resulted in splits between agency decision-makers and stakeholders, chief among them, the academic community. The FDA decision to approve aducanumab for Alzheimer's disease contrary to an overwhelming Advisory Committee vote against it led to three committee member resignations and to on-going controversy in the literature [78].

As an example of a divisive split within the academic community, in 2016, during the Peripheral and Central Nervous System Advisory Committee deliberations regarding eteplirsen treatment of patients with Duchenne's muscular dystrophy, the committee voted 7-6 that the drug did not qualify for accelerated approval, but in a less well-publicized letter from 36 DMD clinical experts, there was strong support for approval. And within the patient stakeholder community, there was also strong support for approval of eteplirsen. The Agency approved

eteplirsen on September 19, 2016, through the accelerated approval mechanism. [37]

Returning to the question of pressure testing as seen through the pandemic lens, stresses in FDA's structure are evident: 1) Political pressure applied at the Commissioner's level is felt down through the organization and recurrent exposures risk further compromises. The recent resignations of very senior, veteran Agency managers lend weight to this consideration. [97] 2) Well-intended regulatory flexibility is more limited in its potential than might be imagined, especially in a highly charged and extremely dynamic environment where the terrain is unfamiliar. For example, recall CDRH's experience with COVID-19 antibody test discussed above under *4.1 PPE, Diagnostic Test Kits, and Ventilators*: Created value [90]. 3) More recently instituted regulatory mechanisms, such as EUAs, are still relatively untested and may go only so far to meet broader policy expectations. [94] Deeper integration with established mechanisms may be needed.

5.4. Lessons Learned

What can we learn from the larger scope and longer time frame of events beyond the COVID-19 case study? First, FDA has been hampered by a long, gradual diminution of its independence, exemplified by the change in the Commissioner's status to a PAS position, transfer of reporting responsibility to the Secretary, Health and Human Services, and establishment of OMB oversight for FDA rulemaking. [6] Even the introduction of user fees, long recognized as a successful program regarding improvements in timeliness of reviews and decision-making, is recognized as having an insidious effect on the Agency's independence [6, 10].

Second, FDA's reputation has been damaged by sporadic faux pas on different fronts: 1) controversial internal decision-making (aducanumab approval), 2) external interference with decision-making (political pressure for multiple drug authorizations), and 3) significant disruptive, scientific disagreements with expert advisory committees (eteplirsen, aducanumab).

Third, the conflicts among the stakeholders are reminiscent of the early HIV era when FDA began to experience a deep shift toward recognition of and gradual consideration for patient stakeholder interests that started with HIV/AIDS activists, and expanded to include the many small populations of patients with orphan diseases, the devastated populations of patients with cancers, and others. Accelerated approval complicated the dynamics by providing a means by which an approval could be contingent upon eventually obtaining longer-term clinical benefit to support shorter-term surrogate marker improvements. Results have been mixed [64, 75].

Herder offers the following creative perspective on a comparable analysis:

... I attempt to make sense of these findings by developing a concept of institutional incumbency. ... With the term institutional I refer not just to the agency, but also how the FDA operates in dialogue with regulated industries and, increasingly, patient groups, to generate, shape, and delimit knowledge about drugs and biologics. And by incumbency, I mean to evoke the strategies that established firms deploy to preserve positions of dominance and extend this idea of defense-by-offense to the FDA. Through this conceptual lens of institutional incumbency, I aim to reveal not simply an agency in transition, but an agency on guard, engaged in an effort to reproduce key features of the regulatory system — in concert with regulated industries and others — while simultaneously sanctioning significant changes to the regulatory standards the FDA has long applied. In the name of lifecycle regulation, the agency is preserving who produces information about the safety and effectiveness of drugs and biologics, while altering when, and under what circumstances, that information production occurs [65].

There are three components of the title that provide opportunities for comment: COVID-19 as a case study, the concept of value, and FDA as an agency at the right place and the right time.

5.5. Case Study that Provides a Measure of Value

COVID-19 as a case study. COVID-19 has challenged every aspect of medical products under FDA's jurisdiction: range of products (drugs, biologics, vaccines, medical devices, diagnostic test kits), product development conditions (routine and accelerated), regulatory pathways (expedited mechanisms), types of approvals (use of Emergency Use Authorization and full approval), manufacturing quality (contaminated and counterfeit products), and post marketing safety (reporting rare and unusual adverse drug reactions). Thus, it can provide a sweeping context against which to conduct a meaningful exploration of value.

