國立臺灣大學法律學院法律學系

碩士論文

Department of Law
College of Law
National Taiwan University

Master Thesis

緊急授權適用緊急標準？
——以美國 COVID-19 期間疫苗緊急授權為例

Emergency Standards for Emergency Use?
－US Vaccine EUAs during the COVID-19 Pandemic

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中華民國 112 年 8 月

August 2023

doi:10.6342/NTU202302527

Acknowledgements

I would like to express my deepest gratitude to my thesis instructor, Prof. Jiunn-Rong Yeh. From the beginning, Prof. Yeh provided utmost encouragement and inspiration for setting my topic, was extremely supportive while I explored different research methods, and gently nudged and reassured me to keep me on track. It was he who reminded me to proceed with my goal in mind, and also he who led me out of the various mazes that I wandered into during my expanded duration of thesis writing. Thank you for sharing your time and wisdom.

I would also like to thank my two oral examination committee members, Prof. Wen-Chen Chang and Prof. Wen-May Rei. Prof. Rei provided insightful comments from a social technological studies and comparative perspective, and prompted me to enhance contextual analysis in my thesis. Prof. Chang reminded me to not neglect basic administrative law principles, and literally sent me back to textbooks for answers. I am grateful for their kindness and expertise.

I am also in debt to several professors that have inspired me and helped me acquire the tools needed to complete this thesis: Prof. Wen-Tsong Chiou for asking the key questions that sparked the beginning of this thesis, Prof. Chuang-Feng Wu for guiding me through various public health and international law research, Prof. Hui-Chieh Su for teaching me how to read and write scholarly, Prof. Nai-Yi Sun, for introducing conceptual legal analysis, and Prof. Chao-Ju Chen for negating my fear for American law. I have learned so much from all of you.

Finally, allow me to leave thanks for all those that have provided the much needed mental support throughout my entire graduate studies. This thesis could not have been possible without you.

doi:10.6342/NTU202302527

中文摘要

本文研究主題為美國緊急授權制度下審查 COVID-19 疫苗的「緊急標準」，分析在緊急狀態下，美國是否採取了相較於平常時期更低的標準審酌科學證據。為了解美國食品藥物管理署（下稱食藥署）在不同情形下採擇科學證據的標準，本文首先檢視新藥審查中採用的多種加速機制，並以兩個具指標性的新藥：新型口服抗凝血劑以及 C 肝藥物作為分析個案，發現經歷過去二十年的修法以及資源投注，美國食藥署流暢、有系統地運用彈性的試驗設計、解讀試驗結果。相較之下，疫苗的發展與審查涉及較為複雜的試驗設計與執行考量，並且需要更為謹慎地處理安全性審查。Agriflu 以及 Flublok 兩支流感疫苗分別使用已知技術與新技術研發，二者的上市審查則呈現美國食藥署雖然高度仰賴指引文件設定的標準，但也並非毫無彈性。最後，在 COVID-19 疫情的緊急狀態之下，美國食藥署運用指引以及高密度的對話溝通平順地作成了兼顧公共衛生目的的緊急授權決策。與美國相較，台灣食藥署對本土疫苗的審查受到地緣政治特性、欠缺大規模疫情以及資訊揭露不足等多重因素的影響。綜觀美國食藥署藥物、疫苗上市審查的軌跡，其在 COVID-19 疫情下所為的科學證據評價，立基於其過往多年累積的審查架構但不失彈性，同時也仍維持一定程度的資訊揭露，在政治性決策與科學證據採擇間取得平衡。

關鍵字：緊急授權、科學證據審酌、疫苗上市審查、藥物上市審查、COVID-19 疫苗

doi:10.6342/NTU202302527

Abstract

This thesis aims to understand what constituted the “emergency standards” for the COVID-19 vaccine under US Emergency Use Authorizations (EUAs), in particular whether the standards for evaluating scientific evidence were lowered compared to that under normal conditions. To gain a basic understanding of US Food and Drug Administration (FDA) assessment of scientific evidence under different circumstances, this thesis begins with an examination of expedited pathways for new drug approvals, using dabigatran and sofosbuvir, two landmark new drugs to demonstrate approval metrics. With updated legislation and increased resources in the past two decades, the US FDA is able to apply flexible standards for trial design and allow extrapolations of trial data in an organized and streamlined fashion. However, vaccine development and approval involved more complex trial design and implementation considerations, as well as greater attention to safety issues. The approval of two influenza seasonal vaccines Agriflu and Flublok, the former utilizing a well-known technique and the latter a novel technique, showed that the US FDA relied heavily on guidance documents for standard setting but were still subject to uncertainty. Finally, in the COVID-19 public health emergency, the US FDA utilized guidance documents and intense communication to conduct a smooth review process that reflected the political considerations during the pandemic. In comparison, Taiwan FDA’s approval of domestic vaccines was complicated by local concerns, including geopolitical issues, lack of infections and transparency. This thesis concludes that the evaluation of scientific evidence in US COVID-19 vaccine EUAs references the past, maintains resilience, and demonstrates adequate transparency, reflecting its political nature.

doi:10.6342/NTU202302527

Keywords: Emergency use authorization, evaluation of scientific evidence, vaccine approval, drug approval, COVID-19 vaccines

doi:10.6342/NTU202302527

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Chapter 1 Introduction

I. Foreword

COVID-19 rushed the world into a pandemic unparalleled by anything this world has seen in more than a century. With the virus quickly sweeping across country borders and taking hundreds of millions of lives, both governments and developers raced to find solutions to the pandemic. Vaccines was an obvious solution to the emerging infectious disease. Unfortunately, even in the US, where major pharmaceutical companies reside and have been ebbing with breakthroughs in biotechnology, vaccines for new diseases have taken years to be developed and approved for use. Mercifully, the emergency use authorization (EUA) procedure has been in place for nearly two decades to address emergencies such as this. The United States Food and Drug Administration (US FDA) issued emergency use authorizations to three different COVID-19 vaccines, within 12 months of the disease landing in the United States. These vaccines have been administered to both Americans and people all over the world, successfully protecting people from death and disease. As a licensed doctor studying public law in Taiwan, I followed the development of the COVID-19 vaccines in awe, inspired by not just the scientific and pharmaceutical marvel behind vaccines, but also the regulatory miracle that played out the EUAs.

It appears that USA's EUA process has been effectively utilized in this unprecedented pandemic, but before the pandemic little attention has been given to this administrative instrument. The process was designed with terrorists activities in mind, and has been employed to confront epidemics that concerned the US, including the H1N1 influenza, the Ebola virus, and the Zika virus.

doi:10.6342/NTU202302527

However, compared to the FDA's other reviewing operations, the EUA process has received little scrutiny, and its rapid widespread use has drawn suspicions from some. First and foremost, many instinctively believe that the EUA requires a lower level of scientific evidence compared to traditional approval procedures, the New Drug Application (NDA) or Biologics License Application (BLA). Is this true regarding the COVID-19 vaccines that have been issued emergency use authorizations? If it is true, what has the US FDA done to address the potential issues arising from administering a novel and perhaps "scientifically uncertain" medical product to the general public? If not, what has the US FDA done to enable such swift development and review of the EUA products?

On the other hand, even though the pandemic itself is unprecedented, this is not the first time that federal agencies have been faced with the dilemma of making pressing policy decisions with insufficient scientific evidence. In fact, this is the nature of the reviews that the FDA have been conducting since the 1960s, or as one might declare that such decisions reflect political considerations as much as scientific considerations. Successfully incorporating advisory networks outside of the agency and with careful boundary work, the FDA has resolved crises such as anti-arrhythmic drug risk stratification arising from propranolol incidents. In particular, the modernization efforts of the FDA since the 1980s have contributed to more diverse and robust review pathways, and have laid the foundation for the FDA to react immediately and appropriately in the face of crisis. I am also curious to know whether this foundation has had any influence on the operation of the EUA review process, not only in terms of evaluations of the safety and efficacy based on the totality of scientific evidence, but also from the pre-submission activities between the US FDA, the

doi:10.6342/NTU202302527

sponsor, and other actors that facilitate, or at other times, hinder the approval process.

Evidently, the COVID-19 pandemic has triggered the most EUAs ever issued by the US FDA. The US FDA has issued EUAs for medical devices (including but not limited to *in vitro* diagnostic sets for COVID-19),[1] therapeutics (drugs),[2] and vaccines.[3] The former two have not been without controversies, but the most contentious has obviously been the COVID-19 vaccines. Although vaccines have been reviewed under the biologics category along with many other products such as serum and fecal microbiota treatment, the US FDA has always viewed vaccines as a distinct genre of medical product, because it is generally administered to widely healthy populations. This is also true and certainly a source of wariness for COVID-19 vaccines, because to achieve herd immunity and assist in returning to pre-pandemic social interactions, the vaccines would need to be developed fast, be effective individually, and be administered to a high proportion of the population. I could not help but wonder, how has the US FDA employed EUAs to achieve these goals? For example, what kinds and levels of evidence were required of COVID-19 vaccines? How are these evidence interpreted both inside and outside of the agency, by developers, experts, critics, or the courts? How has the US FDA responded to various analyses and criticism? Has the US FDA redrawn

[1] Food and Drug Administration, *In Vitro Diagnostics Euas,* FOOD AND DRUG ADMINISTRATION (January 12, 2023), https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas#:~:text=There%20are%20several%20types%20of,tests%20that%20analyze%20breath%20samples. (last accessed April 15, 2023).
[2] Food and Drug Administration, *Coronavirus (Covid-19) Drugs,* FOOD AND DRUG ADMINISTRATION (April 19, 2023), https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs (last accessed April 15, 2023).
[3] Food and Drug Administration, *Covid-19 Vaccines,* FOOD AND DRUG ADMINISTRATION (April 18, 2023), https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines (last accessed April 15, 2023).

doi:10.6342/NTU202302527

the boundary of its reviewing authority in the face of such an emergency? If so, how has it done so and what are the effects of doing that?

It is not every day that the world is faced with an emergency like the COVID-19. Developing vaccines that will be effective both clinically and socially is a challenge for the governments across the globe, where it needs to exercise its reviewing expertise and policy making discretion with limited information and time. The US FDA serves as an icon, and perhaps more importantly a reference to other similar agencies in different countries with its long, bountiful and nevertheless diverse regulatory interactions with drug and vaccine developers and advisory bodies. I hope to reveal how the US FDA has performed its functions regarding the COVID-19 vaccines EUAs, based on an understanding of classic US FDA approvals and through observing the interactions and interpretations within the regulatory process.

II. Shaping the Question: What are Emergency Standards for Vaccine EUAs?

The US FDA has been engaged in reviewing drugs and vaccines for approval for decades, based on standards shaped by statutory requirements, agency guidance, and practical experienced gained from reviewing thousands of products. Obviously, there are manufacturing, chemistry, and quality control standards to be followed for any product, but the most illuminating interaction between regulation and scientific standards lie in the determination of the efficacy and safety of drugs and vaccines. Any drug or vaccine that seeks to be approved for use in the US needs to provide substantial evidence that it is effective for the purpose it was intended, and also safe for use. The former is what we call efficacy of the product, and the latter simply safety. The US FDA

doi:10.6342/NTU202302527

is charged with the responsibility to determine whether the statutory criteria has been met.

Scientific evidence to demonstrate the efficacy and safety of products generally refers to data from clinical trials, which means research conducted on humans to evaluate the effect of certain interventions on humans. Modern clinical trials utilize the concepts of control groups, randomization and blinding, meaning trial results are compared between subjects that received intervention or not (controlled group), subjects are allocated to each group randomly, and subjects and/or those that conduct the research do not know the group designation of each subject.[4] Furthermore, clinical trials need to be prospective, which means that they will be followed forward in time, and mostly followed for certain period of time according to protocol.[5] These are the textbook standards that a clinical trial providing evidence for the efficacy and safety of a medical product should maintain. On top of the above characteristics, modern pharmaceutical trials have been divided into phases I through IV. Phase I studies aim to estimate tolerability and pharmacodynamics, which provides basic understanding of how the drug or vaccine works in the human body, and how well the human body tolerates it. Phase II trials are designed to determine whether the drug or vaccine has any anticipated effect, and often to test a range of different doses to find the best option. It is often used to support the a new drug or vaccine's further development.[6] Phase III trials are the classic forms of clinical trials on which US FDA approvals are based, and are engineered statistically to evaluate the efficacy and safety of the trial drug or vaccine on

[4] LAWRENCE M FRIEDMAN et al., FUNDAMENTALS OF CLINICAL TRIALS 1 (Springer 5 ed. 2015).
[5] *Id*. at 2.
[6] *Id*. at 6-7.

doi:10.6342/NTU202302527

trial.[7] Phase IV trials are similar to phase III trials, but are often conducted after approval has been gained to confirm or explore relevant evidence. Under normal conditions, as opposed to public health emergencies, drug and vaccine developers are required to go through the various stages, and present their trial designs, data and analysis results, with an emphasis on their phase III efficacy and safety results, to the reviewing body and await a verdict on whether they can be sold and used on human beings.

The approval of drugs and vaccines is not exactly a one-way street, but involves constructive bipartisan dialogue. The US FDA publishes guidance documents that describe what constitutes substantial evidence and safety evaluation for different diseases or conditions, which it generates from past experience with the disease or condition and often incorporates recent advances in the field. Sponsors of drugs or vaccine for the disease or condition therefore consult the guidance documents in preparation for drug and vaccine development, often designing clinical trials accordingly. When the data are finally submitted for approval, the US FDA often examines whether it has met guidance document requirements, and if not, the US FDA seeks for acceptable explanations and acknowledgement from advisory committees. Therefore, US FDA guidance documents provide insight into the US FDA's current thinking on trial design, statistical concerns and efficacy and safety standards for specific diseases and conditions. For example, guidance document on seasonal influenza vaccines require applicants to demonstrate vaccine efficacy of at least 40-45% through placebo-controlled studies for the product, and a safety database of several thousands.

[7] *Id*. at 9-10.

doi:10.6342/NTU202302527

That being said, how much of the above understandings between the US FDA and drug or vaccine sponsors will stay in place under the COVID-19 pandemic were just simply unknown. It was anticipated that some standards may be lowered or even abandoned in the face of such an unprecedented emergency. For example, there might not be the time or need to complete all three phases of clinical trials as sponsors usually do. Or, it may be unrealistic to require the COVID-19 vaccines to be as effective as vaccines that have taken years to develop. Or perhaps, the US FDA will require a shorter safety follow-up period, or a smaller safety database. Even with the EUA as an legal instrument in place, all of these questions were just up in the air. We did not know what kind of "sacrifices" will be made, whether they will be made, or how the decisions to make the sacrifices are to be made. We also did not know, what these compromises in the face of emergencies would cost us in the long run. We simply did not know. In the case of the most anticipated COVID-19 vaccines, this was especially of concern, because that was the human's shot to end the pandemic.

By 2023, we know how things ended. COVID-19 vaccines were developed and authorized for emergency use in under a year, billions of people are vaccinated across the globe, the threat of the virus has been mitigated, and the world is almost back to normal. It is therefore the objective of this thesis to understand what constituted the "emergency standards" for the COVID-19 vaccine EUAs: what kind of trial designs were found to be adequate? How effective did the vaccines aim to be? How are the vaccine's safety guaranteed? And also, how were these decisions made, and how were the standards implemented? Fundamentally, this thesis will focus on the standards taken on by

doi:10.6342/NTU202302527

the US FDA in the development and authorization of COVID-19 vaccines, with an emphasis on their similarities and differences compared to past US FDA approval processes.

III. Literature Review

A. US FDA Drug and Vaccine Approval Decision Making

Drug and vaccines review and approval, whether in normal times or under public health emergencies, is hardly a purely scientific process with straightforward yes or no answers. Sheila Jasanoff's research on the roles of advisory committees providing scientific advice to the Environmental Protection Agency and the FDA from the 1960s to 1980s, illuminates how the US FDA utilizes boundary work and a systemic structure to reduce conflicts over interpreting controversial scientific evidence. By comparing the advisory committees of the FDA and the EPA, looking at cases of Propanonol and Zomax, Jasanoff showed how the FDA's the interactions with the advisory committees are not without glitches, but that advisory committees are still valuable in making fundamentally political judgements in the face of controversies. Jasanoff also touches on how guideline development by the FDA has successfully bridged science and public policy, and how the FDA still maintains the freedom to construe science and make policy to serve the public better with selective use of expert committees, public review of advisory reports, and occasional overruling of recommendations.[8] In terms of risk evaluation, Jasanoff contends that risks involve personal and social values, and thus should be determined by experts alone, and should involve the negotiation

[8] SHEILA JASANOFF, THE FIFTH BRANCH : SCIENCE ADVISERS AS POLICYMAKERS 155-179 (Harvard University Press. 1990).

doi:10.6342/NTU202302527

among scientists and the between scientist and the lay public. Jasanoff finally describes elements of good science: validation of long-term research strategies, certification of study protocols and analytical methodologies, definition of standards of adequacy for scientific evidence, and approval of inferences from studies and experiments.[9] However, for normative implications preserving some maneuvering room,[10] maintaining a balanced membership to the advisory committee, avoiding conflicts of interest, circumscribing the target of review and subjecting issues to non-adversarial review process can best improve policy making based on scientific evidence.[11]

In a later work, Jasanoff updates her observations of the risk-based regulatory process in the US. She noted that scientific analysis and political deliberation are starting to be intertwined from the earliest stages of the process, and that through feedback and recursion, closure of controversies comes from the needs of decision making. Assessing risk requires social and political exercise, and experts can contribute to the complex decision making process by balanced opinions in the face of uncertainties. Jasanoff emphasizes that framing of expert legitimacy problems in a reductionist rhetoric of "good science" blurs the lines of expert accountability, and that there is still the need for public review of expert judgements in an institutional setting of advice-giving.[12] It remains to be seen, however, whether such proceedings and critic have evolved over the past two decades, whether the balance and framing is altered when the

[9] *Id*. at 230-240.
[10] *Id*. at 242.
[11] *Id*. at 243-247.
[12] Sheila Jasanoff, *Judgment under Siege: The Three-Body Problem of Expert Legitimacy*, *in* SCIENCE AND PUBLIC REASON 150,147-153(Sheila Jasanoff eds., 2012).

doi:10.6342/NTU202302527

US FDA is faced with acceleration demands, and whether they still function effectively in times of emergency.

In addition to Jasanoff's deep analysis of the US FDA's drug and vaccine approval decision making process rooted in a constructivist approach, Arthur Daemmrich adds a comparative and somewhat social structural perspective. Daemmrich realizes that no matter how hard regulators try to establish a standardized testing regime, safety and efficacy evaluation involves rich informal practices and testing methods. The design and operation of clinical trials themselves reflect the dynamics between patients, clinicians, and regulators, but then decisions based on these clinical trials involve wider social and institutional commitments. Daemmrich based his analysis on the comparison between the practices of the regulatory agencies in the US and Germany, finding that the US is more adaptable to change as opposed to maintaining continuity. When decision makers try to predict future outcomes, the interaction of different actors under its unique institutional context is important. Since the 1950-80s, the US FDA has mandated and refined the standards for quantitative methods and statistical evaluations.[13] Daemmrich thus recognizes that regulators, practitioners, patients and pharmaceuticals are all integral to the risks assessment of drug and vaccine regulation, and that such regulations is based on an interlinked web of public involvement, democratic representation, and modes of organizing the state and civil society.[14] Daemrich's work provides an update on the constructivist view of the workings of the US

[13] ARTHUR DAEMMRICH, PHARMACOPOLITICS 12-20 (Allan M. Brandt & Larry R. Churchill eds., The University of North Carolina Press. 2004).
[14] *Id*. at 160.

doi:10.6342/NTU202302527

FDA, but understandably has not touched on the efforts to accelerate approvals, not to mention the agency's operations under an emergency timeline.

B. Legal, Historical, and Technical Aspects of the EUA Program

The emergency use authorization process was introduced after the 911 attacks through the 2004 The Project Bioshield Act by enacting Section 564 to the Food, Drug and Cosmetic Act (FDCA). Since its introduction, little discussion or attention has been given to the process. Although the FDA issued a guidance on emergency use authorizations,[15] the 40 page guidance document focused largely on the format and information required for application, and dwelled little on the interpretation of evidence under such circumstances. Most of the literature involving EUAs in before the COVID-19 pandemic focused on the specific uses of the EUA for H1N1 influenza,[16] the Zika virus,[17] and the Ebola virus,[18] none of which resulted in the development of successful vaccines against the diseases. Since the pandemic unrolled, the emergency use authorization has been given closer scrutiny, including some examination into why and how this procedure was established and the concerns it was framed to address.[19]

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[15] FDA, Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders, 2017/01, available at:https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities (last seen 02/01/2022).

[16] See Susan E Sherman et al., *Emergency Use Authority and 2009 H1n1 Influenza*, 7 BIOSECURITY AND BIOTERRORISM: BIODEFENSE STRATEGY, PRACTICE, AND SCIENCE 245 (2009); Alfred Sorbello et al., *Emergency Use Authorization for Intravenous Peramivir: Evaluation of Safety in the Treatment of Hospitalized Patients Infected with 2009 H1n1 Influenza a Virus*, 55 CLIN INFECT DIS 1 (2012).

[17] See Andrea M Bingham et al., Comparison of Test Results for Zika Virus Rna in Urine, Serum, and Saliva Specimens from Persons with Travel-Associated Zika Virus Disease—Florida, 2016, 65 MORBIDITY AND MORTALITY WEEKLY REPORT 475 (2016); Elitza S Theel & D Jane Hata, Diagnostic Testing for Zika Virus: A Postoutbreak Update, 56 J CLIN MICROBIOL e01972-17 (2018).

[18] See Chris A Whitehouse et al., United States Fda's Emergency Use Authorization of Ebola Virus Diagnostics: Current Impact and Lessons for the Future § 15 (Taylor & Francis 2015).

[19] Efthimios Parasidis et al., *Assessing Covid-19 Emergency Use Authorizations*, 76 FOOD & DRUG LJ 441 (2021).

doi:10.6342/NTU202302527

Jacob Sherkow described the US FDA's approach to approving emergency use authorization to COVID-19 vaccines as a regulatory sandbox, which he believes to be one of the most radical programs to introduce new technologies in U.S. history. Regulatory sandboxes are operations where developers can "*conduct limited tests on innovations with fewer regulatory constraints, real customers, less risk of enforcement action, and ongoing guidance from regulators.*"[20] Sherkow observes that the EUA program exhibits elements of regulatory sandboxes, including collection of experimental data, industry-input based, flexibility but deployed in real-world settings, and with certain limits on scope, use, and duration. Sherkow also briefly introduced the controversies arising from EUAs given to diagnostics and therapeutics, and noted that EUAs for COVID-19 vaccines were designed to mimic formal approval processes, which might defeat the purpose of establishing an extraordinary route authorization.[21] Narrating recent EUAs, Sherkow recognizes the uniqueness of health and the FDA even among administrative agencies, observing that FDA relies heavily on industry guidance, uses external advisory committees frequently and actively, and can be especially protective when faced with risks.[22]

Other literature commenting on the COVID-19 vaccine EUAs before and during the pandemic were mostly on the technical aspects of developing a vaccine, or listed a number of factors that might or might have contributed to the rapid authorization by the US FDA. Prior to any COVID-19 vaccine EUAs

[20] Jacob S Sherkow, *Regulatory Sandboxes and the Public Health*, 2022 U ILL L REV 357,357-359 (2021).
[21] *Id*. at 382-385.
[22] *Id*. at 400-407.

doi:10.6342/NTU202302527

were granted, Jie Chen and Naitee Ting described a number of vaccine clinical trial considerations specifically for the COVID-19 vaccines, under the premise of developing a vaccine as soon as possible. Adaptations were from both clinical and academic settings, including master protocol designs, the feasibility of human challenge studies, adaptive trial designs, and using realword data to validate vaccine safety and efficacy.[23]

After COVID-19 vaccine EUAs were granted, Thoyaja Koritala and colleagues pointed out characteristics of the EUA that may have contributed to vaccine hesitancy, and called for full approvals.[24] Allan Tran and Theodore J. Witek Jr. described the EUA program as a demonstration of dynamic nature of scientific review, gave a brief overview of the EUA program's history, and pointed out the differences of COVID-19 vaccine approval and use between the US, Europe, and Canada.[25] Barbara Kuter and colleagues answered the "Why and how so fast?" question, with past vaccine knowledge and new technology, rapid governmental response, scientific collaborations, unparalleled funding, as well as clinical trial and regulatory aspects of the rapid response.[26] Most of the literature available on COVID-19 related EUAs focus on the technical aspects of the miraculous feat, without looking closely into the constructs of this regulatory mechanism. While some mentioned the US FDA's guidance documents and its adaptations throughout the pandemic, none really weighed the EUA standards against traditional or accelerated approval standards.

[23] Jie Chen & Naitee Ting, *Design Considerations for Vaccine Trials with a Special Focus on Covid-19 Vaccine Development*, 18 JOURNAL OF DATA SCIENCE 550 (2020).
[24] Thoyaja Koritala et al., *A Narrative Review of Emergency Use Authorization Versus Full FDA Approval and Its Effect on Covid-19 Vaccination Hesitancy*, 3 INFEZ MED 339 (2021).
[25] Allan Tran & Theodore J Witek, *The Emergency Use Authorization of Pharmaceuticals: History and Utility During the Covid-19 Pandemic*, 35 PHARMACEUT MED 203 (2021).
[26] Barbara J Kuter et al., *The Development of Covid-19 Vaccines in the United States: Why and How So Fast?*, 39 VACCINE 2495 (2021).

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Furthermore, a lack of scrutiny was given to whether the COVID-19 vaccines that ultimately achieved EUA followed or deviated from the standards, and how the US FDA interpreted their decisions.

IV. Theories and Methods

A. Building the Analytical Method

There is no doubt that the EUA program, as well as traditional and accelerated approvals, are legal instruments under the FD&C Act, giving the US FDA the power to adjudicate scientific evidence of medical products under varied circumstances. The statutes serve as a regulatory framework for the regulatory actions of the US FDA, and reflect the understanding and requirements of the legislature of the US FDA's operations under different circumstances. Thus, the evolution of relevant regulations will illuminate on how the law has reflected change, and a comparison between different paradigms shows how the legislature levels the US FDA authority to interpret scientific evidence.

At the same time, the COVID-19 pandemic has presented a realm of intense scientific uncertainty coupled with urgent need to mitigate existing threat, which is a priceless opportunity to observe the social processes and negotiations surrounding the emerging scientific evidence. The achievement of timely COVID-19 vaccine EUAs is not simply the result of rigorous testing and scientific analyses, but from the pressures and constraints by the adjudicating community. Brian Martin and Evelleen Richards identify this as sites for a sociology of scientific knowledge approach, which applies social analysis to

doi:10.6342/NTU202302527

scientific knowledge claims as well as to wider social dynamics.[27] As such, an investigation into the micro-level actions and interaction between actors involved in the COVID-19 vaccine EUA, such as the US FDA through guidance documents and review summaries, the sponsors through communications with the US FDA and expressions in academic circles, and other commentators on vaccine development, would help reveal how the COVID-19 vaccine EUAs came into place.

To capture a comprehensive picture of the operations of the US FDA in approving and authorizing use of drugs and vaccines, a narration of symbolic cases under certain paradigms makes it possible to investigate the micro-level actions and interactions between the US FDA, sponsors, and other actors. These interactions may happen before submission for approval or authorization, during the review process, or even after the product has been approved or authorized. The difference or convergence in the interpretation of scientific evidence throughout these interactions from different actors are of particular interest in this thesis on the quest to understanding how COVID-19 vaccines EUAs were achieved.

B. Research Materials and Scope

The focus of this thesis will be on US FDA decisions based on different approval/authorization paradigms. This thesis will be limited to the operations of the US FDA not only because the USA is the leading pharmaceutical market, but also because the EUA program of the US is well-documented and the US

[27] Brian Martin & Evelleen Richards, *Scientific Knowledge, Controversy, and Public Decision Making*, *in* HANDBOOK OF SCIENCE AND TECHNOLOGY STUDIES Sheila Jasanoffet al. eds., 1995).

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FDA has endeavored to publish data and analysis of products it has reviewed and approved or authorized.

In order to construct an analysis on the FDA's operations regarding drug and biologics approval and EUAs, I will first present the relevant federal laws, namely the FD&C Act sections which regulate the circumstances and scientific evidence to be reviewed by the US FDA under various paradigms. After depicting the statutory requirements, I intend to review FDA guidance documents and information from past approvals to visualize the regulatory framework. With the regulatory framework of specific paradigms in mind, I will proceed to examining the US FDA review documents, including letters of approval, clinical review summaries, and amendments from selected products to observe the interaction between sponsors and the US FDA. Congressional discussion on lawmaking and committees overseeing the issues, views of experts and developers in the form of scientific publication or opinions, and news and court cases regarding the selected case studies will also be presented as views from different actors.

To date, the US FDA has not released data for products that it has not approved or authorized, and therefore a full discussion on these vaccine products would regrettably not be possible at the current time. A more critical picture may be presented if further information shall be revealed in the future. Furthermore, although there is a single EUA program for drugs, diagnostics, and vaccines, this thesis has chosen on focus on COVID-19 vaccines because of its social implications, and also because of the careful deliberation based on the scientific evidence by various actors in the field.

V. Thesis Structure

doi:10.6342/NTU202302527

This thesis will be composed of five chapters. The first chapter gives a brief introduction of the question, provides literature review, and describes the analytic approach and methods of the thesis.

Chapter 2 sets the stage to understanding the US FDA review of scientific evidence in drug approvals, with a focus on the differences between a traditional approval and accelerated approval. Chapter 2 is also an attempt to continue work on analyzing the US FDA's approval schemes from a constructivist perspective, especially in terms of US FDA's reactions to pressures to speed up approval timelines. Chapter 3 takes note of the difference between drug and vaccine approvals, outlining characteristics of vaccines, and examines mechanisms used to accelerated vaccine development and approval. Using the approval of two influenza vaccines, Chapter 3 presents the US FDA's decision making for a vaccine against a virus very similar to SARS-CoV-19, and identifies limitations to further accelerate vaccine approval under non-EUA settings. Chapter 4 will take a deep dive into the emergency use authorization process of the US FDA. In addition to reviewing the Congressional history of introducing the regulation and the regulatory framework constructed by the US FDA since then, this part will examine the COVID-19 vaccines EUAs granted by the US FDA. The analysis in Chapter 4 will focus on what has made rapid vaccine development and authorizations possible: what is done in reference to past approval actions, and what is done differently. This chapter will also include a brief comparison to the Taiwan's FDA actions during the pandemic, to highlight the effects of the US EUAs abroad. Finally, Chapter four reviews the findings of this research and seek lessons for the way forward.

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Chapter 2 Gearing Up for Priority: Review of Evidence in New Drugs

The operations of the US FDA have evolved over time. Having established the need and authority to review substantial evidence for drugs and vaccines of the US FDA, the US FDA also faced immense pressure to speed up its reviews to meet patient and social demand. Through the US FDA's efforts to streamline new drug application review, several different pathways were installed into the FDA's reviews, which added innovations in clinical trial designs, biostatistics analysis, as well as post-approval requirements to the regulatory mechanisms. Some of these additions were established by law, while others were developed by the US FDA and then incorporated into law. Either way, diverse adjustments to new drug applications were implemented on even the most novel therapies at the time, and significantly reduced US FDA review time even under normal times. This chapter will first give an overview of the law and regulations related to the acceleration methods employed by the US FDA, and take a close look at two groundbreaking drugs for a long-standing diseases to understand whether the pressure to review and approve new drugs faster has affected how the US FDA evaluates "substantial evidence".

I. Overview of the FDA drug and biologics approval procedure

The current new drug application regulations are an aggregate of bills that reformed the Food, Drug, and Cosmetic Act (FD&C Act) over the course of several decades. Several features acquired through the numerous revolutions to the drug approval processes sheds light on how FDA evaluates scientific evidence, including what evidence it considers, how it gathers these evidence,

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what actors are brought into play, and how the FDA interacts with these actors. This section of the chapter will first give an overview of the major amendments regarding FDA drug approval regulations, beginning from the Kefauver-Harris Bill, and describe the current procedures for drug approval regulations in brief.

A. History of Acceleration: Law and Regulations

The 1962 Kefauver-Harris Amendment installed a provision to grant FDA the authority to review both safety and efficacy of drugs for market approval. Although the FDA has been taking drug efficacy into account when making judgements since the 1950s, it was the Kefauver-Harris amendments that shifted the burden of proof for drug efficacy to drug companies and that really standardized the drug approval process.[1] In 1963, the FDA proposed a structure of phased clinical experiment through a guidance document.[2]

In 1992, in view of prolonged drug reviews even under the HIV/AIDS pandemic, the Prescription Drug User Fee Act (PDUFA) required the FDA to streamline efficacy requirements so that drug reviews may be expedited. In response to the legislature's requirement, the FDA issued a final rule that established the Accelerated Approval Program, which recognized the use of surrogate markers as valid endpoints for clinical trials that would be used as the basis of drug approvals. The program was finalized as a Manual of Policies and Procedures for the Center for Drug Evaluation and Research, named Review Designation Policy: Priority (P) and Standard (S). The Manual came into effect on April 22, 1996. On the other hand, PDUFA also established goals for Special

[1] Daniel Carpenter et al., *The Drug Efficacy Study and Its Manifold Legacies*, *in* FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 306,307 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).
[2] *Id*. at 309.

doi:10.6342/NTU202302527

Protocol Assessment and Agreement, which was recognized as the most important reform of the Investigative New Drug/New Drug Application (IND/NDA) process since 1962.[3] Despite several withdrawals and black box warnings after the PDUFA that led to criticism of the FDA rushing through drug approvals and neglecting safety issues of newly approved drugs, drug approval timelines were improved greatly after the agreement between the FDA and the Congress. Studies showed that drugs that were approved close to the deadline of the timeline agreed by the FDA and the Congress had a greater tendency to be withdrawn from the market for safety concerns or received black-box warnings after it was marketed.[4]

The 1997 FDA Modernization Act made several small changes to the marketing approval process established by the FDA that incrementally aided to review drugs and biologics faster. In addition to allowing for new drug approvals to be based on data from a single clinical trial, which some viewed as a relaxation of the "substantial evidence standard", it also reinforced data requirements for drugs and biologics and clinical investigations.[5] Furthermore, the FDA Modernization Act introduced the fast track drug designation based on the FDA's 1988 regulations to expedite study and approval of drugs meant for the treatment of life-threatening or serious. It finally gave federal recognition to surrogate endpoint as a valid endpoint for clinical investigations, after the FDA already using it for accelerated approvals since 1992. Also worth noting of the 1997 FDA Modernization Act was the amendment to the Public Health Service

[3] PETER BARTON HUTT et al., FOOD AND DRUG LAW 694 (Robert C. Clark et al. eds., Foundation Press 4th ed. 2014).
[4] Daniel Carpenter et al., *Drug-Review Deadlines and Safety Problems*, 358 N ENGL J MED 1354,1354 (2008).
[5] LARS NOAH et al., LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS 210-211 (Lars Noah et al eds., Foundation Press. 2002).

doi:10.6342/NTU202302527

Act to eliminate the establishment license and the product license originally required for biologics, codifying FDA's administrative BLA/biologics license such that the FDA's processes for reviewing BLAs paralleled those of NDAs. Since then, vaccines, considered a type of biologics, have been reviewed under processes similar to drugs in the FDA.[6]

It was not another two decades later that a comprehensive amendment to the FD&C Act focused on instituting risk evaluation and management into drug approvals. Although the FDA's risk management system was first introduced by Commissioner Jane Henney's Task Force on Risk Management's report Managing the Risks from Medical Product Use: Creating A Risk Management Framework (1999),[7] it was the FDA Amendments Act of 2007 (FDAAA) that authorized FDA to require manufacturers to develop Risk Evaluation and Mitigation Strategies (REMS) for product with exceptional circumstances.[8] The FDAAA also requires the FDA to establish strict registration and results reporting mechanism for all Phase II-IV trials, adding the emphasis on the need for transparency. Furthermore, the FDAAA created the Sentinel System for post-marketing safety surveillance, in an attempt to make reporting widely available across different actors, not limited to sponsors.[9] Specifically, this resulted in the addition of the following to Title 21 of the United Stated Code: clause (3) and (4) to subsection 355(k), imposing post-approval risk identification and drug safety data analysis responsibilities on the FDA. Several

[6] HUTT et al., *supra* note 3, at 1130-1132.
[7] *Id*. at 724.
[8] Shannon Gibson & Trudo Lemmens, *Overcoming "Premarket Syndrome": Promoting Better Postmarket Surveillance in an Evolving Drug-Developement Context*, *in* FDA IN THE 21ST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 268, 276-279 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).
[9] Geoffrey Levitt, *Drug Safety Communication*, see id. at 328,331.

doi:10.6342/NTU202302527

subsections were added to construct a comprehensive post-approval risk management and mitigation structure, including risk evaluation and mitigation strategies (Sec. 355(p)), postmarket drug safety information for patients and providers (Sec.355(r)), risk management strategies to be proposed by sponsors (Sec. 355-1(a)), definitions related to terms used in the above-mentioned regulations (Sec. 355-1(b)), contents of risk evaluation strategies (Sec. 355-1(c)), minimal strategy (Sec. 355-1 (d)), and a subsection for the establishment of a Drug Safety Oversight Board (Sec. 355-1(j)).

Five years later, the FDA Safety and Innovation Act of 2012 (FDASIA) officially codified the numerous existing pathways for approval, and introduced the new breakthrough therapy pathway to allow both surrogate and preliminary clinical endpoints for evaluation of drug efficacy in market approval reviews. This new pathway is available to investigational drugs for serious or life-threatening conditions, whose preliminary clinical evidence shows that the drug brings substantial improvement over existing therapies, not only for when there is unmet medical needs.[10] Thus Section 356 was amended to include breakthrough therapy pathway into fast track, with the designation of accelerated approval (using surrogate or intermediary endpoints) and priority reviews (requiring reviews to be concluded within 60 days of receiving the application). The 21st Century Cures Act, signed into law at the end of 2016, further accelerated the development of medical product development by incorporating diverse perspectives, modernizing clinical trial designs and providing development assistance for medical countermeasures. In terms of modernizing clinical trial designs, the Congress mandates the US FDA to

[10] Gibson & Lemmens, *supra* note 8, at 273.

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provide guidance on complex and adaptive clinical trial designs, and allow for public meetings to discuss alternative clinical trial designs with sponsors. Furthermore, the Congress also recognizes the utility of realworld data for new drug approvals, especially in the post-market evaluation phase.[11]

To address the "Drug Lag" since the US FDA overtook the evaluation of drug efficacy in 1962, the US FDA has created a bundle of four programs to speed the development and approval of drugs addressing serious unmet medical needs. While the Fast Track Designation was the first to be included in the FD&C Act in 1997, the Priority Review Designation was established through CDER Manual of Policies and Procedures was initiated even before the 1997 FDA Modernization Act. Although both tracks provide for sped up approval through increased meetings with the FDA and providing information and data on a rolling basis, the two tracks are independent of each other and must be applied for separately. Eligibility for both tracks are similar, but the priority review designation requires the FDA to complete review within 6 months. Furthermore, the breakthrough therapy designation introduced as part of the 2012 FDASIA focuses on therapies that may demonstrate substantial improvement on a clinically significant endpoint over available therapies. Finally, the most confusing of which would be the accelerated approval process, majorly because of the discrepancy between the FDA regulations and the amendments enacted by Congress. FDA published Accelerated Approval Subpart H as early as 1992 to approve NDA's on the basis of validated surrogate endpoints that are reasonably likely to predict clinical benefit. The Congress enacted its own version of accelerated approval as part of the FDA

[11] See subtitle C: Modern Trial Design and Evidence Development of 21st Century Cures Act.

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Modernization Act of 1997, allowing both a clinical and surrogate endpoint, but did not authorize restricted distribution.[12] Observers noted that in combination, the staggered approval model combines flexible market entry and more substantial post-market evidence generation and assessment.[13]

B. Evidence Considered in Acceleration Programs

The current regulations on drug marketing approval are coded in Subchapter V of the FD&C Act. Section 355 of Title 21 describes the regular market approval application process and standards, Section 356, 356-1 is dedicated to accelerated approval pathways, including fast track products, expedited approval for new qualified infectious diseases, and accelerated approval of priority countermeasures. Section 360a-1 deals with clinical trials, Section 360n, 360n-1, 360aa-ff-1 sets exceptions for certain diseases and treatments, such as for tropical diseases, particular infectious diseases, rare diseases and conditions, and rare pediatric diseases. Finally, Section 360bbb-3a and below regulates emergency use authorizations. Special attention will be given to the procedures and standards of emergency use authorizations in Chapter 4. This part will focus on the evidence review standards, especially regarding its comparison with standard new drug approvals, as coded in the regulations.

At a baseline, Section 355 requires the US FDA to complete reviews and proceed with a decision within 180 days of completing the filing of submissions. The US FDA is mandated to approve drugs and products for use if no grounds specified in the section to deny the approval exists, but may also propose a

[12] HUTT et al., *supra* note 3, at 756.
[13] Gibson & Lemmens, *supra* note 8,at 274.

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hearing if status is unclear.[14] Of course, the US FDA enjoys the authority to reject the application outright if conditions in Section 355(d) exist: (1) application does not include adequate tests by all methods reasonably applicable to show that the drug is safe for proposed use; (2) results from such tests show drug is unsafe or do not show that the drug is safe for use for proposed use; (3) manufacturing evaluation cannot support the product's identity, strength, quality and purity; (4) there is insufficient information whatsoever to determine that the drug is safe for use; (5) lack of substantial evidence that the drug will have the effect it purports; (6) application lacks patent information; (7) false or misleading labelling information or other considerations based on fair evaluation of all material facts.[15] From the items listed in the clause, the FD&C Act dedicates 3 prongs on safety, and 1 on efficacy. Regarding safety, the US FDA is authorized to evaluate safety based solely on data submitted by sponsor alone, but may also base their determination on additional information not submitted by the sponsor. The data must show that the drug is "safe for use"; if the data shows that the drug is unsafe, or that safety cannot be demonstrated, the drug cannot be approved for use. For efficacy, the section mandates that the US FDA evaluate all information regardless of whether the sponsor submits it. The clause also gives definition for substantial evidence: "*the term "substantial evidence" means 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*

[14] 21 U.S.C. §355(c)(1).
[15] 21 U.S.C. §355(d).

doi:10.6342/NTU202302527

effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." Risk-benefit assessment framework for new drug approval has also been added to the clause in 2012. In other words, in traditional new drug approval schemes, without considerations for acceleration, there must be evidence consisting of adequate and well-controlled investigations (which must include clinical investigations), judged fairly and responsibly by experts with relevant experience that the drug will have alleged efficacy, and safety evaluation must show that the drug is safe for use. The section does not give further explanation as to what is adequate, well-controlled, fair or reasonable.

Section 356 regulates the expedited pathways for drug and biologics approval. Subsection 356(a) is for breakthrough designation, Subsection 356(b) for fast track products, and Subsection 356(c) for accelerated approval. Breakthrough designations are for drugs or biologics for a serious or life-threatening diseases or condition, that demonstrate substantial improvement over existing therapies based on clinically significant endpoints.[16] Expediting actions for breakthrough therapies include: more accessible meetings and communications between sponsors and US FDA review team, increased cross-discipline review team collaborations, and facilitating efficient clinical trial design. For efficient clinical trial designs, due to the substantial improvement potential of the new drug, clinical trials may minimize the number of patients exposed to less efficacious placebos or controls.[17] Fast track products are those that are intended for a life-threatening or serious disease or condition, and have

[16] 21 U.S.C. §356(a)(1).
[17] 21 U.S.C. §356(a)(3)(B).

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the potential to address unmet medical needs or is designated a qualified infectious disease product.[18] No evidence related expedition actions are outlined in the subsection. Accelerated approval is also limited to products for life-threatening or serious diseases or conditions, but is specified to "*has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.*"[19] Surrogate markers indicated in qualifications should be biomarkers that have demonstrated reasonable likeliness to predict clinical benefit, through epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence using scientific methods or tools.[20] In comparison with the breakthrough designation or fast track, accelerated approval also imposed limitations on the approvals it gives. Sponsors are required to conduct post-approval studies to demonstrate the clinical benefits of the product and/or submit all promotional materials to the US FDA for verification prior to dissemination.[21] Furthermore, if the US FDA finds that the sponsor failed to conduct any post-approval trials, or that such trials fail to demonstrate clinical benefit of the drug, the US FDA may withdraw the approval through expedited procedures.[22]

[18] 21 U.S.C. §356(b)(1).
[19] 21 U.S.C. §356(c)(1)(A).
[20] 21 U.S.C. §356(c)(1)(B).
[21] 21 U.S.C. §356(c)(2).
[22] 21 U.S.C. §356(c)(3).

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However, in terms of evaluation of evidence, the FD&C Act does not relinquish on the standards of efficacy and safety. The two clauses that comprise subsection 356(e) seem to present contradicting views of US FDA evaluation of evidence under different approval schemes. Clause 1 specifies that "*The amendments made by the Food and Drug Administration Safety and Innovation Act and the 21st Century Cures Act to this section are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.*" On the other hand, clause 2 dictates that: "*Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 355 of this title (including the substantial evidence standard in section 355(d) of this title). Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective.*"[23] A plausible explanation is that even though flexible and innovative approaches to assessments may be made, the most basic requirements for new drug approvals still require that well-controlled clinical trials support the efficacy of products, as well as sufficient data to show the product is safe for use. As for the adequacy or reasonableness of trials, may be subject to individual standards based on the characteristics of the illness/condition and unmet medical needs not specified on the level of federal law. By way of explanation, this means that the US FDA is endowed with wide discretion as to what constitutes "substantial evidence" when acceleration needs

[23] 21 U.S.C. §356(e).

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are apparent for certain medical products, either through guidance documents or practices reflected in individual approvals.