A Measure of Value: The title opens with "A Measure of Value" for which a definition of "value" is provided under the section Approaches to Value: "the regard that something is held to deserve; the importance, worth, or usefulness of something." [84] Value is an attribute that reflects the perspective of the beholder, and thus includes the historical events that are considered attributable to the institution. For FDA, the sum of twelve decades of experience since passage of the founding statutes comes down to the following goals that provide value to the degree with which each is successful:

- The manufacturing process must meet standards of quality and be secured
- Medical products must be shown, through scientific evidence and based on evidentiary standards, to be safe and effective for human use
- Risks must be identified and mitigated, by labeling at a minimum, with additional strategies as necessary
- Provisions must exist that can address extraordinary circumstances of unmet medical needs and of threats to public health and national security

Place and Time: The subheading of the title is "An agency in the right place at the right time." FDA is clearly an agency

"…in the right place…" because, of all the federal government agencies with responsibilities that have any bearing on the lives of the people in the country associated with the pandemic, only FDA has been in a strong position to actually flatten the pandemic's epidemiological curve and to provide support that has led to meaningful improvements in professional and personal circumstances and protection of their well-being: protecting health care workers [through facilitating rapid access to PPE], caring for the critically ill [through facilitating rapid access to mechanical ventilators and their substitutes, medical oxygen, and extracorporeal membrane oxygenation (ECMO) machines], identifying and tracking responsible pathogens, including variants [through rapid access to diagnostic test kits], developing and evaluating new vaccine candidates [through prompt review of INDs for the ethical conduct of clinical trials], evaluating repurposed, previously approved drugs and biologics [through prompt review of INDs for the ethical conduct of clinical trials], manufacturing bulk and finished vaccine products [through timely inspections of state-of-the-art manufacturing facilities], reviewing the experimental clinical data to assure integrity, validity, and transparency [through sharing and conferring with subject matter experts on agency advisory committees who discuss the results and provide assessments at publicly available meetings], and maintaining the safety profile of the vaccines with EUAs [through real time surveillance of FDA's and CDC's safety data bases].

FDA is just as clearly an agency "…at the right time…." because, for over the past twelve decades, despite the institutional, that is, structural, limitations and occasional faux pas in other, non-pandemic-related areas, FDA has learned to respond to myriad disasters and tragedies and to work with stakeholders to learn the difficult essential lessons from the issues at hand. COVID-19 has challenged every aspect of products under FDA's jurisdiction: range of products, product development conditions, regulatory pathways, types of approvals, manufacturing quality, and post-marketing safety. FDA has learned to work on different terrains, in different political environments, on different missions, at different speeds, and under different existential risks.

The subheading also implies how all aspects of the COVID pandemic that have been under FDA's jurisdiction were managed well and in a timely way. FDA never found itself the focus of an investigation for bureaucratic ineptitude or scientific faux pas.

Two basic strengths have contributed to FDA's ability to well manage its resources under a wide range of conditions: its regulatory structure and its professional staff. First, no matter how much FDA must negotiate and compromise, in the final analysis, FDA has the statutory and regulatory authority to act, backed up by twelve decades of experience in making difficult decisions under a variety of risks and a range of fraught conditions. FDA is responsible for regulatory aspects of the products under its jurisdiction, including development, manufacturing, communication, advertising, and promotion. FDA has generally succeeded in basing its actions on what the science says about the subject under discussion, and not on political ideologies or whims of the day that attempt to influence its decisions. FDA is deeply grounded in a set of regulations that have evolved over decades and become mutually reinforcing. Second, FDA is a highly bureaucratic organization, in the best sense of that word, with a high degree of active, bidirectional vertical alignment, timely flow of information, clear assignment of responsibilities, coordination, and collaboration among its functions – top-down and bottom-up. It has been managed by a relatively stable, if at times stressed by understaffing [73], professional staff with extensive experience under varied circumstances, and that possesses a firm grasp of the agency's mission and maintains a clear sense of its purpose – values that have only been sharpened by a pandemic crisis that has posed an existential threat.

5.6. Limitations

This focused review has limitations that come of using a singular lens. First, this has been a strictly descriptive, qualitative assessment that features many of the issues that FDA had occasions to face in other circumstances over decades, such as the early desperate years of HIV, the long slow, halting improvements in cancer treatments, the long-ignored orphan diseases, and multiple episodes of contaminated, adulterated, and counterfeit manufactured products. Second, there has been no effort to identify and assess the considerable effects resulting from the influence that user fees have had on the process, but rather to accept the role of user fees as a constitutive part of FDA's regulatory fabric, aware that there are recognized risks to this model. And third, this has been an unconventional approach to assessing value with no evident precedent because regulatory agencies are more often thought of as a drag on value, rather than as value added; but the ideas discussed here may offer a novel conceptual approach to thinking about value that could be applied to other highly regulated fields and in comparative work versus other national or regional jurisdictions.

6. Conclusion

In response to a long history of disasters and tragedies that occurred over twelve decades since the beginning of the twentieth century, Congressional passage of ground-breaking statutes and development of innovative regulations have transformed FDA into a peerless regulatory agency that has played a critical role in the COVID-19 pandemic and, in the process, has brought new meaning to the concept of value.

FDA has been the singular regulatory agency in the federal government to have had a sweeping salutary effect on virtually every disease-related and healthcare-related aspect of the pandemic. FDA has expedited access to personal protective equipment, diagnostic testing kits, mechanical ventilators and ECMO machines, and expedited clinical development and regulatory review of new vaccine candidates. It has conducted inspections of the manufacturing processes of active pharmaceutical ingredients and maintained the safety profile of vaccines that have been given to hundreds of millions of individuals. All of these actions have occurred in a transparent environment and under the glare of 24/7 publicity for nearly 2 years. FDA has served well as a regulatory agency of its place and time.

7. Declaration of Conflicting Interest

The author declares that the review and assessment was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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