C. Clinical Trial Requirements: Well-Controlled and Adequate?

The US FDA has since published several guidance documents to describe the evidence requirements of different approval schemes. Guidance documents are neither formal rulemaking nor informal rulemaking under the the Administrative Procedure Act.[24] They are non-binding documents that release the FDA from procedural restraints of binding rulemaking, and have been relied upon by the FDA since the early 1990s in various fields. Although critics have condemned guidance documents and guidelines that operate as de facto rules for escaping procedural safeguards, and pointed out such guidance documents do not offer the an equivalent level of enforceability either inside or outside of the agency, guidance documents that "confer agency views on specific topics" have been recognized by federal law to facilitate FDA day to day operations.[25] While FDA guidance documents setting compliance standards have been more controversial,[26] those giving standards and instructions for drug and vaccine approvals have been relatively well-received. With Code of Federal Regulations outlining only requirements for surrogate markers,[27] the FDA relies heavily on guidance documents to relay its standards for review evidence under different approval pathways.

In a guidance document providing integrated guidance on different expedited schemes published in 2014, the US FDA compares between the

[24] 5 U.S.C. §§554(a), 553(c).
[25] 21 U.S.C. §371.
[26] *See* e.g. Washington Legal Foundation v. Kessler, 800 F. Supp. 26 (D.D.C. 1995), United States v. Bioclinical Systems, Inc., 666 F. Supp. 82 (D. Md. 1987).
[27] 21 C.F.R. §341 Subpart H.

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different schemes and gives some examples for the level of evidence required for each scheme. For breakthrough designations, the guidance allows early communication between the sponsor and US FDA to discuss alternative clinical trial designs, such as adaptive trial designs, enrichment strategies, use of historical controls, and even interim analysis by data monitoring committees. The US FDA also recognizes the potential need for smaller trials or even single-arm trials (meaning it could be without controls) especially in the context of rare diseases for which clinical trials would be difficult to conduct but mechanisms and disease development are relatively well-understood, such that clinical trials are more efficient and exposer fewer patients to less efficacious treatments.[28]

For accelerated approval, the guidance document first iterates that the pathway would be most useful for diseases that take extended periods of time to development (such as cancer and HIV/AIDs), but also potentially useful in acute diseases where mortality or morbidity incidents occur rarely.[29] The guidance also defines the two basis for which accelerated approval pathways are based on: surrogate endpoints and intermediate clinical endpoints. Surrogate endpoints are defined as: "*a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.*"[30] Examples of surrogate markers include HIV viral load, outcomes of 6-month follow-up treatment for pulmonary tuberculosis, and tumor shrinkage on radiographic imaging. These

[28] DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS - DRUGS AND BIOLOGICS 14 (2014).
[29] *Id*. at 16.
[30] *Id*. at 17.

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markers do not speak directly to the mortality or morbidity of the disease, but can predict mortality and morbidity reasonably. Intermediate clinical endpoints are clinical endpoints other than mortality or morbidity. These endpoints may be used for both traditional approval or accelerated approval. The latter is required only when the relation between the intermediate clinical endpoint and mortality and morbidity is not well-established, such as when short-term clinical benefit is reasonably likely to predict long-term benefit, or when the clinical benefit is reasonably likely to predict mortality and morbidity of the illness.[31] Although the guidance document reiterates the federal law wording to emphasize that products undergoing accelerated approval need to meet the same statutory standards for safety and efficacy as that in traditional approval, the guidance states that the difference lies in the "type" of evidence submitted to the FDA. In the case where surrogate or intermediate endpoints are used as endpoints, the applicant should also provide evidence to support the surrogate or intermediate endpoint's relationship with desired clinical benefit. Such evidence would need to include pharmacologic activity and preferably clinical data as well. The guidance document thus provides some instructions on the type and nature of the evidence required to establish such relationship.[32]

In the case of accelerated approval, conditions such as reviewing promotional materials and confirmatory trials may be imposed on the applicants. Confirmatory trials must be conducted with due diligence, meaning it must be completed promptly to make a final determination. If the applicant

[31] *Id*. at 18.
[32] *Id*. at 19-21.

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fails to do so or the trials results do not predict the clinical benefit of the product, the FDA is authorized to withdraw the accelerated approval.[33]

Priority review designations can be made when the product exhibits the potential to be a significant improvement in safety or efficacy, such as when it reduces treatment-limiting adverse events, increases patient compliance, or shows efficacy and safety for a new subpopulation. The guidance document points out that in such cases, although randomized trials comparing the product and existing treatment are preferred, trials with historical controls or other kinds of controls are tolerated. Once a product is given priority review designation, the FDA must take action on its application within 6 months.[34]

According to the guidance document, the FDA seems to be rather reluctant, or perhaps held back by the requirements of the federal law, to loosen the standard of safety and efficacy in expedited approval schemes. However, there seems to be some room in the "type" of evidence for approval: not only are surrogate markers and intermediate clinical endpoints acceptable to shorten trial duration, adaptations to clinical trials are also heavily relied upon by the FDA to bring medical products to the market faster. The guidance document also requires for every type of expedited approval scheme, that the applicants communicate their decisions for trial design and administration as early as possible, and that type of evidence can only be determined on a case-by-case basis. Therefore this Chapter will proceed to examine two cases that utilized expedited approval under different circumstances to elucidate how far the FDA

[33] *Id*. 22-24
[34] *Id*. 25.

doi:10.6342/NTU202302527

is willing to go in terms of alternative trial designs and perhaps even safety and efficacy requirements under time pressure.

II. Risk and Benefit Analysis Under Priority: the First NOAC Approval

A. Introduction of a New Hope or New Risks?

When dabigatran (marketed as Pradaxa) was approved by the FDA for stroke prevention in non-valvular atrial fibrillation patients in 2010, it was the first new oral anticoagulant for over half a century, leading the new class of anti-coagulants: novel oral anticoagulants (NOAC). Indeed, since its development and the publication of its RE-LY trial on the New England Journal of Medicine (NEJM) in 2009, dabigatran has been widely anticipated to revolutionize the prevention of stroke. It was not surprising that it was granted priority review status in early September, 2010, and the advisory committee that reviewed its application recommended its approval unanimously within a month. Even so, throughout its investigation, trial proceedings, and even after its approval, questions were raised regarding trial design, determination of superiority, and its safety with a lack of antidote. These concerns subsequently led to lawsuits against the sponsor Boehringer Ingelheim that were ultimately settled in large sums, but dabigatran eventually established its place for control of cardiovascular diseases.

Thromboembolic disease is a major cause of mortality and morbidity caused by an excessive stimulation of coagulation, thus anticoagulant therapy that inhibits the blood coagulant cascade has been important to patients with high coagulation risks.[35] Longstanding anticoagulants like heparin and warfarin

[35] Joanne van Ryn et al., *The Discovery of Dabigatran Etexilate*, 4 FRONT PHARMACOL 12-1,12-1 (2013).

doi:10.6342/NTU202302527

have problems of slow onset, narrow therapeutic window, need for frequent constant monitoring of coagulation status, and strict dietary restrictions, which made the medication difficult to administer for a mass of patients. On this background, scientist began investigating agents that targeted different steps of the coagulation cascade beginning in the 1990s. Ximelagatran was the first orally available direct thrombin inhibitor to reach phase 3 clinical trials,[36] whose results of non-inferiority to warfarin propelled the drug to be approved in the EU for stroke prevention in 2005. Unfortunately, increased cases of liver injury after long-term use of the drug and concerns about its efficacy led to its withdrawal the next year.[37]

Dabigatran stood out as a another promising candidate with its favorable selectivity profile and activity performance, and quickly entered clinical trials after an orally active prodrug was synthesized.[38] Several trials for the drug commenced worldwide, for indications like replacement of dual anti-platelet treatment (RE-DEEM), acute deep vein thromboembolism treatment (RECOVER), and stroke prevention. A total of 40 phase 1 studies, 6 phase 2 studies and 4 phase 3 studies were completed at the time Boehringer Ingelheim submitted its application for drug approval at the FDA.[39]

Boehringer Ingelheim first submitted a new drug application to the FDA on December 15, 2009,[40] but their application was returned with a Refuse to File letter due to easily detected errors in the databases in early 2010.[41] The sponsor

[36] Charles W Francis, *Ximelagatran: A New Oral Anticoagulant*, 17 BEST PRACTICE & RESEARCH CLINICAL HAEMATOLOGY 139,143 (2004).
[37] Christopher J Boos & Gregory YH Lip, *Ximelagatran: An Eulogy*, 118 THROMB RES 301,301 (2006).
[38] van Ryn et al., *supra* note 35, at 2.
[39] FOOD AND DRUG ADMINISTRATION, CLINICAL REVIEW FOR NDA 022512 28 (2010).
[40] FOOD AND DRUG ADMINISTRATION, APPROVAL LETTER FOR NDA 022512 1 (2010).
[41] FOOD AND DRUG ADMINISTRATION, CROSS DISCIPLINE TEAM LEADER REVIEW FOR NDA 22512 5 (2010).

doi:10.6342/NTU202302527

met quickly with the FDA to discuss the refusal, performed a quality check on the data accordingly, and resubmitted their application on April 19, 2010.[42] Following a filing meeting in May, the Priority Designation Letter was issued July 2, 2010. After several information requests, the FDA held an Advisory Committee meeting for dabigatran on September 20, 2010, which finally approved dabigatran for use in patients with atrial fibrillation.[43] Throughout the review, advisory meeting and even post-approval, trial design, efficacy determination and risk benefit analysis proved to be challenging for all actors involved.

B. Trial Design: Challenging the Double-Blind Gold Standard

The Randomized Evaluation of Long term anticoagulant therapY (RE-LY) trial was the single pivotal trial for Boehringer Ingelheim's application. The study began enrollment in 2005, and eventually enrolled 18,113 patients diagnosed with atrial fibrillation with at least one risk factor for stroke by 2007. Subjects were followed to 2008-2009 for incidence of stroke (including hemorrhagic) and systemic embolism (the designated primary endpoint). Not only was the size unprecedented for patients with atrial fibrillation,[44] trial indication to prevent stroke in all patients with atrial fibrillation was also considerably ambitious. Nonetheless, the trial design had a major imperfection that led to complicated discussions within the approval process and relentless critic after its marketing.

[42] FOOD AND DRUG ADMINISTRATION, *supra* note 40, at 1.
[43] FOOD AND DRUG ADMINISTRATION, REGULATORY PROJECT MANAGER OVERVIEW FOR NDA 022512 3 (2010).
[44] Michael D Ezekowitz et al., *Rationale and Design of RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared with Dabigatran*, 157 AM HEART J 805,806 (2009).

doi:10.6342/NTU202302527

The RE-LY trial was designed as a hybrid study, which involved using a double-blind and an open-label approach to designating subjects into three branches of the trial. Randomization to warfarin or dabigatran was open-label, while the subjects that received dabigatran were randomized to the 110mg branch or 150mg branch in a double-bling approach. As we know, a double-blinded prospective randomized controlled trial is the golden standard for investigating a new medical product.[45] So how was this phase III clinical trial involving so many subjects accepted by the US FDA as "substantial evidence" to approved dabigatran for stroke prevention?

After approving the drug for Investigational New Drug clinical trials in 2003 and an End of Phase 2 meetings in 2005, the sponsor submitted the protocol for their single pivotal phase 3 trial, the RE-LY trial to the US FDA for advice and a Special Protocol Assessment. The US FDA gave direct instructions for trial design in the proceedings, most notably of which emphasized establishing non-inferiority compared to optimal warfarin control, need of a large safety database with a special note on liver toxicity, and concerns on trial design. The US FDA repeatedly expressed its preference for a double-blind trial and questioned the sponsor for justifications for its open-label design, but eventually gave in to the explanations the sponsor provided.[46] The sponsor responded that given the difference in administering and monitoring the two different drugs, blinding the trial could result in inaccurate representation of warfarin's safety and efficacy (if, for example, it were not monitored), and

[45] Ted J Kaptchuk, *The Double-Blind, Randomized, Placebo-Controlled Trial: Gold Standard or Golden Calf?*, 54 J CLIN EPIDEMIOL 541,541 (2001).
[46] FOOD AND DRUG ADMINISTRATION, *supra* note 39, at 18.

doi:10.6342/NTU202302527

would make evaluating when to stop the anticoagulants in the need of surgery or other procedures difficult.[47]

During the approval process, the review team and the advisory committee also felt compelled to explain their rationale for accepting an open-label study for the basis of approval. The reviewer stated frankly that were they to review a single open-label study, the interpretation would be difficult, especially with the inconsistency between the double-blinded and open-label studies of ximelagatran in mind. However, the review team declared that its confidence was boosted by the RE-LY's move to incorporate a randomized double-blind comparison of the lower and higher doses of dabigatran, and the statistically compelling difference convinced the review team that the study was "fairly well managed."[48] Particularly, the reviewer accepted the PROBE design, a prospective, randomized, open-label, blinded endpoint evaluation study, despite the somewhat unfavorable rate of unblinding that occurred during adjudication.[49] The medical reviewer still made a detailed comparison between the reporting of endpoint incidences between the warfarin arm and the dabigatran arms to look for hints of bias, and concluded that it was negligible.[50] In other words, the reviewer found the study design and conduct to be not optimal, but reasonable for the conclusions that it set.[51]

C. Was Superiority Important?

Whether dabigatran was actually superior to warfarin in stroke prevention for patients with atrial fibrillation also sparked debate both within

[47] FOOD AND DRUG ADMINISTRATION, MINUTES OF ADVISORY MEETING FOR DABIGATRAN REVIEW 115 (2010).
[48] FOOD AND DRUG ADMINISTRATION, SUMMARY REVIEW FOR NDA 22512 7 (2010).
[49] FOOD AND DRUG ADMINISTRATION, *supra* note 47, at 115-116.
[50] FOOD AND DRUG ADMINISTRATION, *supra* note 39, at 76-78.
[51] FOOD AND DRUG ADMINISTRATION, *supra* note 47, at 119.

doi:10.6342/NTU202302527

the reviewers and among physicians and patients receiving the drug. The RE-LY trial was initially designed as an non-inferior trial, and despite some difference of opinion on where the standard for inferiority is drawn, that did not present as the major issue after the trial was completed.[52]

The review team initially found the RE-LY trial to show dabigatran non-inferior, but not superior, to warfarin for stroke prevention in patients with atrial fibrillation. In the trial with more than 18,000 subjects, the hazard ratio of dabigatran compared to warfarin was 0.66 (95% confidence interval 0.53-0.82, $p<0.003$ for superiority) for the 150mg dose and 0.91 (95% confidence interval 0.74-1.11, $p<0.0001$ for noninferiority) for the 110mg dose.[53] The medical reviewer on efficacy took a close look at the data for the primary endpoint and all of the secondary endpoints, taking care to point out the subjects whose data included errors or that should have been excluded from analysis.[54] The reviewer specifically addressed whether dabigatran could be found to be superior to warfarin for the endpoints of the study, but concluded that it was the quality of control of INR for patients taking warfarin that was the determining factor. The review report described dabigatran's superiority over warfarin as basically non-existent, adding that "there is little incentive ……. to migrate a patient well controlled on warfarin to dabigatran." [55] Furthermore, the reviewers pointed out that the superiority of dabigatran was mostly gained in centers where cases in the warfarin arm had poor INR control, stating plainly that "virtually all of the reduction in death was attributable to centers where INR control was worse than

[52] FOOD AND DRUG ADMINISTRATION, *supra* note 39, at 54.
[53] *Id*. at 9.
[54] *Id*. at 58-66.
[55] FOOD AND DRUG ADMINISTRATION, OFFICE DIRECTOR MEMO FOR NDA 22512 2 (2010).

doi:10.6342/NTU202302527

the median."[56] The reviewers concluded that "even if dabigatran had been statistically significantly superior to warfarin after correction for multiplicity, we would have been reluctant to declare superiority because the efficacy of warfarin appears to be dependent on how it is used."[57]

However, the battle for superiority did not end here. In early 2012, Boehringer Ingelheim applied for a change in labelling and approval for dabigatran, so that they could claim superiority without having to address INR control quality in warfarin control groups. Absent any further clinical trials, the FDA approved of the sponsor's application to amend 2010 approved labelling, such that the labelling stated "Pradaxa 150 mg twice daily was superior in reducing ischemic and hemorrhagic strokes relative to warfarin." The reviewer stated "a superiority claim does not guarantee superior efficacy (over another therapy) in all patients with a disease, just as an efficacy claim should not be taken as a guarantee of efficacy in all patients who receive a drug." The review further added that though information on INR control in different settings was accurate, it was not essential scientific information for the safe and effective use of the drug. Furthermore, rivaroxaban, which was approved in mid-2011, was not required to include similar language in its labelling.[58] This small episode did not go unnoticed by physicians and patients struggling with dabigatran. The Project on Government Oversight Report on Dangerous Decision-Making at the FDA bombarded the US FDA for permitting Boehringer Ingelheim to make a stronger claim for dabigatran than what it was approved for, citing an email

[56] FOOD AND DRUG ADMINISTRATION, *supra* note 48, at 15.
[57] *Id*. at 10.
[58] FOOD AND DRUG ADMINISTRATION, MEMORANDUM: DABIGATRAN (NDA 22-512) AND LABELING PERTAINING TO EFFICACY 3 (2012).

doi:10.6342/NTU202302527

revealed from the class-action lawsuit against Boehringer Ingelheim that the FDA wanted to avoid discussion on this change with other actors.[59] After the change, dabigatran promoted itself as superior to warfarin in preventing stroke. The lengthy discussion on whether dabigatran achieved superiority essentially disappeared for patients and clinicians that were not part of the approval process.

D. Unavailable Safer Options: Antidotes and Testing

Bleeding and liver injury were the two safety issues of major concern for dabigatran. Liver toxicity was watched closely due to prior experience with ximelagatran. The safety reviewer and two hepatologist experts scoured the dataset for potential cases of liver injury, and examined their clinical history and data closely,[60] and declared neither warfarin or dabigatran responsible for the liver injuries. 4 post-market cases reported from countries where dabigatran has been approved for prevention of thromboembolism were also investigated, but there was insufficient detail to permit an adequate review.[61] Luckily, or perhaps because of this precaution, liver injury cases did not become central to the discussion of the safety of dabigatran, at least not compared to bleeding.

Since dabigatran is a blood-thinner that disrupts coagulation equilibrium, bleeding is an expected adverse event. The problem is, how much bleeding, how severe of bleeding can be tolerated in light of the drug's efficacy? Additionally, a question that was not directly addressed in the approval process but fiercely debated by victims of bleeding was: was the bleeding manageable?

[59] PROJECT ON GOVERNMENT OVERSIGHT, PROJECT ON GOVERNMENT OVERSIGHT, DRUG PROBLEMS: DANGEROUS DECISION-MAKING AT THE FDA 19 (2015).
[60] FOOD AND DRUG ADMINISTRATION, *supra* note 39, at 102-110.
[61] FOOD AND DRUG ADMINISTRATION, *supra* note 48, at 12.

doi:10.6342/NTU202302527

If safer options to using the drug was unavailable, should the US FDA have waited in granting approval?

Finding a dose-related risk to bleeding, the medical reviewers were careful to analyze the risks and benefits of using dabigatran as prevention for stroke. The reviewers emphasized that the value of preventing strokes when compared to the value of preventing life-threatening bleeds is likely not equivalent. The reviewers evaluated the bleeding events by stratifying the types of bleeding by different scores of severity,[62] and finally made the judgement that reducing the high occurrence of irreversible and debilitating or mortal strokes (about 70% of all stroke events) was more worthwhile than preventing a major or even a life threatening bleed, but that the difference between the two could be partially mitigated by controlling dabigatran concentrations.[63]

The Advisory Committee also discussed whether to approve both doses studied in the RE-LY trial, and whether there was the need to explore the benefits of an even higher dose. While they agreed that the higher dose was superior to the lower dose, the primary reviewer put the difference between them in simple numbers: "for every 1000 patients treated for 1 year with dabigatran 150mg instead of 110mg, you will have perhaps one fewer death, 4 fewer strokes, and maybe as many as 4 hemorrhagic events likely to require some kind of intervention." The reviewers also responded to calls for approving the 110mg dose to provide an alternative to patients and physicians who observe bleeding on a higher dose,[64] by expressing their concern that a lower dose may be over-utilized by doctors who like to "play it safe", and thus made the

[62] FOOD AND DRUG ADMINISTRATION, *supra* note 39, at 85-100.
[63] FOOD AND DRUG ADMINISTRATION, *supra* note 41, at 30.
[64] FOOD AND DRUG ADMINISTRATION, *supra* note 55, at 2-4.

doi:10.6342/NTU202302527

difficult decision to approve only the 150-mg dose.[65] The primary reviewer further elaborated that the proper response to dosage concerns would be "a marketing and educational campaign to get patients and physicians to understand the risk-benefit calculus so that they make the correct therapeutic decision, rather than enabling an incorrect decision."[66] This speaks to the reality that patients and practicing physicians play little role in the approval process.

Finally, the Advisory Committee utilized its authority endowed by Section 505-1 of the FD&C Act to require the submission of a risk evaluation and mitigation strategy (REMS) for concerns of bleeding for the drug. The FDA deemed providing a Medication Guide to make patients aware of serious risks of the drug sufficient,[67] in addition to post-marketing requirements based on Section 505(o)(3) of the FD&C Act. Considering the incomplete development of the new pharmacovigilance system the FDA is required to establish under section 505(k)(3) of the FD&C Act, the FDA determined that further post-market in vitro studies on drug mechanism for GI bleeding and drug interaction would be needed. The sponsor is also required to report periodically on the status of any study or clinical trial undertaken to investigate a safety issue, as well as other details of such studies per risk evaluation and mitigation strategy requirements.[68]

After dabigatran obtained market approval and became widely used for stroke prevention for patients in atrial fibrillation and other off-label indications, devastating stories of patients bleeding to death drew attention to

[65] FOOD AND DRUG ADMINISTRATION, *supra* note 48, at 14-15.
[66] FOOD AND DRUG ADMINISTRATION, *supra* note 55, at 4.
[67] FOOD AND DRUG ADMINISTRATION, *supra* note 48, at 16.
[68] FOOD AND DRUG ADMINISTRATION, *supra* note 40, at 3.

doi:10.6342/NTU202302527

the risks of the drug.[69] The adverse reactions were first reported as cases in medical journals and dramatic coverage on the news,[70] but then came in the form of lawsuits. New York Times first told stories of devastating bleeding and helpless doctors, pinning the blame on the fact that there was no existing antidote for the bleeding caused by dabigatran at the time. Interestingly, the article pointed out how the medical community responded differently to the drug: "The problem is that people that prescribe this…… are cardiologists and family practitioners…… the people that see the harm are your E.R. docs and your trauma doc." The article cited critics that called for better disclosure and limitation on use of the drug until an antidote is available.[71] A non-profit organization that follows adverse events of FDA approved drugs in the USA by analyzing US FDA adverse event reports and data from the IMS, Institute for Safe Medication Practices (ISMP), reported more than 300 cases of hemorrhages and thromboembolism in patients using dabigatran within 12 weeks of the drug obtaining FDA approval, leading them to question whether the drug is effective in preventing clot-related adverse events.[72] Into the second and third year of observing oral anticoagulants constituting a significant part of adverse events reporting and dabigatran's death risk 5-fold compared to warfarin, the organization called for US FDA to reconsider the single dose approval, promoting regular testing of anticoagulation effect, and identifying suitable populations for dabigatran to make using this drug safer and not just

[69] Mary Ross Southworth et al., *Dabigatran and Postmarketing Reports of Bleeding*, 368 N ENGL J MED 1272,1272 (2013).
[70] See e.g. Sarah T Garber et al., *Neurosurgical Complications of Direct Thrombin Inhibitors—Catastrophic Hemorrhage after Mild Traumatic Brain Injury in a Patient Receiving Dabigatran: Case Report*, 116 J NEUROSURG 1093 (2012).
[71] Katie Thomas, *A Promising Drug with a Flaw*, THE NEW YORK TIMES, November 3, 2012.
[72] INSTITUTION FOR SAFE MEDICATION PRACTICES, QUARTERWATCH: 2010 QUARTER 4 12 (2010).

doi:10.6342/NTU202302527

easier to use.[73] The organization brought the results of their analyses and suggestions to Boehringer Ingelheim, the sponsor responded that an meta-analyses pooling 5 different clinical trials showed similar major bleeding outcomes between dabigatran and warfarin.[74]

Thousands of lawsuits were brought against Boehringer Ingelheim since 2010 in federal courts, most claiming that the manufacturer misled physicians and patients about the bleeding risks of dabigatran by hiding the need to monitor coagulation status and failure to develop an antidote alongside the blood thinner. The cases were consolidated into a class action against Boehringer Ingelheim and the researchers that led the RE-LY trial in May 2013,[75] and focused on the four topic areas: (1)the launch of Pradaxa (dabigatran's commercial name) in the United States; (2)the sales and marketing of Pradaxa; (3)involvement with the cross-sectional relationship between sales and marketing and regulatory affairs; and (4) international sales and regulatory issues related to Pradaxa.[76]

The presiding federal judge David R. Herdnon of the United States District Court in East St. Louis, ordered the company to release internal documents that revealed discussions on the need for and difficulty to blood monitoring in patients taking dabigatran.[77] The employees have noted that regular testing might have made taking dabigatran safer for patients and reduce bleeding, however, this would essentially strip dabigatran of its advantage over

[73] INSTITUTE FOR SAFE MEDICATION PRACTICES, QUARTERWATCH: 2012 QUARTER 2 (2012); INSTITUTE FOR SAFE MEDICATION PRACTICES, QUARTERWATCH: 2011 QUARTER 4 (2011).
[74] INSTITUTE FOR SAFE MEDICATION PRACTICES, QUARTERWATCH: 2012 QUARTER 2, at 14-16.
[75] Steve Buist, *Trial and Errors? MAC, HHS Sued over Drug Safety*, THE HAMILTON SPECTATOR, 2014.
[76] Case Management Order Number 50 at 2, In Re Pradaxa (Dabigatran Etexilate) Products Liability Litigation, SD Ill. MDL No.2385 (2014) (3:12-md-02385-DRH-SCW).
[77] Katie Thomas, *New Emails in Pradaxa Case Show Concern over Profit*, THE NEW YORK TIMES, Feburary 7, 2014.

doi:10.6342/NTU202302527

warfarin.[78] The revelation of these emails caused uproar among victims and eventually Boehringer Ingelheim conceded to settle 4100 lawsuits with $650 million.[79]

Besides Boehringer Ingelheim, US FDA responses to the safety issues of dabigatran centered on the numerical analyses of bleeding incidents, and never mentioned the possibility of monitoring to improve safety. A safety announcement on dabigatran in 2011 was based on post-marketing events monitoring through a new initiative called "Mini-Sentinel Program" that assessed medical product safety using administrative-observational databases to investigate the risk of bleeding. Compared to assessing risk through the Adverse Event Reporting System database (AERS), the sentinel program was considered more reliable because it records both the number of patients on either drug and the number of events to calculate the actual rates of bleeding. Initial analyses showed that the incidence of intracranial bleeding and gastrointestinal bleeding was lower in patients using dabigatran compared to warfarin. [80] Additional studies using a similar database collected data on more than 134,000 Medicare patients over 65 using dabigatran and warfarin, and recorded events of intracranial bleeding, gastrointestinal bleeding, myocardial infarction, and death. The observational study found that though intracranial bleeding, clot-related strokes and death risks were lower for patients on dabigatran, rate of gastrointestinal bleeding was higher, supporting US FDA's claim that

[78] Katie Thomas, *Study of Drug for Blood Clots Caused a Stir, Records Show*, THE NEW YORK TIMES, Feburary 6, 2014.
[79] Katie Thomas, *$650 Million to Settle Blood Thinner Lawsuits*, THE NEW YORK TIMES, May 28, 2014.
[80] Food and Drug Administration, *FDA Drug Safety Communication: Update on the Risk for Serious Bleeding Events with the Anticoagulant Pradaxa (dabigatran),* US DEPARTMENT OF HEALTH AND HUMAN SERVICES (November 2, 2012), http://wayback.archive-it.org/7993/20170112031650/http:/www.fda.gov/Drugs/DrugSafety/ucm326580.htm (last accessed May 28, 2022).

doi:10.6342/NTU202302527

dabigatran had a favorable benefit to risk profiles and that no changes were warranted for use.[81] However, such observational studies were harshly criticized by clinicians who performed meta-analysis of existing randomized clinical trials to show that there was a discrepancy between the results.[82] FDA's actions supporting dabigatran use was fiercely attacked by ISMP. The Institute accused US FDA of neglecting the large number of adverse events resulting from dabigatran by only emphasizing the drug's non-inferiority to warfarin, and criticized the US FDA's lack of justification and action to address bleeding risks.[83]

The trials for the four leading cases in the dabigatran case never started because Boehringer Ingelheim settled the 4,100 cases with $650 million on May 28, 2014.[84] Boehringer Ingelheim denying any wrongdoing in agreeing to the settlement, maintaining that the settlement allows "the company to avoid the distraction and uncertainty of protracted litigation over years and years."[85] Boehringer Ingelheim further issued a statement emphasizing patient safety as a

[81] Food and Drug Administration, *FDA Drug Safety Communication: FDA Study of Medicare Patients Finds Risks Lower for Stroke and Death but Higher for Gastrointestinal Bleeding with Pradaxa (dabigatran) Compared to Warfarin,* US DEPARTMENT OF HEALTH AND HUMAN SERVICES (May 13, 2014), http://wayback.archive-it.org/7993/20170111080324/http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm (last accessed May 28, 2022)..

[82] Ilke Sipahi, Seden, Celik, Tozun, Nurdan, *A Comparison of Results of the Us Food and Drug Administration's Mini-Sentinel Program with Randomized Clinical Trials: The Case of Gastrointestinal Tract Bleeding with Dabigatran*, 174 JOURNAL OF AMERICAN MEDICAL ASSOCIATION INTERNAL MEDICINE 150 (2014).

[83] INSTITUTE FOR SAFE MEDICATION PRACTICES, QUARTERWATCH: 2012 QUARTER 4 AND ANNUAL REPORT (2012).

[84] Elaine Silvestrini, *Pradaxa Lawsuits,* DRUGWATCH (June 6, 2022), https://www.drugwatch.com/pradaxa/lawsuits/ (last accessed May 28, 2022).

[85] *Boehringer Ingelheim Announces Comprehensive Settlement of U.S. Pradaxa® (Dabigatran Etexilate Mesylate) Litigation,* BOEHRINGER INGELHEIM (May 28, 2014), https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-announces-comprehensive-settlement-us-pradaxa-dabigatran#:~:text=Ridgefield%2C%20CT%2C%20May%2028%2C,the%20amount%20of%20%24650%20million. (last accessed May 28, 2022).

doi:10.6342/NTU202302527

priority and declaring the company stands behind Pradaxa, though it did not provide additional information or data to be discusses.[86]

Concerns for the risks of using dabigatran did reflect in the delayed approval for its other indications. As previously stated in this chapter, phase III trials for other indications for dabigatran were underway about the same time as the RE-LY trial. For example, the RE-COVER trial studied the safety and efficacy of dabigatran for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Although the results of the RE-COVER trial were also published in 2009, the non-inferiority to warfarin in efficacy and similar safety profile demonstrated in the randomized, double-blind clinical trial with more than 2500 subjects failed to persuade the FDA that dabigatran could be approved.[87] In fact, the drug was not approved until 3 years later, after the results of another three clinical trials that followed trial subjects for a much longer time were published and analyzed that the FDA granted supplement approval for the new indication.[88] Indication for prophylaxis of DVT and PE for patients who have undergone hip replacement surgery was not approved until late 2015,[89] despite the earliest trial showing dabigatran as an effective prophylactic agent being published in 2007.[90]

E. Safer or Faster? – A Privileged Determination

[86] *Response to Recent Media Coverage of Pradaxa® (Dabigatran Etexilate Mesylate),* BOEHRINGER INGELHEIM (February 27, 2014), https://www.boehringer-ingelheim.us/press-release/response-recent-media-coverage-pradaxa-dabigatran-etexilate-mesylate (last accessed May 28, 2022).
[87] Sam Schulman et al., *Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism*, 361 N ENGL J MED 2342 (2009).
[88] FOOD AND DRUG ADMINISTRATION, SUPPLEMENTAL APPROVAL LETTER FOR NDA 022512/S-018 (2014).
[89] FOOD AND DRUG ADMINISTRATION, SUPPLEMENTAL APPROVAL LETTER FOR NDA 022512/S028 (2015).
[90] Bengt I Eriksson et al., *Dabigatran Etexilate Versus Enoxaparin for Prevention of Venous Thromboembolism after Total Hip Replacement: A Randomised, Double-Blind, Non-Inferiority Trial*, 370 THE LANCET (2007).

doi:10.6342/NTU202302527

The debates of the safety of dabigatran seemed to come to an end with the approval of a reversal agent, idarucizumab in late 2015. The antidote received not only priority review but also accelerated approval to address the urgent need to stem bleeding caused by dabigatran.[91] Unfortunately, thousands of deaths have been associated with dabigatran use even before the antidote went into clinical trials. It is true that warfarin, a less than ideal option due to its multiple limitations, has not been adequate for the great number of patients that need to prevent embolisms. In the race to finding an alternative, drug companies looked for easier and faster clinical trial designs, that do not always provide answers to all of the questions. On the one hand, the FDA has called on speed-up functions installed in the previous three decades by basing the approval on a single pivotal trial, discussing the utility of a hybrid trial design with sponsors, and learned from previous experience to watch out for potential adverse effects. On the other hand, the speed and standard with which the FDA approved the drug coupled with the fact that the FDA continued to support the marketing status of the drug failed to promptly answer questions that arose post-market. As Dabigatran makes its standing as standard prophylactic treatment for patients with atrial fibrillation, the post-approval controversies spoke to how practicing physicians and patients, who increasingly did not have roles in the approval process, were shunted aside when their experiences and observations did not match that of the results from well-negotiated and planned trials. Despite the fact that the questionable practices and decisions were made within the applicant Boehringer Ingelheim, and led to the pharmaceutical paying millions in settlements, the intense decision-making process that occurred largely

[91] FOOD AND DRUG ADMINISTRATION, APPROVAL LETTER FOR BLA 761025 (2015).

doi:10.6342/NTU202302527

between the US FDA and the applicant seemed to have consolidated the efficacy and safety determinations for the drug.

III. Breakthrough for Hepatitis C Treatment: sofosbuvir

Another product that presented a major breakthrough and rapid but complicated decision-making process by the US FDA within the past two decades was the antiviral agent sofosbuvir, which targeted hepatitis C. Hepatitis C (HCV) is a disease that affects 3.2 million Americans, and is a direct cause of hepatocellular carcinoma and liver cirrhosis that kills an estimated 10,000 every year in the United States.[92] However, the then treatment regimens using pegylated interferon and ribavirin have been cumbersome, and unavailable to a great portions of patients.[93] With the development of antivirals for different diseases, new regimens for the treatment of HCV free of pegylated interferon and/or ribavirin emerged in the hope of reaching more HCV carriers. Gilead introduced the oral nucleotide inhibitor that would become the backbone of the first all-oral regimen for HCV, sofosbuvir.

The development and review of sofosbuvir is an exciting chronicle of FDA consolidating response to rapid research development by issuing and revising guidance for industry, and a fine example of how FDA handled and received data on a rolling basis. On the other hand, the post-market controversy of the drug involving both approval and patents was mostly spurred by the high price of the drug. Gilead priced sofosbuvir (tradename Sovaldi) at $84,000 per 12 week treatment in the United States, sparking discussion on global marketing strategies and cost-effectiveness of treating HCV.

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[92] Alessio Aghemo & Raffaele De Francesco, *New Horizons in Hepatitis C Antiviral Therapy with Direct-Acting Antivirals*, 58 HEPATOLOGY 428,428 (2013).
[93] FOOD AND DRUG ADMINISTRATION, SUMMARY REVIEW FOR NDA 204671 1 (2013).

doi:10.6342/NTU202302527

A. Synchronized Dancing Partners: the FDA, the FDA, and the Big Pharma

Before we delve into Gilead's development of sofosbuvir and its review, it is helpful to put this narrative in the context of the competitive but cooperative field of direct oral antivirals for hepatitis viruses. HCV treatment is complicated due to the nature of the virus and the diseases it imposes on the human. Different genotypes of the virus have been known to exhibit different levels of disease severity, and have responded differently to the same treatments. On top of this, although HCV may be contracted early, morbidity and mortality resulting from hepatic failure and liver cancer may occur in anytime in the subsequent years of life. This means that clinical trials aimed at evaluating the efficacy of HCV treatments need to differentiate between different genotypes, and may need to rely on intermediate clinical endpoints to evaluate the effect of the products within a designated period of time. As more is known about the virus and disease, the more sophisticated research and approval programs were planned.

Research on Direct-Acting Antivirals (DAA) flourished near the second decade of the 21st century, and came under the spotlight in major gastroenterology conferences. More than 100 abstracts published in the 2010 Annual Meeting of the American Association for the Study of Liver Disease (or the so called the Liver Meeting) addressed preclinical and clinical trial and developments on DAAs. These included the most recent results of various phases of clinical trials, and studies on what factors should be considered when designing trials for DAAs, such as whether to differentiate between specific genotypes, what endpoints to observe, and specific adverse events of interest. In

doi:10.6342/NTU202302527

the 2011 Liver Meeting, studies on 20 different DAAs were published by big pharmaceutical companies like Janssen Pharmaceuticals, Pfizer, Merck, and Gilead.[94] The detailed observations and analysis for development of DAAs for HCV were not only noted by the US FDA, but reciprocated in the guidance documents published to facilitate drug approvals.

The Center of Drug Evaluation and Research (CDER) published a Draft Guidance for Industry on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drug Treatment in September, 2010, and made the document open for public comments. This was introduced after the Antiviral Drugs Advisory Committee held meetings to discuss clinical trial design issues as early as 2006.[95] The Draft Guidance Document was revised in 2013 and 2016, finalized in 2017, and revised again in 2020. For the purposes of understanding its role in the development and approval of sofosbuvir, this chapter will only focus on the 2010 and 2013 draft guidance versions. Overall, the guidance's detailed instructions on clinical trial design reflected the FDA's two major concerns: the benefit of trial subjects and accelerating development. The first concern was addressed by utilizing immediate versus deferred placebo-controlled trials, ensuring trial subjects received effective treatment as soon as possible, and limiting exposure to monotherapy to prevent resistance. The second concern was palpable throughout the entire guidance. The guidance set standards for phase I to phase III trials like number of subjects, preferred regiment and placebo arrangement, and different trial designs for different

[94] Curtis Cooper, *Hepatitis C Treatment Highlights from the 2011 American Association for the Study of Liver Disease Meeting*, 55 CLIN INFECT DIS 418,419 (2012).
[95] Poonam Mishra et al., *Direct-Acting Antiviral Drug Approvals for Treatment of Chronic Hepatitis C Virus Infection: Scientific and Regulatory Approaches to Clinical Trial Designs*, 62 HEPATOLOGY 1298,1299 (2015).

doi:10.6342/NTU202302527

genotypes as prior clinical and research experience has shown that the genotype of virus affected treatment effect immensely.

The draft guidance was revised in 2013 to garner more energy into putting effective DAAs onto the market. One major revision was the need to enroll different genotypes and develop treatment strategies accordingly, reflecting the emerging sense in the academia that response rate to DAAs varied greatly among different genotypes. Another critical adjustment to protocol design was updating the primary endpoint from SVR24 to SVR12. Sustained virological response (SVR), defined as HCV RNA levels below a designated threshold of quantification at certain weeks (12 weeks or 24 weeks) after end of treatment, was the established endpoint for cure.[96] The 2013 guidance added more than a dozen observational studies that supported using SVR24 as the primary endpoint for its correlation with mortality and morbidity outcomes, and cited a study conducted by the FDA examining the correlation between SVR24 and SVR12 in more than 13,000 subjects to justify the use of SVR12 instead of SVR24.[97] This was obviously a significant move to accelerate clinical efficacy studies, because this meant that study outcomes could be analyzed as fast as 6 months from the enrolment of the last subject. However, the guidance still encourages sponsors to submit SVR24 data as post-marketing commitment. Other important acceleration tactics include using historical controls and modeling when appropriate and scientifically sound.[98]

[96] Aghemo & De Francesco, *supra* note 92, at 57.
[97] CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY: CHRONIC HEPATITIS C VIRUS INFECTION: DEVELOPING DIRECT-ACTING ANTIVIRAL DRUGS FOR TREATMENT (DRAFT GUIDANCE REVISION 1) 21 (2013).
[98] Mishra et al., *supra* note 95, at 1299.

doi:10.6342/NTU202302527

Prior to sofosbuvir, boceprevir and telaprevir were bestowed with hope to revolutionize HCV treatment. Despite increased cure rate, the treatments involving the two protease inhibitors still required injections of interferon, had complex dosing schedules, retained undesirable side effects, and did not shorten treatment period. Thus, a window was still left open for better treatment options for HCV, ones that could address more diverse genotypes, and that were easier and more tolerable for patients.[99] Gilead designed and operated clinical trials for sofosbuvir in careful observation of the FDA guidance and academia advancements. Starting in late 2011, Gilead commenced several Phase III efficacy trials, each recruiting specific genotypes and treatment status of HCV infectants, all designating SVR12 as the primary endpoint, and added additional trials to incorporate patients with HIV coinfection and transplant patients. The open-label Phase III Study of Sofosbuvir and Ribavirin (FISSION) that began recruiting in 2011 focused on genotype 2 and 3 treatment naïve patients, compared the efficacy of sofosbuvir + ribavirin for 12 weeks versus pegylated interferon + ribavirin for 24 weeks. On the other hand, the double-blind POSITRON trial, while also studying the efficacy of a 12-week sofosbuvir + ribavirin treatment for genotype 2 and 3 patients, focused on patients that were interferon intolerant, ineligible, or unwilling to take interferon. Efficacy for genotypes 1,4,5 and 6 were studied in the open-label single arm NEUTRINO trial, using a combination regimen of sofosbuvir + ribavirin + pegylated interferon.[100] All trial designs followed the US FDA guidance document closely. If anything fell short of the requirement of the guidance documents, not all

[99] Aghemo & De Francesco, *supra* note 92, at 57.
[100] Please see ClinicalTrials.gov website for trial details: *Clinicaltrials.Gov,* U.S. NATIONAL LIBRARY OF MEDICINE, https://clinicaltrials.gov/ (last accessed May 9, 2022).

doi:10.6342/NTU202302527

populations mentioned in the guidance were studied by Gilead. For example, there were no trials addressing the needs of interferon intolerant type 1 patients. However, in accordance with the guidance, modelling was used to evaluate the possibility of using sofosbuvir in combination with ribavirin in that population.

Interestingly, US FDA officials published an overview of FDA regulations and guidance in a leading hepatology journal explaining its rationale for reviewing HCV DAAs in 2015, elaborating on how and why SVR can be used as primary outcome, historical controls can be used, and modelling to supplement issued unaddressed by clinical trials.[101] This shows that the US FDA not only intakes academic publications to form its guidance, but also takes to the academic forum to campaign and communicate its policies. The reciprocation is a sign that US FDA's loosening of standards based on its observations of scientific evidence were challenged by researchers, and the US FDA found it necessary to reiterate its stance in an open forum. The exchanges of opinions ultimately led to a smoother approval process, as we can observe in the approval for sofosbuvir.

B. Improved Acceleration: PDUFA V

Gilead first submitted its New Drug Application on April 8, 2013, a Antivirial Drugs Advisory Committee Meeting was convened on October 25, 2013,[102] and approval was issued on December 6, 2013. Chronologically, the application was reviewed by the advisory committee at a bit over 180 days after submission, and approved about two months after the advisory committee meeting, marking its reviewing term at 242 days. Albeit not remarkably fast for

[101] Mishra et al., *supra* note 95, at
[102] FOOD AND DRUG ADMINISTRATION, MEDICAL REVIEW(S) FOR NDA 204671 2 (2013).

doi:10.6342/NTU202302527

FDA approvals at that time, the review exceeded the Prescription Drug User Fee Act (PDUFA) V program expectations, which was part of the FDA's efforts to systematically speed up drug reviews.

Introduced in 1992, the PDUFA programs aimed to revolutionize the slow and unpredictable FDA drug review process. With added funds from user fees, the FDA hired additional staff and upgraded its information technology systems, so as to meet review performance goals and predictable timeframes for NDAs and BLAs. PDUFA was originally authorized for a five year term, and has since been reauthorized every five years.[103] PDUFA V, authorized for fiscal years 2008-2012, included a new review program for New Molecular Entity (NME) NDAs and original BLAs to improve transparency and communication between the FDA and applicants.[104] Under the PDUFA V program, the target time for application review for priority reviews and standard reviews were 6 months and 10 months respectively. However, for New Molecular Entities (NMEs) and original Biologics License Applications (BLAs), the review clock would only start ticking after the FDA filed the application for review, instead of the on the date of receiving the application, which gives the FDA an additional 60 days.[105] Pre-submission, mid-cycle and late-cycle meetings were

[103] Effectively, the PDUFA programs were revised every five years. PDUFA I begin collecting user fees and using them to fund reviews, PDUFA II expanded the use of funds to investigational phases and increase communication between FDA and relevant actors. PDUFA III further expands the use of funds to preclinical periods and a three-year post-approval period. PDUFA IV focused on improving post-market drug safety monitoring. See SUSAN THAUL, PRESCRIPTION DRUG USER FEE ACT (PDUFA): 2012 REAUTHORIZATION AS PDUFA V 4 (Congressional Research Service. 2013).

[104] Food and Drug Administration, *Assessment of the Program for Enhanced Review Transparency and Communication for New Molecular Entity New Drug Applications and Original Biologics License Applications in PDUFA V (Statement of Work for Assessment of the Program),* FOOD AND DRUG ADMINISTRATION (April 14, 2017), https://www.fda.gov/media/83345/download (last accessed June 23, 2022).

[105] FOOD AND DRUG ADMINISTRATION, ASSESSMENT OF THE PROGRAM FOR ENHANCED REVIEW TRANSPARENCY AND COMMUNICATION FOR NME NDAS AND ORIGINAL BLAS IN PDUFA V (FINAL REPORT: 10/1/2012-6/30/2016) ES-13 (2016).

doi:10.6342/NTU202302527

added to the review process, in the hope of avoiding additional review cycles on issues that could be resolved within the first cycle. Concrete steps were taken to ensure that these meetings were carried out efficiently, including selecting FDA attendees based on anticipated needs, arranging informal "heads-up" communication via phone or email about meeting topics, and permitting two-way communication to clarify questions.[106] The practice of involving signatory authority early was also established, and flexible settings for priority reviews were maintained and incorporated into formal review procedures.[107] Overall, these improvements accelerated average review times by two months, and allowed more applications to be approved in the first cycle of review.[108] As such, the finetuned version of review timelines for NMEs and original BLAs were maintained when the PDUFA was renewed once again in 2016 as PDUFA VI.[109]

Parenthetically, close communication between the FDA and sponsors are not *ex parte* communications prohibited by the Administrative Procedure Act, because FDA new drug approvals do not require hearings.[110] The PDUFA's

[106] *Id*. at ES-6.
[107] *Id*. at ES-7.
[108] *Id*. at ES-12.
[109] Stephen Barlas, *Drug Companies Breathe Easier as PDUFA VI Heads for Approval*, 42 PHARMACY AND THERAPEUTICS 357,357 (2017).
[110] Reading the definition given by 5 U.S.C. §551(14), and the prohibiting rules in §557(d) in conjunction with §§556, 553 and 554, *ex parte* communications are only prohibited in official rulemaking and adjudications that require hearings. Furthermore, §557(d)(1)(E) states that such prohibitions shall begin "*beginning at such time as the agency may designate, but in no case shall they begin to apply later than the time at which a proceeding is noticed for hearing unless the person responsible for the communication has knowledge that it will be noticed, in which case the prohibitions shall apply beginning at the time of his acquisition of such knowledge.*" If we look closely at 21U.S.C.§§355(c) and 355(d), whereas refusals require hearings, hearings are not mandatory for approvals. Moreover, §355(b)(5)(B) and (C) explicitly authorizes the FDA to communicate with applicants the size and type of clinical trials to be conducted. Thus, since new drug approvals are not formal adjudications that require hearings, they are not subject to *ex parte* communication prohibitions. Even when they do involve hearings, such prohibitions do not apply until a notice for hearing is given. Besides, as indicated in FDA rules, all communications between the FDA and the applicant shall be documented and published along with application.

doi:10.6342/NTU202302527

increased communication requirement was built on top of communications requirements set out by the 21 CFR Section 314.102-103, which mandate the FDA to communicate scientific, medical and procedural issues during the review process, and may do so though telephone conversations, letters or meetings. Furthermore, all communications must be appropriately documented, and revealed with the approvals. While whether or not the procedures set for by the FD&C Act is appropriate or not is not the focus of this thesis, I extend a plausible explanation: FDA approvals not requiring hearings and thus not being subject to *ex parte* communications restrictions is because approvals allow drugs to reach the market, where competition is welcome (from the FDA's point of view) to spur drug innovation and development. On the other hand, when the FDA is inclined to reject a new drug application, the applicant's rights are in peril and thus requires a hearing to ensure that all comments have been taken and discussed.

Taking a close look at the data analyzed for the PDUFA V and prior programs revealed interesting observations of the limits and possibilities of US FDA review timelines. Firstly, the PDUFA IV, which took place in the previous 5-year cycle, did not allow a two-month processing time when calculating review times. Thus, even though data showed a lower rate of meeting review timeline goals in the baseline PDUFA IV program, if one compared the time taken from receipt of application to first-cycle approval, applications under PDUFA V actually took longer than those in PDUFA IV, albeit the difference was shorter than the two month difference in review clocks.[111] Furthermore, the US FDA reviewers conceded that the additional two months were used for a

[111] FOOD AND DRUG ADMINISTRATION, *supra* note 105, at ES-17.

doi:10.6342/NTU202302527

variety of review work, ranging from administrative review to seeking approval of signatory authorities.[112] This implies a bottleneck in limiting review time for US FDA approvals, as the two additional months were indeed needed for the US FDA to set realistic goals for its day-to-day operations. On the other hand, the final assessment of the PDUFA V program also noted that early action has been taken for cases that would serve significant public health purposes, which means the approval could be processed a month or even earlier than the target goal.[113] Acceleration was nevertheless resource-intense. US FDA asked for additional information and amendments more frequently in applications on breakthrough or fast track, reflecting the practice of accepting data on a rolling basis and the need for increased communication in such cases.[114] Notably, US FDA reviewers commented that implementing tighter goals and facilitating better communication did increase workload, but not to an intolerable degree.[115] These observations support endowing the US FDA with more flexibility under a wider timeframe in arranging reviews, such that full acceleration could be geared for priorities while not imposing unmeaningful delays in others.[116] In fact, the PDUFA programs present a series of trials among the US FDA, sponsors and other actors to find the sweet spot for setting review timeframes and dispersing resources.[117]

[112] *Id*. at ES-13.
[113] *Id*. at ES18-19.
[114] *Id*. at ES27-28.
[115] *Id*. at ES-14.
[116] The Congress apparently had similar ideas when reauthorizing the PDUFA V, drafts to introduce new fast track pathways with more flexibility were discussed. *See* Asher Mullard, *2011 in Reflection*, 11 NATURE REVIEWS DRUG DISCOVERY 6 (2012).
[117] See similar projections and analyses about the program in Asher Mullard, *PDUFA V Goes Back to Basics*, 11 NATURE REVIEWS DRUG DISCOVERY 586 (2012).

doi:10.6342/NTU202302527

The review for sofosbuvir was a smooth exercise of the PDUFA V review program. Before submission, end-of-phase meetings were held during 2011-2012 to confirm trial designs for the next phase, pre-submission meetings were held as early as October 17, 2012, as well as a pre-IND meeting was held on March 14, 2013. The pre-submission meeting minutes served as agreement between the US FDA and the sponsor regarding submission details like including SVR24 data for trials where available, that late submissions would not be made, and that there would be an advisory meeting.[118] The application was eventually received April 8, 2013, filing was completed on June 7, 2013, setting its PDUFA V goal date on December 8, 2013.[119] During review, teleconferences were held to address specific questions, including whether to include new supporting evidence from ongoing clinical trials.[120] Several emails were delivered back and forth to ask for specific data and responses to concerns for certain adverse events. The mid-cycle meeting was held on July, 17, 2013 (where no significant issues were raised) and the breakthrough designation was requested and approved on October 3rd, 7th respectively.[121] Late cycle meeting held October 10th discussed potential issues to be addressed on the October 25th Advisory Meeting, in which significant issues like treatment duration for genotype 3 patients were discussed. Finally, the approval came through on December 6th, 2013.

Post-market requirements were given in detail in the approval letter and directed the developer to cooperate with FDA for expanding use of sofosbuvir

[118] FOOD AND DRUG ADMINISTRATION, ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS FOR NDA 204671, at 181.
[119] *Id.* at 152-156.
[120] *Id.* at 48.
[121] *Id.* at 60-80 and 83-88.

doi:10.6342/NTU202302527

to different populations. Notably, despite a favorable safety profile compared to the traditional regimens, the FDA still imposed safety data collection responsibilities to the sponsor.[122] It seems like the US FDA has achieved a reasonable balance between speedy approvals and quality of review.

C. Breakthrough and Acceleration through Adjustments and Extrapolation

A total of seven different clinical trials were submitted to the FDA for review, covering different populations and experimenting with different regimens. To provide a background for understanding the approval, below is a brief description of the complicated clinical trials involved in the review. 4 different phase III clinical trials supported the use of sofosbuvir in combination with ribavirin for treatment of hepatitis C (FISSION, FUSION and POSITRON or genotypes 2 and 3, NEUTRINO for genotypes 1,4,5 and 6), and after the application was submitted, two additional phase III trials (VALENCE and PHOTON-1) for more specific subpopulations, and a phase II trial for patients awaiting liver transplant (NEUTRINO) were also evaluated by the reviewers. Succinctly, sofosbuvir demonstrated high cure rates compared to the traditional treatment with interferon and ribavirin across all genotypes, without unique safety signals. This is on top of its edge of being administered as a single dose, once-daily oral regimen with few dosing restrictions, and low rates of treatment dropout.[123]

Priority review and breakthrough designation were granted swiftly. sofosbuvir is a nucleotide inhibitor of hepatitis C virus, and is a first-drug-in-

[122] FOOD AND DRUG ADMINISTRATION, APPROVAL LETTER FOR NDA 204671 (2013).
[123] Eric Lawitz et al., *Development of Sofosbuvir for the Treatment of Hepatitis C Virus Infection*, 1358 ANN N Y ACAD SCI 56,65 (2015).

doi:10.6342/NTU202302527

class submitted for marketing application in the United States. Priority review was granted because hepatitis C is a serious and life-threatening disease, and sofosbuvir would provide a significant improvement in treatments. It was also designated as breakthrough therapy because preliminary clinical evidence indicated substantial improvement over available therapies.[124] This allowed the FDA to accept and review clinical data with more flexibility, including reviewing data on a rolling basis even under its limited review time.

Of particular, the VALENCE trial design was adjusted according to knowledge that gradually came to light. The phase III VALENCE trial was a randomized controlled trial for HCV genotype 2 and 3 subjects. The original plans to treat all subjects for 12 weeks were extended to 24 weeks when FUSION trial results showed that extended treatment could benefit genotype 3 patients.[125] US FDA not only approved of this change, and took the liberty to include results of the non-IND study for analysis late in the review cycle.[126]

PHOTON-1 underwent a similar route and was also assessed later in the review cycle. At the time of approval, PHOTON-1 was a still ongoing phase III trial. The reviewers cited key factors for accepting preliminary data for this trial: the trial targeted subjects that had HCV/HIV-1 coinfection, which the reviewers described as "an important subgroup". Additionally, the trial experimented with interferon-free regimen, which would allow the expansion of treatment to patients that were interferon intolerant.[127]

[124] FOOD AND DRUG ADMINISTRATION, *supra* note 93, at 2-3.
[125] FOOD AND DRUG ADMINISTRATION, *supra* note 102, at 7.
[126] FOOD AND DRUG ADMINISTRATION, *supra* note 93, at 11.
[127] *Id*. at 14.

doi:10.6342/NTU202302527

For subjects that were excluded from trials but might benefit from the new drug, extrapolation was permitted by reviewers to consider treatment for these populations. Genotype 1 patients that did not respond to the traditional PEG/RBV regimen were not the subject of any clinical trials submitted to the US FDA. However, the reviewers offered two exploratory analyses based on existing data and presented the extrapolations to the advisory committee. The advisory committee appeared to be split on whether the evidence supported use of SOF/PEG/RBV in patients that previously failed PEG/RBV treatment, but in the end the US FDA believed the modelling and simulations used provided adequate confidence for treating treatment experienced genotype-1 patients with sofosbuvir in combination RBV and interferon.[128]

Indeed, sofosbuvir is a long-awaited breakthrough for patients that have suffered from chronic hepatitis C infection. The diverse genotypes and infectious status of the virus also makes developing a regimen more complex and resource-consuming than that for many other diseases. To mitigate excessive complexities that would hinder the approval of the drug, the FDA allowed for more flexible trial adjustments and analyses methods in its review such that the drug could be available to those in need.

D. Approval Concerns: Cost-Effectiveness?

Sofosbuvir was warmly welcomed to clinical settings, as the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV recommendations quickly recommended sofosbuvir-containing regimens as first-line treatment for HCV patients of all genotypes. Following the approval of sofosbuvir, US FDA also approved

[128] *Id*. at 21-22.

doi:10.6342/NTU202302527

Harvoni, a combination treatment using ledipasvir and sofosbuvir, both developed and sold by Gilead, on October 10, 2014. Harvoni became the first treatment that did not require interferon or ribavirin.[129] More than 30,000 patients initiated treatment with sofosbuvir in its first quarter on the market, with sales hitting nearly $2.3 billion in the first quarter of 2014.[130] A standard course of treatment by taking 12 weeks of Harvoni costed $84,000, which Gilead argued to be reasonable given the fewer side effects and higher cure rate. Gilead claims that in the long run, the additional costs of Sovaldi will be balanced off by the reduced medical care for treating patients with chronic cirrhosis.[131]

The Institute for Clinical and Economic Review (ICER) scorched Gilead for the pricing of sofosbuvir. The Boston-based independent non-profit organization provides clinical and cost-effectiveness analyses of health technologies, and holds regional forums such that the public may engage in discussions of healthcare value.[132] The NPO published a report comparing the clinical effectiveness and value of sofosbuvir and simeprevir, both second generation DAAs approved by the US FDA to be used singularly with ribavirin to treat hepatitis C on April 15, 2014. In addition to performing a network meta-analysis on the clinical efficacy of the existing treatments, the potential clinical and economic impact of the new DAAs were also examined by a hypothetical

[129] Lawitz et al., *supra* note 123, at 65.
[130] Eric Palmer, *Gilead Litigation Says Claimsby Merck, Abbvie on Sovaldi Are Patently Wrong* (July 21), https://www.fiercepharma.com/pharma/gilead-litigation-says-claims-by-merck-abbvie-on-sovaldi-are-patently-wrong (last accessed June 15, 2022.
[131] The Editorial Board, *How Much Should Hepatitis C Treatment Cost?*, THE NEW YORK TIMES, March 16, 2014.
[132] Laura T. Pizzi, *The Institute for Clinical and Economic Review and Its Growing Influence on the Us Healthcare*, 9 AMERICAN HEALTH & DRUG BENEFITS 9,9 (2016).

doi:10.6342/NTU202302527

cohort model.[133] The model showed that even if only 50% of infected individuals in California came forward for treatment, drug costs could increase by $22 billion in a single year with the current pricing of the two DAAs. On the other hand, if all patients switched to the new effective drugs, the liver-related events prevented in 5 years and 20 years would not completely offset the increase in drug expenditure. Only when HCV patients with advanced cirrhosis were treated with the new regimens, would the estimated cost offsets produce a net saving to the healthcare system.[134] The report was presented in a public meeting, where the CTAF Panel discussed and voted on the assessments from the view of a public payer, and recommendations were delivered after discussion at a Policy Roundtable with clinical experts, patients advocates, payer representatives, and manufacturers.[135] The panel found none of the new DAA treatments to be of "high value" compared to the then standard treatment due to its high costs, and recommended prioritizing patients to be treated immediately with the new drugs.[136] One of the clinical experts noted the lack of head-to-head large scale clinical trials to compared the different new treatments, stating that future research should focus on these as new combinations emerge for treatment of HCV.[137] Single-arm, open-label, and non-randomized studies with small number of patients were considered limited evidence, and the US FDA review relied on some of these for the approval of new DAAs including sofosbuvir.[138] However, the greatest concern was still over the pricing of the

[133] JEFFREY A. TICE et al., INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW, THE COMPARATIVE CLINICAL EFFECTIVENESS AND VALUE OF SIMEPREVIR AND SOFOSBUVIR IN THE TREATMENT OF CHRONIC HEPATITIS C INFECTION: A TECHNOLOGY ASSESSMENT (FINAL REPORT) ES2 (2014).
[134] *Id*. at ES7.
[135] *Id*. at ES8.
[136] *Id*. at 88-91.
[137] *Id*. at 92.
[138] *Id*. at 97.

doi:10.6342/NTU202302527

new drug, as sofosbuvir was priced at nearly $1,000 a pill and $ 48,000 per treatment course, which obviously was not subject to review by the FDA despite its impact on treatment.

Despite concerns in pricing, which the US FDA steered clear of, challenges to the scientific evidence reviewed for efficacy of sofosbuvir did not find much resonation in academic or medical circles. The years of vibrant dialogue between researchers, the pharmaceuticals and the US FDA has generated firm consensus among these actors, resistant to noise that did not factor in their pre-approval discussions.

IV. Conclusion

US FDA regulation regarding drug review and the US FDA itself underwent serious revamping in the past two decades to accelerate reviews by streamlining administrative measures and incorporating more flexible assessment of efficacy evidence, and the cases of dabigatran and sofosbuvir gave a clearer picture of how the acceleration was possible.

Representing a whole new class of drugs for a long existing condition, dabigatran's review demonstrated the range of possibilities for "substantial evidence" for both efficacy and safety. Although a large randomized controlled trial was done, it was not conducted double-blind. Even though reviewers had varying opinions as to whether dabigatran was superior to warfarin, that did not keep the drug from the market. And despite hundreds of patients left to bleed to death before the introduction of an antidote, and evidence that developers of the drug being concerned of this, the drug was used on millions of patients for prevention of stroke. For a disease so life-threatening and inflicting so many, the US FDA did not wait for better answers that may or may not have been

doi:10.6342/NTU202302527

found with more time, on the foundation of its well-rounded negotiations with the applicant that was later revealed to be somewhat shady.

In about three years' time, the approval of sofosbuvir exhibited an even more streamlined and organized approach to accelerating reviews for new drugs of priority. Faced with a complicated chronic disease, hepatitis C, the US FDA teamed up with the academia and industry to accumulate data and experience. They established consensus through academic publications and meetings early on, with the final version consolidated into US FDA guidelines for developers. Furthermore, the US FDA had a clear timeline and goals to follow with the PDUFA V review program, which was also result of effort from the US FDA, industry and patients groups. Looking closely into the guidelines and matching them with the comments and issues that arose during the approval, we could see the US FDA becoming even more flexible with trial designs, extrapolations, and accepting data from ongoing clinical trials.

The US FDA has been on a track to improve drug review efficiency for over two decades. Such acceleration was achieved not just by increased resources and smoothing out administrative wrinkles, but also by applying more pliable interpretations for "substantial evidence". Effective and safe drugs have been benefiting patients suffering from life-threatening conditions with the revolutionized review scheme. But is this also true for vaccines, which are administered to bigger, and more importantly, healthy populations? This is a question to be explored in the next chapter.

doi:10.6342/NTU202302527

Chapter 3 Guarding the Healthy: Reviewing Vaccines On Time

Vaccines has joined human's fight against microorganisms that inflict illnesses for more than a century by now. Unlike drugs, which are administered to sick people, vaccines are used on large numbers of healthy people, in the hope of preventing them from becoming sick. Thus, approving vaccines can be more complicated than drugs, because in addition to being effective, they are also expected to have minimal negative consequences on the subjects. This chapter will give an overview of the US FDA's vaccine approval regulations and guidance documents, and use the case studies of two influenza vaccines, Agriflu and Flublok, the former approved through accelerated approval in 2009 and the latter a traditional approval in 2012, to illustrate the weighing of efficacy and safety concerns in vaccine approval in the USA.

I. Overview of FDA Biologics Approval

Vaccines are a type of what we call biologics, and was originally regulated by the 1902 Biologics Control Act that focused on the "safety, purity and potency of vaccines, serums, toxins, antitoxins, and similar products." In 1944, the regulatory pathway for biologics and manufacturing facilities was recodified as the Public Health Service Act (PHSA). After the regulation of biologics moved to the FDA in 1972, both the PHSA and the Food, Drug, and Cosmetics Act (FD&C Act) applied to the approval of biologics.[1] The major differences between biologics and traditional pharmaceuticals lies in manufacturing and processing. Biologics are mostly produced by living organisms such as eggs, bacteria, yeast, and mammalian

[1] Mary Ellen Cosenza, *Chapter 4 - Biologics*, *in* AN OVERVIEW OF FDA REGULATED PRODUCTS 85,86 (Eunjoo Pacifici & Susan Bain eds., 2018).

doi:10.6342/NTU202302527

cells. In the case of vaccines, traditional methods may be developed in eggs, while newer products may be produced in cell-lines, and even use recombinant DNA technology.[2] In the US FDA, vaccines are regulated by the Office of Vaccines Research and Review under the Center for Biologic Evaluation and Research (CBER).[3]

A. Safe, Pure and Potent

Before the Food and Drug Administration Modernization Act (FDAMA) in 2007, biologics sponsors had to file both Product License Application (PLA) and an Establishment License Application (ELA). The application has since been consolidated into a single Biologics License Application (BLA). The BLA is similar to an NDA, except that it requires more information on manufacturing facilities, as regulated by the PHSA.[4]

The rules to applying for an BLA are detailed in 21 C.F.R. Part 601. Part 601.4 regulates the issuance and denial of the BLA, and states that authority to issue the license lies in the Director of Center for Biologics Evaluation (CBER), after determining that the establishments and product meet requirements of this chapter.[5] On the other hand, in the case the establishment and products do not meet the requirements of this chapter, the Commissioner of the department shall deny the BLA request.[6] After the BLA is issued, if the Commissioner finds the licensed

[2] *Id*. at 86-87.
[3] *Id*. at 88.
[4] *Id*. at 89.
[5] 21 C.F.R. 601.4(a) (2005): A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked.
[6] 21 C.F.R. 601.4 (b) (2005): If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to § 12.21(b) of this chapter.

doi:10.6342/NTU202302527

product to be unsafe or ineffective, or manufacturing of the products fail to meet regulatory requirements, the Commissioner has the authority to revoke the license after notification and enough time has elapse.[7] In the case where the product poses a danger to health, the Commissioner may suspend the license.[8] In all cases, the sponsor of the drug have the right to a hearing.[9] The regulations also endow the US FDA with publishing guidance documents to aide sponsors in complying with requirements of the application, and the CBER is responsible for maintaining the guidance documents.[10]

B. Accelerated Approvals for Vaccines

The same expedited pathways available to new drugs are also available to vaccine sponsors: Fast Track, Accelerated Approval, and Breakthrough Therapy Designation.[11] Subpart E of Code of Federal Register Title 21 lists the qualifications, determination and effects of an accelerated approval designation for biological products for serious or life-threatening illnesses. Biologics that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments qualify for accelerated approval. The CFR gives some examples of what it means to "provide meaningful therapeutic benefit to patients over existing treatments," including "ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy." [12] Furthermore, there is a specific category for biologics that can be approved based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or

[7] 21 C.F.R. 601.5 (1999).
[8] 21 C.F.R. 601.6 (2005).
[9] 21 C.F.R. 601.7 (2009).
[10] 21 C.F.R. 601.29 (2015).
[11] Cosenza, *supra* note,at 96.
[12] 21 C.F.R. 601.40 (1992).

doi:10.6342/NTU202302527

irreversible morbidity.[13] The US FDA also reserves the option to restrict distribution postmarket to ensure the safety in using such biologics.[14] In the case where products are approved through surrogate endpoints or approved with restrictions, the US FDA may withdraw its approval following a hearing if the US FDA finds evidence that the biological product is not safe or effective as indicated.[15]

The Guidance Document for developing vaccines to protect against global infectious diseases published in 2011 provides and overview of FDA's requirements for vaccines against infectious diseases. Although this guidance document was intended for vaccines against infectious diseases or conditions endemic in areas outside of the United States,[16] it is the only guidance document on the general requirements for vaccines against infectious diseases. Therefore, it will be relied upon to depict FDA's idea of what developing a vaccine entails.[17] In general, the document refers to Title 21 of the Code of Federal Regulations for vaccine licensure, the guidance documents "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products"[18] for more details on vaccine trials and approval. However, considering the rapid advancements

[13] 21 C.F.R. 601.41 (1992): FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

[14] 21 C.F.R. 601.42 (1992).

[15] 21 C.F.R. 601.43(a) (1992).

[16] DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDANCE FOR INDUSTRY: GENERAL PRINCIPLES FOR THE DEVELOPMENT OF VACCINES TO PROTECT AGAINST GLOBAL INFECTIOUS DISEASES 1 (2011).

[17] Furthermore, the guidance document states that "The laws and regulations applicable for the licensure of vaccines to protect against global infectious diseases apply to diseases endemic in areas outside the U.S. as well as diseases endemic in the U.S." See *id*. at 3.

[18] DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS (1998).

doi:10.6342/NTU202302527

in vaccine technology and the changes to US FDA approval procedures, the 1998 guidance document may have become out of date and may not reflect the operations of the US FDA approval process at this time accurately.

C. Special Regulations on Vaccine

Subpart H of the Code of Federal Regulations Title 21 deals with approval of biological products when human efficacy studies are not ethical or feasible. Emphasizing clearly that products that can be approved based on efficacy standards set forth in accelerated approval do not qualify, the regulation states that this part only applies to products where definitive human efficacy studies cannot be conducted because it is unethical to deliberately expose healthy human volunteers to lethal or permanently disabling agents. Safety evaluation would also still need to adhere to standard application requirements.[19] As can be expected, the scope of this pathway is strictly narrowed, with an entire section dedicated to describing the types of disease, pathology and animal studies that may qualify for this pathway. On top of that, approvals were to be subject to postmarketing studies, restrictions to ensure safety and information providing responsibilities.[20]

Having given a brief introduction of the different accelerating pathways for vaccine development and approval facilitated by the US FDA, I will now turn to the best case study to further illustrate how the US FDA utilizes these pathways to bring much needed vaccines onto the market on a shorter timeline: influenza vaccines. While accelerated approvals were widely used for seasonal influenza vaccines using well-known techniques, several influenza vaccines experimenting with new techniques have also been approved following the traditional pathway. The

[19] 21 C.F.R. 601.90 (2002).
[20] 21 C.F.R. 601.91 (2002).

doi:10.6342/NTU202302527

following two parts will record accelerated approval of one seasonal influenza vaccine, and the traditional approval of another, both of which occurred after the standardization of the vaccine guidance documents in the modern era.

II. Long and Prosperous: Influenza Vaccines

The flu has such a long and rich history of interacting with humans, that we have numerous vaccines aimed at preventing it, and the US FDA has dedicated several guidance documents to the licensure of influenza vaccines. Furthermore, the influenza vaccine is also similar to the COVID-19 in the disease it results in, and also in its infectious route. Therefore, observing the influenza vaccines approvals in recent years allows us to compare the decision-making of the US FDA in relatively normal times and under emergencies. Case studies will also reveal approval standards that were not written into hard text, and shed light on under what conditions the standard for safety and efficacy may be altered. This section will begin with an introduction to the disease and virus, and outline the written standards the US FDA have published.

A. Decades Old But Always Refreshing

Influenza viruses have been documented to be affecting the human population for more than a century, and two types of influenza variant strains have emerged from frequent mutations in the HA and NA glycoproteins. The frequent mutations have brought about global pandemics with the emergence of each subtype, leading scientist to seek pathways to limit the spread of new viral strains among humans in recent years through understanding the composition of viruses, and developing influenza vaccines that could address the rapidly changing nature of the virus.[21] While the emergence of new Type A hemagglutinin subtypes emerge

[21] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 16, at 2.

doi:10.6342/NTU202302527

has a greater tendency to cause large scale outbreaks among human populations, relatively minor mutations also bring about seasonal influenza that appear with a new outfit each year. An analogy of the variety of influenza viruses could be made to fashion, in which every 1-2 times a year, some particular tweak and cut may trend for a while, but over the course of a few years a breakthrough may impact the entire globe.

Due to its rapid evolution and variable impact on the human population, the WHO has developed a system with which to keep up, namely by identifying potential viruses and reformulating vaccines each year accordingly. This is known as the seasonal influenza vaccine program, where vaccine developers use the same vaccine mechanism and manufacturing process, but create vaccines for 3-4 virus strains identified by the WHO every year around April under the coordination of WHO Global Influenza Surveillance and Response System (GISRS)[22]. Influenza virus strains that have the potential to spiral into pandemics, often strains that are significantly different from circulating strains, such that fewer people have been exposed to them before and thus immunity has not been established, are also under close observation by the GISRS. If such potential is recognized, the WHO alerts relevant agencies and prepare for the development of a pandemic influenza vaccine. In the case of the 2009 influenza pandemic, a newly emerging virus was found to be different from the selected seasonal influenza strain, and eventually identified to be of pandemic character.[23]

[22] WHO, Virus Sharing, https://www.who.int/initiatives/global-influenza-surveillance-and-response-system/virus-sharing (last visited: February 27, 2023).

[23] The 2009 influenza pandemic made vaccine manufacturers and the US FDA scrambling to get enough pandemic vaccine available in a timeframe much shorter than that of annual seasonal vaccines. However, this will not be described in detail in this thesis, because US FDA approvals were not involved in the process. In fact, the pandemic influenza vaccines that were made available came from manufacturing existing vaccines using the newly identified pandemic strain, which did not require an US FDA approval.

doi:10.6342/NTU202302527

B. General Guidance and Accelerated Approval

Both seasonal influenza vaccines and pandemic influenza vaccines seeking licensure from the US FDA need to submit their applications by either a traditional or accelerated pathway, the former according to 21 CFR 601.2, and the latter following provisions in 21 CFR Part 601 Subpart E. The US FDA issued an guidance regarding the clinical data to be considered by CBER for seasonal influenza vaccines in 2007, which provides the standards of effectiveness and safety seasonal influenza vaccines to meet for approval.[24] This guidance, along with a similar guidance for pandemic vaccines, was part of the 2005 National Strategy for Pandemic Influenza prompted by the 2003 SARS pandemic and the shortage of vaccines in 2004-2005, where the US government pledged to enhance domestic production of influenza vaccines and develop vaccination plans.[25]

While inactivated and live attenuated vaccines both exist, the guidance document focuses on inactivated influenza vaccines, which can be approved through either a traditional approval or accelerated approval pathway. Vaccines using a technique that is already used to manufacture licensed influenza vaccines are naturally eligible for accelerated approval, and those using new techniques should opt for a traditional approval. As stated in chapter 2, accelerated approval allows for approvals to be made based on clinical immunogenicity trials, with additional effectiveness and safety information to be collected after the vaccine has been approved for use, and traditional approval requires data that supports the vaccine's clinical efficacy. In traditional approvals, the clinical endpoint means the efficacy

[24] DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDANCE FOR INDUSTRY: CLINICAL DATA NEEDED TO SUPPORT THE LICENSURE OF SEASONAL INACTIVATED INFLUENZA VACCINES (2007).
[25] Wendy E Parmet, *Pandemics, Populism and the Role of Law in the H1N1 Vaccine Campaign*, 4 LOUIS UJ HEALTH L & POL'Y 113,118 (2010).

doi:10.6342/NTU202302527

trial should evaluate whether subjects develop influenza disease. The guidance document sets the standard for traditional approvals as the use of placebo-controlled trial to evaluate clinical efficacy of the vaccine, meaning subjects need to be followed for a period of time after vaccination and the number of subject developing influenza illness should be recorded and compared. The guidance document requires the trial to be powered to evaluate vaccine efficacy with two-sided 95% confidence interval, aiming for the vaccine efficacy to be well above 0, preferably above 40-45%. However, due to ethical considerations for populations at increased risks for influenza disease complications, the guidance document allows for non-inferiority trials and using immunogenicity trials to compare with the clinical efficacy trials. The guidance document also encourages the use of culture-confirmed endpoints and virus typing in case strain prediction did not go well at the year of the trial.[26]

Safety evaluations in a traditional approval requires the sponsors to record reactogenicity events for all age groups, and create a grading scale for adverse event severity. Follow-up period is designated to be 6 months at the least, with clinical or phone follow-ups, with a focus on serious adverse events. Although the guidance document seems to give wide flexibility in the size of the safety database, based on the technique used, the age group and indication, but it does anticipate that thousands be included in the safety database.[27]

For accelerated approval, the guidance document first affirms the utility of using hemagglutinins antibody (HI) antibody in the subject's serum as a surrogate marker for accelerated approval of influenza vaccines. The guidance document requires well-controlled studies designed to meet immunogenicity endpoints for

[26] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 24, at 4-5.
[27] *Id*. at 6-7.

doi:10.6342/NTU202302527

accelerated approvals, but does not rule out the possibility that influenza vaccines using a new technique to be approved through accelerated approval, but requests that sponsors discuss with the US FDA in advance. For efficacy, the guidance document recommends two routes: a non-inferiority immunogenicity trial comparing the HI antibody titers of the trial vaccine and a licensed vaccine. The co-primary endpoints are recommended to be: The upper bound of the two-sided 95% CI on the ratio of the GMTs ($GMT_{U.S.\ licensed\ vaccine}/GMT_{new\ vaccine}$) should not exceed 1.5; or The upper bound of the two-sided 95% CI on the difference between the seroconversion rates ($Seroconversion_{U.S.\ licensed\ vaccine} - Seroconversion_{new\ vaccine}$) should not exceed 10 percentage points. The other route is to conduct a placebo-controlled immunogenicity trial, to assess the co-primary endpoints 1) seroconversion rates, and 2) percentage of subjects achieving an HI antibody titer ≥ 1:40. The guidance document cited the Committee for Medicinal Products for Human Use of the European Medicines Agency standards for approval: for adults under 65, seroconversion rate should exceed 40%, and those with antibody titer ≥ 1:40 should be greater than 70% (with 95% confidence intervals). For older populations, the standard is lowered to 30% and 60%, respectively. Note that the guidance document requires the immunogenicity results to be strain-specific, meaning that the HI antibody titers should be measured for the three different circulating strains of the season in question.[28]

Safety-wise, the guidance document requires that the safety monitoring match that of traditional approvals, but state that for vaccines using a well-known and understood manufacturing process, safety database be large enough to identify adverse events that occurs at a rate of 1 in 300, and any serious adverse event

[28] *Id*. at 7-9.

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present in a safety database in about 1000 subjects should be carefully evaluated. Obviously, post-marketing requirements apply.[29]

The guidance for industry developed by the FDA Center for Biologics Evaluation and Research team as early as May 2007 gives us a good idea of how the US FDA differentiates between the data required for traditional or accelerated approval for influenza vaccines (see Figure 1). We can see that in additional to requiring only immunogenicity data, the accelerated approval may also be based on a safety evaluation on a smaller number of subjects (but with the same follow-up duration and methods) if the vaccine uses a well-known method.

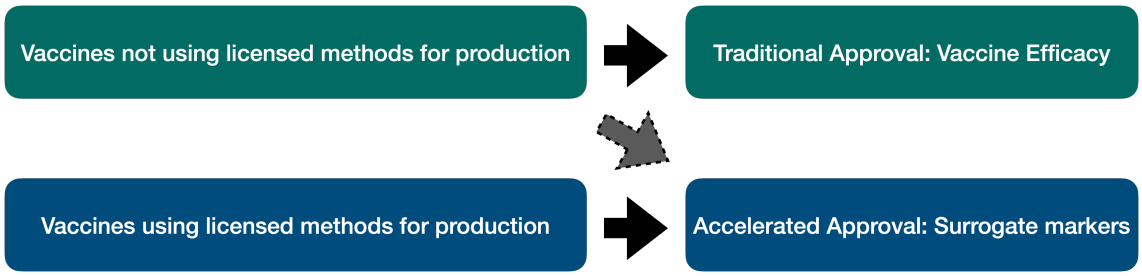

Figure 1: Approval Pathways for Influenza Vaccines

III. How Fast Can We Get? –Accelerated Approval for Influenza Vaccines

Speed is always an issue in drug or vaccine approval, but it plays an unequivocal role in influenza vaccines. Within a century, humans have experienced 2 to 3 influenza pandemics, and the virus is still shows no signs of leaving. In the United States in particular, the contamination of a offshore vaccine plant led to drastic depletion of seasonal influenza vaccine supplies.[30] Even more famously, the 2009 H1N1 pandemic shows how when a pandemic strain hits, the little number of vaccine suppliers and the unavoidable constraints in traditional egg-based vaccines

[29] *Id*. at 10-11.
[30] See a chronicle of the year's shortage in TIM BROOKES, A WARNING SHOT: INFLUENZA AND THE 2004 FLU VACCINE SHORTAGE (American Public Health Association. 2005).

doi:10.6342/NTU202302527

left little room for response.[31] Since then, the accelerated approval of influenza vaccines has been made a priority of the US FDA. But exactly how fast could an influenza vaccine possibly be approved? Does the US FDA have to compromise its efficacy and safety standards? What are the obstacles?

Novartis's seasonal influenza vaccine approval went through at about that time. Novartis first submitted its BLA for the seasonal influenza vaccine, Agriflu, in early 2007, but its application was not formally considered until May, 2007 due to chemistry and manufacturing concerns. Agriflu was eligible for the accelerated approval pathway, and used Seqirus's Fluvirin, first approved in 1988, as a reference point for comparison. Even so, Agriflu did not gain accelerated approval until December 2009, after the influenza season that year. This part will sift through the US FDA's evaluation of Agriflu's data, to see what efficacy and safety assessments were deemed necessary under the conditions at that time.

A. As Fast As You Can: Accelerated Efficacy With Predetermined Surrogate Marker Criteria

Efficacy evaluation in accelerated approvals depend on surrogate markers, and hence are based on the foundation of prior products. Agriflu's accelerated approval sheds light on the foundation of influenza vaccine that has been built over decades. As outlined in the guidance documents, the seasonal influenza vaccine accelerated approval was based on a surrogate endpoint considered "reasonably" likely to predict that patients will derive clinical benefit from Agriflu. Several phase II and phase III trials were therefore submitted by Novartis for US FDA approval. For efficacy, all trials evaluated the surrogate endpoint stated in the guidance

[31] V Baldo et al., *The New Pandemic Influenza a/(H1N1) Pdm09 Virus: Is It Really" New"?*, 57 J PREV MED HYG E19 (2016).

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document: seroconversion and HI antibody titer ≥ 1:40. Criteria for the former was 40%, and 70% for the latter.[32]

The pivotal phase III trials were designed as a randomized controlled immunogenicity trial. Subjects were randomly assigned to Agriflu (the trial vaccine) or Fluvirin (an US FDA approved vaccine), stratified by age, and blood was drawn from all subjects at before vaccination and 20 days after vaccination to evaluate serum antibody level. In the first pivotal trial, V71P5, 360 evaluable subjects were recruited for each age group, thus the sponsor calculated that the percentage of subjects achieving post-vaccination HI titers no lesser than 1:40 should be at least 75%, and that for seroconversion to be at least 46% to meet US FDA criteria.[33] The results from the pivotal trial V71P5 showed that Agriflu met the criteria readily for all three strains of viruses, however, Agriflu did not appear to be superior over Fluvirin, gaining only a slight advantage in influenza B strains.[34]

The efficacy results of a second pivotal trial was also scrutinized carefully. The study V71P6 was conducted to evaluate lot consistency between three different lots of Agriflu, as well as to evaluate its immunogenicity compared to Fluvirin. A total of 1507 adults were enrolled and studied in this study, with a total of 1290 in the Agriflu arms and 217 in the Fluvirin arm. All arms met the criteria for immunogenicity endpoints defined by the US FDA guidance document, both for seroconversion and titer level.[35]

Additionally, Novartis submitted immunogenicity results of two other studies, V58P4 and V58P9 to the FDA, and FDA requested the results of V58P2,

[32] FOOD AND DRUG ADMINISTRATION, BLA REVIEW FOR BLA 125297 4 (2009).
[33] *Id*. at 18.
[34] *Id*. at 22-23.
[35] *Id*. at 44-45.

doi:10.6342/NTU202302527

which was of almost identical study design to V58P4. The phase II trial V58P2 compared Agriflu, an egg-based trivalent inactivated vaccine, to a cell-culture based inactivated vaccine, and followed trial designs outlined by CPMP Note for Guidance on Harmonisation of Requirements for Influenza Vaccines, which differed slightly from the corresponding US FDA guidance.[36] V58P2 had an almost identical design to V58P4, both of which met CPMP criteria for immunogenicity. However, the results from V58P2 did not meet the more stringent criteria listed by the US FDA guidance document. Specifically, seroconversion criteria was not met for any of the three strains tested, and titer level criteria was only met for one virus strain. The reviewer did note that subgroup analyses showed that subjects without previous vaccination showed higher titer levels and seroconversion rates, but then concluded that this was not relevant outside of the clinical trial setting. The reviewer finally decided to let this pass, considering the trial was designed to meet the CPMP criteria and not the CBER standards, and also the fact that the sample size was relatively small (only 223 adults were enrolled).[37]

V58P4, the fourth clinical trial reviewed by the US FDA for the approval, was a phase III randomized trial that was identical in design to V58P2 conducted in Poland. A total of 2654 adults were enrolled in this study; the large sample size was based on the non-inferior study design. About half of the subjects were adults 18-60 years old, and the other half 61-years-old and above. Approximate half of each age group received Agriflu, and the other half received the cell-derived vaccine. The immunogenicity results from V58P4 was spectacular: both the seroconversion and antibody titer endpoints set by CBER were met for all three strains tested, for both

[36] *Id*. at 52-53.
[37] *Id*. at 56.

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vaccines (egg-based Agriflu, and cell-based vaccine), and both age groups, despite it being designed for the less stringent CPMP standards. The reviewer noted that the discrepancy between V58P2 and V58P4 was unexplained, though possibly due to the different vaccine strains used in the two studies.[38]

The fifth clinical trial, V58P9, was a phase III randomized, controlled, observer-blind, multi-center study, and like the pivotal trial two V71P6, was designed to evaluate the immunogenicity of Agriflu and three lots of a cell-based vaccine. A total of 1199 adults were enrolled, and randomized in a 2:2:2:1 ratio for the three lots of cell-based vaccine and Agriflu, in that order. The trial was also designed according to the CPMP guidelines instead of the US FDA guidance document. The immunogenicity results met the CBER criteria successfully.

In sum, in addition to the two pivotal trials in which data from a total of 2185 healthy adults that received Agriflu, data of another 4077 adults from three other studies supported the immunogenicity results. Although all trials were randomized, at least observer-blinded, and controlled, only the two pivotal trials were designed specifically to meet the US FDA. In terms of efficacy, we can see that data from roughly 2000 subjects was deemed sufficient if the trial settings and clinical endpoints of the US FDA CBER guidance documents were met for accelerated approval. Secondly, even in accelerated approval, the US FDA took care to scour for all relevant trials, and not depend solely on trials that the sponsor submitted. This prevents the sponsor from hiding undesirable trial results, and result in a skewed and inadequate analysis. Finally, despite data from a trial designed for European standards failed to meet the US FDA CBER criteria, the reviewer was not too concerned about the single discrepancy and did not rule Agriflu out from

[38] *Id*. at 59-62.

doi:10.6342/NTU202302527

consideration. In fact, the BLA review noted the unfavorable results of that trial and described brief comparisons between it and other similarly designed trials, the reviewer did not request further analysis to determine the cause of difference. The fact that Agriflu has been approved for use in Europe for several years may contribute to the reviewer's confidence in the product.

B. No Steps to Skip: Acceleration With Standard Safety Requirements

Safety data collection across all clinical trials was pretty standard, mostly collected through follow-up phone contacts at Day 7 and Day 181 in addition to the Day 21 clinic follow-up.[39] Almost all of the clinical trials screened for solicited and unsolicited adverse events, and assembled detail information on every adverse event or death to judge whether they could have been vaccine-related.

In the first pivotal trial, V71P5, safety analysis included records of solicited and unsolicited adverse events rated by gradings in both the Agriflu group and the Fluvirin group, with both groups showing similar percentages of adverse events. Very few medically significant events or serious adverse events occurred in either arm of the trial: only 1% in the Agriflu group, and 1-2% in the adults of the Fluvirin group. The medically significant events included: vomiting, pharyngitis, pyrexia, pneumonia, and appendicitis, and two new onset chronic diseases, from which the reviewer did not detect any safety signals. Only 3 serious adverse events were observed in the Agriflu group during the 21 days after vaccination: an appendicitis, asthma crisis and eye injury, all of which happened in the non-adult age group, and were not judged to be vaccine-related. 6 serious adverse events happened in the adult age-group after 21 days of vaccination, the events included: diverticulitis, transient decrease in visual acuity, dysentery, ovarian cancer, and spontaneous

[39] *Id*. at 15.

doi:10.6342/NTU202302527

abortion. The spontaneous abortion on Day 60 was judged as vaccine-related. Although no statistical analysis was performed, the reviewer commented that the number of adverse event correlated well with the 2:1 randomization, and most were not related to vaccination. The reviewer concluded that the primary endpoints were met, and secondary endpoints and subgroup analyses supported the primary endpoint results for efficacy. As for safety, the reviewer found the safety data of Agriflu to be consistent with that of other vaccines of the same mechanism, namely trivalent inactivated vaccines. [40]

For the second pivotal trial, V71P6, safety objectives were assessed in the same protocol as that of the first pivotal trial, but long-term safety follow up data was not included in the package sent to the FDA for evaluation.[41] The reviewer also assessed systemic adverse events for specific organ systems or syndromes, as the reviewer did for the V71P5 trial, but did not find them to be related to the vaccine. Although several adverse serious events were reproductive-related, the reviewer also excluded their relation to the vaccine. Despite some complications with safety data collection and interpretation, the reviewer found the safety data from V71P6 to be acceptable with the reassurance of the CBER inspection.[42]

In the large supplementary trial V58P4, after reviewing the data for unsolicited and solicited adverse events, and examining the severe adverse events individually, the reviewer concluded that no new safety signals were found. In both V58P2 and V58P9, no new safety signals were detected after undergoing the same analysis.[43]

[40] *Id*. at 31-34.
[41] *Id*. at 37.
[42] *Id*. at 50-51.
[43] *Id*. at 65-70.

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An additional 11 studies with 1831 adults also helped establish safety. These studies were conducted to support annual registration in different regions, for investigating new formulations, and trials for a novel administering schedule. The reviewer commented that of the six trials conducted in support of annual registration, safety follow-up period of three weeks was too short, and the fact that unsolicited adverse events were not collected, made the safety data less useful.[44] As for the other five trials, solicited and unsolicited adverse events were found to be similar to other trials for Agriflu, and no serious adverse events were judged to be related to the vaccine. Throughout all of the trials, no events of Guillain-Barré, anaphylaxis, or oculo-respiratory syndrome were noted. A total of four deaths occurred among all of the trial participants, but none were judged to be related to Agriflu.[45]

The BLA review's documentation of the safety evaluation of data from the multiple trials is a good demonstration of how and what the US FDA looks at to determine the safety of a vaccine. First of all, as the guidance document indicates, solicited and unsolicited adverse events are to be documented at multiple timings: about 30 mins after administering the vaccine, Day 8, Day 22, and finally Day 181 of the trial. This means that duration-wise, the US FDA requires at least a 6-month follow-up and observation period for vaccines seeking accelerated approval based on previously approved vaccines of the same mechanism. Interestingly, this duration is not affected by the fact that the vaccine in question has been approved and in use in other parts of the world for years. In other words, the reviewer did not consider safety data beyond 181 days even for trials that began well before the Novartis

[44] *Id*. at 79.
[45] *Id*. at 88-92.

doi:10.6342/NTU202302527

applied for accelerated approval in the USA. Of course, it may be that none of the trials were designed to follow-up subjects beyond 6 months, on the other hand, it may be that no safety issues arose throughout the years of Agriflu's approval in Europe. Secondly, data from approximately 8000 subjects enrolled in trials were considered in the BLA review. This is a number to keep reference of for future analysis regarding vaccine safety. Thirdly, since the two pivotal trials had Fluvirin arms for comparison, the BLA review matched the number of each kind of adverse event with the ratio of subjects enrolled in each arm. Hence, it can be understood that with an US FDA approved vaccine for reference, it was easier to judge whether adverse events were related to the specific vaccine in question or just vaccine-related in general. Finally, all clinical trials recorded details of individual serious adverse events, for which common vaccine-related issues were ruled out from an organ-system based analysis, and cases were judged to be vaccine-related or not through temporal relations, the subject's medical history, and other factors. As sample sizes are inadequate to evaluate rare complications of vaccines during clinical trial stages, it is important to detect "safety signals", or red flags, at this stage through qualitative analysis. Fortunately, for Agriflu, no new safety signals were recognized in all of its 8000 trial participants, leading to its smooth approval with only a minor glitch in a trial site that did not result in safety data issues.

C. Postmarketing Actions: Establishing Clinical Efficacy

As with new drug approvals described in Chapter 2, postmarketing actions are mandatory for vaccines that were approved through accelerated approval. For Agriflu, Novartis was suggested to complete study No. V58P13, a placebo-controlled clinical endpoint efficacy and safety study for Agriflu for adults, and submit the results and final report by June 2009. Pediatric and older populations also

doi:10.6342/NTU202302527

require further non-inferior immunogenicity trials.[46] Since all clinical trials were aimed at immunogenicity, no further efficacy data from the existing trials was required. There also were no additional requirement to establish safety databases, nor any duty to report future adverse events occurring in trial participants. This could be due to the relatively well-understood nature of the same type of vaccines, egg-born inactivated influenza vaccines, which have been used in the United States for years already before Novartis submitted its approval.

D. Vaccine Acceleration: Immunogenicity, 6-Month Safety Follow-up, Trial Site Monitoring

Agriflu's accelerated approval paints a concrete picture of what took place in the two year approval process. First of all, with the foundation of approved influenza vaccines, the establishment of clear criteria for surrogate markers has made trial design and conducting rather straight forward and evidently shortened trial duration. Since the guidance documents requested immunogenicity results at Day 21, clinical trial efficacy data could be collected within one month, which is considerable acceleration. Secondly, the FDA apparently recognizes 6-month safety follow-up data as adequate for influenza vaccines undergoing accelerated approval, and do not require further safety monitoring if no safety signals were detected among the study population. Finally, what really delayed the approval process was the trial conducting issues at problematic sites, which had to be investigated so as to determine whether the data from that site could be included as material to be reviewed. Of course, not only efficacy and safety review took time, chemistry, manufacturing controls, toxicology reviews, and statistical reviews that were not accounted for in this thesis also call for substantial amount of time. It seems that

[46] *Id*. at 95.

doi:10.6342/NTU202302527

even with the foundation of decades of influenza vaccine development and production, there is a limit to acceleration.

Agriflu's approval contributed to the US CDC's decision to recommend universal influenza vaccination for all persons older than 6 months for the 2010-2011 season.[47] The distributed doses[48] and percentage of adults being vaccinated with the flu vaccine in the United States grew slowly but steadily: from 114 million doses (estimated coverage 41.2%) in the 2009-2010 season,[49] bumping up to 155.1 million doses (estimated coverage 42.3%) in the 2010-11 season,[50] to 132 million doses (estimated coverage 45%) in 2011-12 season,[51] and growing steadily ever since, to 194.4 million (estimated coverage 52.1%) in the 2020-2021 season.[52] Few lawsuits were filed by flu vaccine recipients at that time, and most all vaccine related injuries were covered by the Vaccine Injury Act, there were no relevant court cases targeting vaccine sponsors.[53] This reflects the high level of consensus drawn from the decades of experience with influenza vaccines. In other words, the accelerated approval of influenza vaccines is the product of years of consolidation

[47] Center for Diseases Control and Prevention, Prevention and Control of Influenza with Vaccines: Recommendations of Advisory Committee on Immunization Practices (ACIP), 2010, available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5908a1.htm?s_cid=rr5908a1_w (last accessed: May 14, 2023).
[48] Center for Diseases Control and Prevention, Final estimates for 2009–10 Seasonal Influenza and Influenza A (H1N1) 2009 Monovalent Vaccination Coverage – United States, August 2009 through May, 2010., available at: https://www.cdc.gov/flu/prevent/vaccine-supply-historical.htm (last accessed: May 14, 2023).
[49] Center for Diseases Control and Prevention, Results from the March 2011 National Flu Survey – United States, 2010-11 Influenza Season, available at: https://www.cdc.gov/flu/pdf/fluvaxview/fluvacsurvey.pdf (last accessed: May 14, 2023).
[50] Center for Diseases Control and Prevention, Flu Vaccination Coverage, United States, 2020-21 Influenza Season, available at: https://www.cdc.gov/flu/fluvaxview/coverage-2021estimates.htm (last accessed: May 14, 2023).
[51] Center for Diseases Control and Prevention, Flu Vaccination Coverage, United States, National Flu Survey, March 2012, available at: https://www.cdc.gov/flu/fluvaxview/nfs-survey-march2012.htm (last accessed: May 14, 2023).
[52] Center for Diseases Control and Prevention, Flu Vaccination Coverage, United States, 2020-21 Influenza Season, available at: https://www.cdc.gov/flu/fluvaxview/coverage-2021estimates.htm (last accessed: May 14, 2023).
[53] For example, see Steven Kravitz, Et Al., Plaintiffs V. Evans Medical Ltd., Et Al., Defendants., 741 F.Supp.2d 1299, (United States District Court, S.D. Florida, Miami Division. 2010).

doi:10.6342/NTU202302527

on the virology, epidemiology, immunogenicity, statistics and clinical knowledge of the influenza vaccine. Within the vaccine approval process, efficacy and safety criteria are not foregone, and the level of scientific evidence was only lowered in consideration of at risk populations and not as much for acceleration.

IV. Evaluating Influenza Vaccines Using Novel Techniques

Despite influenza vaccines having been developed in the USA for decades, and inactivated vaccines gaining a steady hold on the market, there is still appreciable uncertainty as to the efficacy of influenza vaccines circulation the US market.[54] This limit is mainly due to randomized placebo-controlled trials being rarely conducted, since vaccines utilizing well-developed manufacturing methods are eligible for the accelerated approval process, immunogenicity trials are deemed sufficient for approval. In other words, there is no incentive nor room for placebo-controlled trials with influenza infection as primary endpoints to take place, unless new vaccine development methods emerge to challenge the existing vaccines. Indeed, with the climbing mortality and enormous numbers of those affected by influenza each year in the US, and the relatively insufficient and unstable production of egg-based influenza vaccine, there is still room for new techniques.

A. Approaching a New Technology: Trial and Error

Protein Sciences Corporation (PSC)'s team began developing the recombinant protein technique for vaccines in 1993.[55] In order to produce a trivalent influenza vaccine, PSC manufactured three recombinant influenza hemagglutinin antigens for two influenza A subtypes and one B type strain. The antigens were

[54] FOOD AND DRUG ADMINISTRATION, CLINICAL REVIEW FOR BLA 125285 12 (2009).
[55] Douglas C Powers et al., *Influenza a Virus Vaccines Containing Purified Recombinant H3 Hemagglutinin Are Well Tolerated and Induce Protective Immune Responses in Healthy Adults*, 171 J INFECT DIS 1595,1596 (1995).

doi:10.6342/NTU202302527

created by inserting a baculorvirus expression vector system (BEVS) into a plasmid, and having the plasmid expressed in cells from an moth, *Spodoptera frugiperda*. At the time of approval, no licensed vaccine manufactured from the same insect cells existed. However, Cervarix, a human papillovirus vaccine approved by the US FDA in 2009, was also a recombinant vaccine utilizing a baculovirus vector, albeit in another insect cell line.[56]

Various clinical human trials for this novel vaccine started with mono- or bivalent vaccines, and finally with about 300 subjects receiving trivalent formulations in preliminary trials, setting a safe and tolerable doing range.[57] In 2004, PSC initiated PSC01, a phase 2 trial that evaluated the immunogenicity efficacy of two doses: 75μg and 135μg, and determined that the latter achieved more favorable efficacy and was well-tolerated. Following the initial clinical trials, PSC submitted its first phase 3 clinical study plans, PSC03, to the US FDA in 2006, aimed at an accelerated approval for the 135μg Flublok. However, the study failed to attract sufficient subjects for enrollment. In 2007, PSC revised its trial protocols and added two phase 3 trials, PSC04 and PSC06, which the FDA found to conform with accelerated approval immunogenicity and safety guidance standards, and the trials commenced.

After a pre-BLA meeting and a type C meeting in 2007, PSC originally submitted their application for accelerated approval in April 2008. Notably, three different clinical study sites were inspected by the Bioresearch Monitoring team, all of which were within the USA. Compared to the Agriflu's clinical trials for accelerated approval, which were all conducted abroad, Flublok's domestically-

[56] FOOD AND DRUG ADMINISTRATION, *supra* note 54, at 13.
[57] *Id*.

doi:10.6342/NTU202302527

located trials seemed to have resulted in fewer trial protocol deviations and made it easier to confirm whether the issues rendered the trial data invalid.[58] Lot consistency issues were resolved through technical support from the US FDA.[59]

After responding to an August 2008 complete response letter and supplementing clinical efficacy and 6-month safety data from two clinical trials, PSC moved for a traditional approval in April 2009. CBER's review on PSC's application was formally decided upon by the Advisory Committee in November that year. While the Committee found the vaccine to be effective in adult populations of 18-49 years old, there were still some doubts about the safety data from the trials. Thus, further safety and efficacy data were required for evaluation. On the other hand, manufacturing inadequacies led to further delay of the approval, namely deficiencies in potency, purity and lot consistency identified by a second complete response letter in January 2010. Communication and verification back and forth on both clinical and non-clinical issues dragged for two years, and the traditional approval did not fruition until August 2012.[60]

From the above records, we can see that developers of Flublok have been in touch with the US FDA regarding the vaccine at least starting in 2006 for IND submission, and it was not until 6 years later that the vaccine obtained approval. We can also observe that there were extensive communication and a certain amount of uncertainty regarding the standard for which this novel vaccine should be subjected to. It seems that the US FDA did not object fervently to Flubok accessing the market through an accelerated approval. However, that PSC designed the major clinical trials to meet both immunogenicity and clinical endpoints, revealed how PSC did

[58] *Id*. at 11.
[59] *Id*. at 40-41.
[60] *Id*. at 13-14.

doi:10.6342/NTU202302527

not bank on the US FDA to be lenient and maintained the option to pursue traditional approval without having to restart clinical trials. While outstanding issues in manufacturing contributed to substantial delay, the US FDA's indecision for application route and ambiguous safety results also held the approval back. Also of interest Cevarix, another recombinant vaccine produced from insect cell lines acquired approval in 2009, leading to wide-spread use that contributed to the confidence for the safety of Flublok, which used the same novel technique. It should be reasonable to say that there was trial and error from both the applicant and the reviewer.

B. Bridging and Achieving: Clinical or Immunogenicity Efficacy Endpoints

PSC submitted 4 clinical trials in which a total of 3,231 adults above the age of 18 were included, although only data from one Phase 3 study was designed to evaluate vaccine efficacy against influenza with pre-specified statistical criteria.[61]

PSC01 was a phase II trial that enrolled 307 adults between the ages 18-49, half of which received the Flublok (and normal saline for the other half). PSC03, PSC04, and PSC06 were all phase III trials conducted in the 2006-2007 and 2007-2008 influenza seasons. While PSC04 enrolled the greatest number of participants, a staggering 4648 subject of whom half received Flublok and half received normal saline, both PSC03 and PSC06 were aimed at older adults (adults older than 65 for the former, and adults between the ages 50-64 for the latter), and had Fluzone (an inactivated influenza vaccine) for comparison. An overview of the phase III trials can be seen in Table 1.

[61] *Id*. at 6.

doi:10.6342/NTU202302527

Table 1: Phase III Trials for Flublok

	PSC03	PSC04	PSC06
Subjects	869	4648	602
Controls	Fluzone	Normal saline	Fluzone
Age groups	≥65	18-49	60-64
Immunogenicity endpoint	Antibody titer & Seroconversion rate at Day 21		
Clinical endpoint	Culture-confirmed Influenza Illness		

Source: compiled from FDA approval documents.

All trials were randomized, (modified) double-blind, placebo-controlled clinical studies conducted in the USA. The phase II PSC01 trial was also a dose finding trial, where PSC determined the dose for Flublok and evaluated the efficacy for that dose. In the major phase III trial, PSC04, the primary endpoint was vaccine efficacy, but 391 subjects in the Flublok group and 127 in the placebo group were selected for immunogenicity and lot-to-lot consistency assessment. [62]

From the immunogenicity data submitted as early as April 2008, the US FDA reviewed whether the data matched that of the standards set forth by the FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, that is, the immunogenicity endpoints specified for accelerated approval: antibody titer over 1:40, or seroconversion rate with a lower bound of the two-sided 95% confidence interval above 40% and upper bound above 70%. In the 2008 complete response letter, FDA encouraged PSC to include a placebo group comparison for immunogenicity analysis, which the sponsor did

[62] *Id*. at 20-21.

doi:10.6342/NTU202302527

provide from stored serum. Statistical analysis resulting from this additional immunogenicity investigation was extremely favorable for Flublok.[63] However, the clinical reviewer emphasized that the guidance criteria for accelerated approval were not relevant to the review going on because Flublok switched to a traditional approval pathway.[64]

Clinical efficacy data from the pivotal trial PSC04 was submitted to the FDA along with the reply to the first complete response letter in April 2009. Clinical efficacy was assessed by establishing a point estimate of 70%, for which the lower bound of the two-sided 95% confidence interval was to be 40%. The clinical endpoint was defined to be culture-confirmed Influenza Illness (ILI), which meant subjects had two out of the following symptoms sets: fever of over 100°F; cough, sore throat, runny nose/stuffy nose; muscle or joint aches, headache, chills/sweat, tiredness/malaise, and subsequently had the influenza virus cultured from nasal or throat swab specimen obtained within 24-72 hours of symptoms being reported. Operation-wise, the subjects were recruited and administered vaccines on Day 0, and were contacted via phone weekly by study personnel to survey for influenza illness during the flu season. The participants could also report influenza illness to the study centers on their own. Flu season was defined to begin when national CDC surveillance isolates for influenza reached 8%, and to end when the surveillance isolates drop to below 10% for influenza, and was estimated to last for at least 6 months. Enrollment of subjects started in September 2007, before the start of the 2007-2008 influenza season, and it only took a little bit over one month to recruit 4300 subjects across 23 trial sites. At about 8 months since the study launched, the

[63] *Id*. at 40-41.
[64] *Id*. at 24.

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influenza season of 2007-2008 ended and the last data were collected in May 2008.[65]

A total of 582 subjects reported more than 2 flu symptoms sets during the 2007-2008 flu season in trial PSC04, and of these subjects, 64 Flublok recipients and 114 placebo recipients were confirmed to have been infected by the influenza virus through culture. However, since the 2007-2008 vaccine strains matched that of the circulating virus poorly, only an extremely small number of trial participants contracted influenza illness from the vaccine strains. In fact, only a total of 8 subjects that cultured positive for influenza virus was infected by one strain from the vaccine composition, 2 in the Flublok arm and 6 in the normal saline control arm. No subject was infected by the two other strains the vaccine was aimed at, and all other participants were infected by other strains. This made statistical analysis extremely difficult and rouse doubt for the primary and secondary efficacy results (for CDC-ILI and non CDC-ILI), as the 95% confidence interval covered 0.[66] Nevertheless, the study also had a pre-specified exploratory endpoint, which was the efficacy of single-dose Flublok protection against any strain of influenza, not limited to the strains contained in the vaccine. It this exploratory analysis, 44 (1.9%) Flublok arm subjects were culture-positive with CDC-ILI, whereas 78 (3.4%) control arm subjects reached the same criteria, resulting in a 44.6% vaccine efficacy, with the lower bounds and upper bounds of the 95% confidence interval at 18.8% and 62.6%, which was not completely satisfactory. On a closer look, vaccine efficacy varied for different virus types, and for type B in particular, the 95% confidence interval also covered 0, creating more complexion to interpreting the

[65] *Id*. at 25-26.
[66] *Id*. at 42-43.

doi:10.6342/NTU202302527

trial results. The reviewer comments that although the US FDA guidance did not specify endpoints for cross-strain efficacy, the protection for mismatched strained exhibited in PSC04 contributed to the approval. All in all, with the background of the 2007-2008 influenza season in view, the clinical reviewer found the overall vaccine efficacy demonstrated in this trial, 44.8%, to be satisfactory, as it could reasonably be deduced that Flublok's protection against strains it was intended for would be higher than its overall protection efficacy.[67]

The timeline for trials in older populations, PSC06 and PSC03 was similar to that of the pivotal trial PSC04. In particular, PSC06 used the same strains as PSC04, and was also conducted in the 2007-2008 season, albeit using Fluzone, a licensed influenza vaccine as control group and was conducted in adults for the age group 50-64. The primary endpoint was designed to meet the immunogenicity endpoints as per US FDA guidance document, while also geared at establishing non-inferiority compared to Fluzone for secondary endpoint.[68] While the efficacy data of PSC06 showed Flublok reached 5 of the 6 immunogenicity criteria specified by the US FDA guidance, only missing out on seroconversion for Type B influenzas, it demonstrated non-inferiority for all three strains rather well. The non-inferiority criteria of Flublok against Fluzone was such that the upper bound of the two-sided 95% confidence interval of the GMT ratio (Fluzone/Flublok) at 28 days post-vaccination not exceed 1.5, and that the upper bound of the two-sided 95% confidence interval on the difference between seroconversion rate (Fluzone-Flublok) should not exceed 10%. In very crude and simple terms, this means that if Flublok is at least 66% as effective as Fluzone, and that Flublok should achieve an

[67] *Id*. at 43-46.
[68] *Id*. at 64.

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seroconversion rate at no lower than 10% lower of Fluzone. Flublok passed this scrutiny with ease, appearing to be better than Fluzone in H1 and H3 strains, and very similar to Fluzone in the Type B strain. The clinical efficacy endpoints in PSC06 was deemed futile, however, as it was inevitably affected by the highly mismatched strains in the 2007-2008 influenza season, resulting in very few culture-positive subjects and therefore a wide confidence interval.[69]

PSC03, aimed at an even older population, recruited a total of 870 adults above the age of 65. The trial was conducted in the 2006-2007 influenza season, in a timeline not unlike PSC04 and PSC06. Both immunogenicity and clinical endpoints were designed to be evaluated in PSC03, as well as non-inferiority assessment with the same standards as PSC06. Nonetheless, the reviewer did not agree that PSC03 was powered to evaluate clinical endpoints. Furthermore, PSC03 failed to procure the 655 subjects per arm at enrollment before the influenza season began, which undermined its overall power.[70] Review of the immunogenicity results showed that similar to PSC06, Flublok passed with flying colors in in H1 and H3 strains, but failed the non-inferiority test against Fluzone for the B strain by wide margins. The reviewers did not find explanations to be acceptable. At the same time, clinical efficacy evaluation also failed, suffering from too few culture-positive subjects in PSC03. Unlike PSC06 though, PSC03 was conducted in the 2006-2007 season, and thus could not be excused by the extreme mismatch between vaccine strains and circulating strains. But with the extremely small number of subjects, the reviewer simply concluded that clinical efficacy results for PSC03 were not meaningful. The reviewer also found similar circumstances in PSC02, which had a clinical efficacy

[69] *Id*. at 72-74.
[70] *Id*. at 86-87.

doi:10.6342/NTU202302527

component, and was conducted in the 2004-2005 season. The reviewer found the clinical efficacy evaluations in PSC02 to exhibit a "favorable trend", but found the sample size too small to draw meaningful conclusions.[71]

Since neither PSC03 or PSC06 achieved the pre-specified clinical endpoints and did not have definitively supportive immunogenicity results, the reviewer stated that: "it has been customary" for US FDA to require a second clinical endpoint efficacy trial in those populations. The reviewer and the Advisory Committee was apparently satisfied with the vaccine efficacy results, which achieved the 40% earmark, for the adult population of 18-50 years old, stating that even though low attack rates and small sample size undermined the estimation, the efficacy of Flublok for the population appeared to be similar to other licensed trivalent influenza vaccines.[72] Furthermore, although the studies were not powered to evaluate the vaccine's protection for mis-matched strains, the fact that the vaccine demonstrated protection for mis-matched strains made it reasonable to believe that it would only have better protection against matched strains. Thus, reviewers agreed that the deduction was sufficient to address the statistical imperfection, and relieved the sponsor of having to administer further trials to confirm clinical efficacy.[73]

C. Watching Carefully: Evaluating Safety of Novel Vaccines

Since Flublok was developed using a novel manufacturing technique that no licensed vaccines existed for, the appropriate sample size for safety evaluation was a critical item for pre-BLA discussions. PSC demonstrated that the protocol design and targeted enrollment number of subjects for the pivotal trial PSC04 set the likelihood of detecting adverse events with occurrence rates of 1 per 1000 was

[71] *Id*. at 94-97.
[72] *Id*. at 135-136.
[73] *Id*. at 138.

doi:10.6342/NTU202302527

above 90%, and for adverse events with occurrence rates of 3 per 1000 was above 99.9%. This was agreed upon by the US FDA in pre-BLA discussions for clinical study protocol design.[74]

For all studies, safety data was collected throughout Day 0 to Day 7 for reactogenicity, up to Day 28 for solicited and unsolicited adverse events, and followed for at least 180 days for severe adverse events. All serious adverse events were followed until symptoms were resolved or at least stabilized. For the pivotal trial PSC04, safety data up to Day 28 were submitted within the first application package for accelerated approval as part of the interim study report, and safety follow-up data and assessment up to 6 months was supplemented in the response to FDA in April, 2009.[75] In the pivotal trial, 30 subjects in the Flublok group experienced serious adverse events, compared to 46 in the control group. Serious adverse events included, viral hepatitis, fractures, bipolar disorder and depression, pulmonary embolism, cholelithiasis, suicide attempts, uterine bleeding, and more. Only a single case with pericardial and pleural effusion was judged to be possibly related to the vaccine, and none of the 2 deaths that resulted from the serious adverse events were found to be related.[76] PSC was therefore requested to administer post-marketing monitoring for pleuricarditis in future trials. On the records of severe unsolicited AEs, there were fewer severe unsolicited events in the Flublok group compared to the placebo group, and events that were judges as related occurred in a single subject receiving Flublok. Considering the novel manufacturing process of Flublok, the trial investigators and the reviewers paid special attention to autoimmune, and hypersensitivity phenomena, by examining

[74] *Id*. at 33.
[75] *Id*. at 26-27.
[76] *Id*. at 47-48.

doi:10.6342/NTU202302527

iconic signs for disorders in the nervous systems, blood and lymphatic systems, and musculoskeletal and connective tissue systems, but no safety signals that would necessitate a halt in licensure were detected. However, since a case presented with hypersensitivity was judged to be related and thus hypersensitivity was also expected to be surveilled in post-marketing studies. Interestingly, in addition to commenting on safety analysis submitted by PSC, the reviewers also extracted safety data for analysis from the safety database provided by PSC. The reviewers found that the safety data aggregation submitted by PSC was only minimally different from that extracted by the reviewers, and were finally content to use the PSC safety data for further analysis. Finally, the reviewers noted that despite a significantly higher portion of subjects reporting reactogenicity events, such as pain at injection site, the reactions were mostly mild and rarely severe, and the frequencies and levels of the reactions in the Flublok group were not unlike those for traditionally egg-based inactivated vaccines.[77]

For the older population trials, PSC06 and PSC03, special consideration was given to enrollment decisions, as the populations presented more complex past medical history and medication. The reviewer examined controversial cases one by one to maintain the integrity of the statistical analysis,[78] which also contributed to evaluating the vaccine's interaction with certain individual drugs. After undergoing the same safety evaluation as with PSC04, the reviewer concluded that no unusual safety signals were noted in the six months safety data.[79]

The safety database comprised of the entirety of the trial participants from all 4 clinical trials, totaling at 3,233 adult cases. Overall, adverse events were

[77] *Id*. at 51-61.
[78] *Id*. at 71,92.
[79] *Id*. at 75,106.

doi:10.6342/NTU202302527

balanced in terms of the ratio of vaccine type received, and no particular safety signals were detected from the safety database. However, the reviewer did take note of the relatively small safety database, especially considering the novelty of the vaccine. Despite a high loss to follow-up rate and small elderly population, the reviewer believed the safety data was strengthened by the indication of low discontinuation rate at Day 28, which was when most adverse reactions would have been expressed, and that the number of subjects followed was enough to detect adverse events with occurrence rates of about 0.1%. Furthermore, since Flublok was manufactured through a novel process, unlike Agriflu or other cell-based or egg-based vaccines, US FDA required PCS to commence with post-marketing studies for adults so that rare adverse events risks could be evaluated.[80] Post-marketing requirements included a Phase IV study with 100,000 individuals, and continuation study for subjects in PSC04 and PSC06 to evaluate safety when Flublok is used in consecutive years.[81]

D. Decision Making: VRBPAC

Unlike Agriflu, Flublok's efficacy and safety data were discussed by the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The committee comprised of, and operated through discussion and voting. According to the clinical review report, a majority of committee members voted in support of Flublok's efficacy for adults. On the other hand, the VRBPAC appeared to be split on whether the relatively small safety database was sufficient to support the vaccine's safety status. In fact, 6 out of 11 members found the submitted safety data unreliable for licensure. However, this only resulted in the requirement of a post-

[80] *Id*. at 8.
[81] *Id*. at 144.

doi:10.6342/NTU202302527

marketing safety study to collect more safety data, and the vaccine was still approved.

The role of the VRBPAC reflects the uncertainty that is often seen in the review of novel agents, and more importantly, how the US FDA react to dubious application data. The advisory committee meetings are attended by committee members, US FDA staff, and speakers from manufacturers whose products are being reviewed. All committee members, even the consumer and industry representatives, had doctoral degrees. Their professional backgrounds included from physicians, epidemiologists, biostatisticians, to public health scientists. All but one of the FDA staff held doctoral degrees, as well as all industry representatives. Therefore, even though stance of attendees varied slightly, there was an obvious common language they spoke in. The meeting transcript and summary of minutes are all published online, where the general public have access to meeting materials and could glimpse at who asked what and how it was answered.[82] In fact, by the year 2022, advisory committee meetings have gone online, and anyone with a link to the conference can observe proceedings real time.[83]

During discussions, committee members debated actively with PSC representatives over whether the trial data could fulfill the "substantive evidence". One member stated directly that "explaining away favorable evidence" is not substantive evidence as required by federal law.[84] Another member looked into the

[82] US Department of Health and Human Services, *November 18-19, 2009: Vaccines and Related Biological Products Advisory Committee Summary Minutes*, https://wayback.archive-it.org/7993/20170113080549/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm225141.htm (last accessed March 25, 2023).
[83] Food and Drug Administration, *Advisory Committee Calendar* (March 28, 2023), https://www.fda.gov/advisory-committees/advisory-committee-calendar (last accessed March 28, 2023).
[84] FOOD AND DRUG ADMINISTRATION, VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE, NOVEMBER 19, 2009 62 (2009).

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details, and was concerned with the lost to follow-up numbers, which surpassed 10% overall. The member commented that such numbers have never been seen in his ten years on the Committee.[85] Regarding older populations, yet another member voiced concerns over whether safety data from younger populations can be extrapolated to older populations, elaborating how the unknown can be deadly.[86] Interestingly, since not all committee members were familiar with the influenza pandemic, the issues of why immunogenicity endpoints were chosen for primary endpoint, and whether influenza vaccines contain different strains yearly but do not require further approval each year also arose.[87] During a public session for general discussion aimed at increasing transparency in advisory meetings, several industry members spoke up from their experiences.[88] Finally, when the votes took place, meeting transcript showed individual voting records, and committee members continued to discuss critical issues regarding the voting item in between votes. When the efficacy vote results came out, the PSC representative blurted that she was "dumbfounded", exasperated over how they followed all the rules by CBER and was instantly lost over what to do about older populations, but the committee carried on to discussions on safety.[89] The committee adjourned after the members proposed a number of additional information they would like to see from Flublok for approval, leading to the two year drag out.

Considering the novelty of the vaccine and the mild ambiguity of the data, it is natural that the US FDA would rely on the VRBPAC to back up their decision making. However, it seems here that the VRBPAC did not completely agree with

[85] *Id*. at 111.
[86] *Id*. at 117.
[87] *Id*. at 130-133.
[88] *Id*. at 128-132.
[89] *Id*. at 142.

doi:10.6342/NTU202302527

their assessment of the US FDA reviewers: although reviewers found the safety data to be adequate for approval but may need post-marketing authorization, their concerns were magnified in the VRBPAC and resulted in a unfavorable vote. In the end, the US FDA took the advice of the VRBPAC and only approved Flublok for young adults, and requested that PSC submit additional information to include older adults. Flublok's approval added to the diversity of influenza vaccines in the US, since it became the second flu vaccine that did not use eggs for production.[90] The technique it uses is being transferred and utilized in other vaccines, and is favorable for upgrading Flublok into a quadrivalent vaccine, meaning it could target one additional strain of the influenza virus.[91] No significant vaccine injuries regarding Flublok was raised in the decade after its approval.

E. Novel Vaccine Approval: Planning Ahead, Matching Results, and Confirming Trends

Needless to say, the approval of an influenza vaccine made from a novel technique was not as straightforward as that of one utilizing an existing and well-known manufacturing process. Despite the well-laid foundation in influenza vaccines, there remained a great deal of uncertainty with regards to the vaccine's efficacy and safety, and neither the sponsor nor the US FDA could predict what would be lurking around the next corner. Overall though, Flublok's approval, which eventually evolved into a traditional approval, did not take significantly more time than Agriflu's accelerated approval. This was made possible by planning ahead,

[90] Lily PH Yang, *Recombinant Trivalent Influenza Vaccine (Flublok®): A Review of Its Use in the Prevention of Seasonal Influenza in Adults*, 73 DRUGS 1357,1364 (2013).
[91] Barry Buckland et al., *Technology Transfer and Scale-up of the Flublok® Recombinant Hemagglutinin (Ha) Influenza Vaccine Manufacturing Process*, 32 VACCINE 5496 (2014).

doi:10.6342/NTU202302527

matching results, and confirming trends, which all took the cooperation of the sponsor and the US FDA.

All of the trials that were reviewed by the US FDA for the BLA were designed with multiple endpoints, and it was definitely the exploratory endpoints (or tertiary endpoints) that stole the show. While some trials were designed to evaluate dosing, some to assess lot-to-lot consistency, and others for different populations and thus had different control arms, all of the trials set immunogenicity endpoints, clinical endpoints, and then more open (non-strain specific) clinical endpoints. In view of the unreliable predictions of virus strain each year, tertiary endpoints for more open clinical determinations and immunogenicity endpoints are necessary, lest the predictions should go off into outer space for the flu season of the study and the study would be found completely useless. It also cannot be neglected that prespecified immunogenicity endpoints were feasible because of the rich amount of data accumulated from dozens of influenza vaccines in the past. In the case of Flublok, PSC01 also demonstrated how dose finding Phase II trials could be designed to supplement subsequent Phase III trials by adding immunogenicity and clinical follow-up.

Since none of the clinical trials provided definite conclusions regarding the efficacy of Flublok for the strains it was intended for either immunogenicity-wise or clinically, the various endpoints set by the clinical trials had to match and supplement each other to establish favorable trends. This was reflected fully in the reviewer's comments, where the reviewers pointed out results that fell short of pre-designated goals, and searched for viable explanations within the same trials. For example, although no clinical trial yielded clinical efficacy results that reached the preferred pre-defined endpoints, the reviewers looked back at how immunogenicity

doi:10.6342/NTU202302527

results corresponded to the numbers that were seen in clinical evaluation. The safety assessment, which went smoothly with no outstanding issues, was also supported by comparing the ratio of different levels of adverse events to the ratio of randomization, and even to that of licensed influenza vaccines. This was probably also inevitable due to the limited size of the clinical trials, as rare adverse events bear little chance of being comprehensively investigated in clinical trial settings.

Finally, although only one trial recruited more than 3000 subjects, and all trials failed prespecified clinical endpoints, all of the 4 clinical trials evaluated showed the same pattern in clinical and immunogenicity results. This evidently boosted the FDA's confidence for Flublok, especially with the FDA's determination to increase the availability of influenza vaccines. The three trials that only recruited hundreds of patients not only served as preliminary support for older populations, but also helped establish a trend in efficacy that encouraged the reviewers to approve Flublok. Furthermore, the safety observations were also similar across the different trials, holding up the idea that Flublok was well-tolerated in the licensed population. Therefore, even though the trials themselves did not offer satisfactory evidence, the FDA took a step back and looked at all of the trials so as to achieve its goal of being better prepared for influenza epidemics.

V. Conclusion

Vaccines have an irreplaceable role in human's combat against infectious disease, and admittingly, also increasingly in other diseases. Being preventive in nature and requiring a certain portion of the population administered for to achieve anticipated protection for the population as a whole, vaccines are different from regular drugs in that they are mostly administered on large numbers of healthy individuals, and they serve an even greater public health role. This has made

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developing and approving vaccines trickier than it is for drugs, and also more public health oriented. Needless to say, since vaccines are preventive in nature, clinical efficacy endpoints require time to achieve, and sometimes cannot be appropriately captured by clinical trials. Furthermore, there is also the question whether the vaccine may have lasting consequences on the youthful healthy individuals it was administered on. When reviewing vaccines, the FDA also has to take into account the size and severity of epidemic, which may affect both the availability of participants and the need of the vaccine. While there is considerable pressure on the US FDA to secure protection against infectious diseases, all hurdles need to be cleared. Close cooperation between the sponsor and the US FDA even during clinical trial designing stages aide in making a smoother approval review. When guidelines are followed, and goals are achieved, approval can be easy as breeze. However, when trials deviate from guidance instructions, or when targets are missed, the US FDA is observed to aggressively request supplemental information from the sponsor, and is not afraid to make decisions based on fortified trends.

For influenza vaccines, accelerated approval appeared to have given applicants a slight edge over those undergoing traditional approval. Agriflu had a relatively smooth approval process, but it still took two years since initial submission for the vaccine to be approved. Flublok, utilizing novel production methods, underwent a traditional approval wrangled by an erratic flu season where strain predictions went all off, and was further complicated by immunogenicity assessment issues that took an additional 3 years to resolve. In terms of clinical trial duration, accelerated approval guidance documents allowed sponsors to apply for approval based on Day 28 immunogenicity results, while trials with clinical endpoints had to commence before an influenza season and could only end with the

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it. As safety data are only required up to 6 months for both pathways, the difference between immunogenicity and clinical endpoints are solely responsible for trial duration, which creates approximately 7-8 months advantage for those undergoing accelerated approval. However, our attention is drawn to non-clinical (neither efficacy nor safety issues) factors that delayed approval. Agriflu was reviewed quickly, however issues at foreign trial sites necessitated a visit and investigation that held the approval back for a few months. The Advisory Committee discussed Flublok's efficacy and safety data as early as November 2009, a little over 2 years from its application, and Flublok was actually on track to be approved had there been no CMC concerns. Instead, the trial antibody assays created so much trouble that Flublok's efficacy was in jeopardy, and slapped another 3 years to Flublok's approval.

For both the accelerated approval and traditional approval of influenza vaccines, the guidance documents and past experience played a critical role. As guidance documents are formulated by US FDA officials through intense discussion and follow-up with the academia and industry, they represent widely recognized consensus both domestically and internationally. Based on these agreements constantly kept up-to-date with research advancement, the sponsors have a set of rules to play with, and the US FDA has a ruler to judge by. In extremely simplistic annotations, influenza vaccines applying for approval in the United States have to achieve at least an 40% vaccine efficacy, or be at least 66.7% as effective as existing vaccines. For vaccines using licensed manufacturing processes, the vaccine had to either stimulate adequate immune response in 70% of subjects, or achieve seroconversion in 40% of subjects. A minimum of 6 months of detailed safety data for comparative and descriptive analysis is also mandatory. These are the widely

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agreed upon standards set out in the rulebook, but it seems the US FDA is not ever so rigid when actually reviewing vaccine in light of yearly influenza epidemics. In the following chapter, we will discuss whether and how these the numbers and narratives above come into consideration in the emergency use authorization process.

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Chapter 4 Emergency Operations: EUAs for COVID-19 Vaccines

From the previous two chapters, we have constructed a clear view of the US FDA approval process for both drugs and vaccines. Drug approvals are based on clinical trial studies conducted in target diseased populations, and even for novel agents, there was considerable flexibility regarding clinical trial designs and trial subjects. Vaccine approvals appear to be under more stringent review, generally requiring larger clinical studies that follow existing guidance documents strictly, especially in the case of novel manufacturing processes. Under this scheme, vaccine traditional approvals take up to 5-6 years, whereas reviews of accelerated approvals took up to 2 years, regardless of the duration of clinical trials. Efficacy reviews for both drugs and vaccines relied greatly on previous experience with the same disease and better yet, similar products. The concept of establishing surrogate markers and/or non-inferiority was commonly used by the US FDA to accelerate the development of new agents, as well as the acceptance of predefined trial adaptations. Safety reviews did not differ much in system between drugs, vaccines, traditional approvals and accelerated approvals. It was well acknowledged that while screening for safety signals was necessary, not all safety issues could be picked up during trial phases.

The COVID-19 pandemic therefore posed a seemingly insurmountable challenge for the US FDA approval system. It goes without saying that a vaccine against the somewhat unfamiliar virus is warranted, and preferably as quickly as possible. However, the US FDA has never been able to complete the approval process within 1 year, and that was even with pre-established guidance

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documents and surrogate markers. If the US FDA were to go faster than that, or in other words, to balance the need for the vaccine and guaranteeing the vaccine's efficacy and safety, what sacrifices may be deemed acceptable? Are there alternative ways to speed things up?

Here I would like to make a quick peek at the ending: the COVID-19 virus was first identified in December 2019, the world went into lockdown in March 2020, and by late December 2020, the US FDA had already authorized use for its first COVID-19 vaccine. Several other vaccines were also brought onto the market through the same approval process, the Emergency Use Authorization, in the following weeks and months. In other words, it took approximately a year for novel COVID-19 vaccine to be developed and approved. In addition to the extremely compressed investigative phases, only 6 months lapsed from the when the pivotal clinical trials began to when the vaccines were authorized for use. How was this possible? How did the US FDA determine the vaccines to be sufficiently effective to protect the human population against the newly emerged virus, and how was US FDA satisfied that these vaccines were safe? And were they?

This chapter looks back on the existing emergency authorization regulations, and the moves that were taken based on these regulations by the US FDA mainly during the year 2020, up to when the first COVID-19 vaccines were approved. The observations will be based on the US FDA decisions for drugs and influenza vaccines described in the previous two chapters, comparing what the US FDA has done differently and what it has not relinquished even in the face of the unprecedented pandemic. I will also take a look at how the US FDA actions influence that of the other reviewing agencies, namely the FDA in

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Taiwan, as part of the reflections on how emergency use authorizations are utilized across the globe in the COVID-19 emergency.

I. Overview of Emergency Use Authorization

The Emergency Use Authorization (EUA) program of the US FDA was established in 2004, as part of the response to the 911 and anthrax attacks in 2001. At that time, the only pathway for non-approved products to be used on human bodies was the investigation new drug protocol (IND), which required institutional review board (IRB) reviews of trial protocols, informed consent of participants, rigorous record keeping, and patient monitoring, and were not aimed at large scale emergencies.[1] For example, in the 1970s and 1980s, investigational drugs were used through INDs to address the then expanding HIV pandemic, and also on soldiers in the Gulf War to prevent infectious diseases. When Project Bioshield Act passed in 2004, Section 564 was added to the Food, Drug and Cosmetic Act, creating the emergency use authorization pathway. The pathway was further supplemented by Sections 564A and 564B in 2013 by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) to address more diverse emergency use.

The emergency use authorization program in the FD&C Act has three basic components. First, an emergency status needs to be declared by the Secretary of the Department of Health and Human Services under specified circumstances. Secondly, the emergency use authorization is available to medical products not have not been approved for use by the US FDA. Thirdly, these medical products will need to demonstrate probable evidence so that one could reasonably believe

[1] Stuart Nightingale et al., Emergency Use Authorization (EUA) to Enable Use of Needed Products in Civilian and Military Emergencies, United States, 13 EMERG INFECT DIS 1046 (2007).

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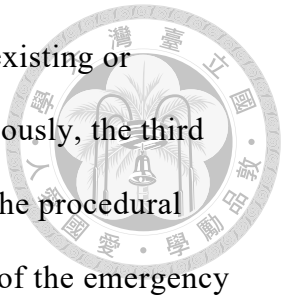

they are effective against the disease in question, and that the existing or potential benefits of the product exceeds that of the risks. Obviously, the third prong will be the focus of this chapter, but I will also go over the procedural aspects of the program, because they reflect the determination of the emergency status, as well as how and when emergency use authorization schemes should come to an end.

A. The Federal Regulations: Emergency Determination, Medical Product Types, and Efficacy Standards

Subclause (b) of Section 564 of the FD&C Act defines the 4 conditions for which the Secretary of the Department of Health and Human Services may declare emergency status that justifies the use of emergency use authorization. The first two are of homeland defense related reasons, and need to be based on the determination of either the Secretary of Homeland Security or the Secretary of Defense, and involve attacks with biological, chemical, radiological or nuclear agents. The third is worded for public health emergencies, both existing and ones with significant potential, that create national security concerns, or may affect the health and security of Unites States citizens. The fourth, while also related to public health issues, requires the prerequisite identification of a material threat according to Section 319F-2 of the Public Health Service Act (for strategic national stockpile and security countermeasures)[2] that may affect national security of the health and security of citizens living abroad.[3] The existence of the above mentioned emergencies is not enough to launch emergency use authorization programs; the HHS secretary also needs to make

[2] 42 USC § 247d–6b.
[3] 21 USC § 360bbb-3(b)(2).

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the determination that emergency use authorizations through this section is justified. This determination needs to be published in the Federal register promptly, as do the termination and advance notices for termination of the declaration.[4]

Two types of medical products are eligible for emergency use authorization. The first type is medical products that have not been approved, licensed or cleared for commercial use either unconditionally or conditionally, under Section 355 (approval for new drugs), 360(k) (clearance for commerce of medical devices), 360(b) (approval for animal drugs) or 360(e) (premarket approval of medical devices) of the FD&C Act or Section 351 (licensure of biologics) of the Public Health Service Act, or conditional approve under Section 360ccc (conditional approval of new animal drugs) of the FD&C Act. The second type are medical products approved/licensed/cleared through the above mentioned processes, but its approved/licensed/cleared uses, or in medical terms, indications, do not include the usage it is currently needed for. The second type is also known as the unapproved use of an approved product.[5] A detailed description of how the EUA program operated will be given in the following sections, but on a brief note and to give an example on the two types of medical products, the early EUAs given by the US FDA in response to the COVID-19 pandemic were mostly EUAs for unapproved uses of an approved product, while COVID-19 vaccines would belong to the first type, unapproved medical products, because evidently no vaccine would have existed for this virus before its existence. One of the first US EUAs for unapproved uses of an

[4] 21 USC § 360bbb-3(b)(4).
[5] 21 USC §360bbb-3(a)(2)

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approved product was the controversial chloroquine phosphate and hydroxychloroquine sulfate, which were originally approved for indications including the treatment and prevention of malaria, amoeba infections, systemic lupus erythematosus, and rheumatoid arthritis, but obviously not for COVID-19.[6] The EUA for chloroquine phosphate and hydroxychloroquine sulfate allowed for use of the products to treat COVID-19 infections, a usage that it was not previously approved for. Other products approved through EUA during the COVID-19 pandemic, including diagnostic assays, drugs and vaccines, are novel products aimed specifically towards the COVID-19 virus, and are therefore the first type of medical products under the EUA program. The major difference between the first and second types of medical products in the EUA program is the availability of safety data: medical products that have been approved for other uses have been used on the market, and therefore have pre-existing safety data that can be used as reference. Its efficacy remains to be supported by additional evidence.

Finally, and also core to the discussions of this thesis, subsection (c) defines the criteria for issuance of EUA as the following:

> *The Secretary may issue an authorization under this section with respect to the emergency use of a product only if, after consultation with the Assistant Secretary for Preparedness and Response, the Director of the National Institutes of Health, and the Director of the Centers for Disease Control and Prevention (to the extent feasible and appropriate given the*

[6] DEPARTMENT OF HEALTH AND HUMAN SERVICES, AUTHORIZATIONS AND REVOCATION OF EMERGENCY USE DRUGS DURING THE COVID-19 PANDEMIC; AVAILABILITY (2020).

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applicable circumstances described in subsection (b)(1)), the Secretary concludes—

***(1)** that an agent referred to in a declaration under subsection (b) can cause a serious or life-threatening disease or condition;*

***(2)** that**, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that**—*

***(A)**the product **may be effective in diagnosing, treating, or preventing**—*

***(i)** such disease or condition; or*

(ii)**a serious or life-threatening disease or condition caused by a product authorized under this section, approved or cleared under this chapter, or licensed under section 351 of the Public Health Service Act [42 U.S.C. 262], for diagnosing, treating, or preventing such a disease or condition caused by such an agent; **and

***(B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product**, taking into consideration the material threat posed by the agent or agents identified in a declaration under subsection (b)(1)(D), if applicable;*

***(3) that there is no adequate, approved, and available alternative** to the product for diagnosing, preventing, or treating such disease or condition;*

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(4) *in the case of a determination described in subsection (b)(1)(B)(ii), that the request for emergency use is made by the Secretary of Defense; and*

(5) ***that such other criteria as the Secretary may by regulation prescribe are satisfied****.*

I will first make a straightforward comparison between the standards set for efficacy and safety for EUAs to those for traditional and accelerated approvals for either drugs or vaccines. Recall the regulations quoted in chapter 2 and chapter 3. For drug approvals, the FD&C Act requires sponsors of new drugs to submit "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed…", and that the results of the tests should show that "the drug is safe for use under such conditions", and that there is "substantial evidence" that the drug will have the effect it purports. Substantial evidence is further 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.*"[7] For accelerated approval of drugs, the standard was: "*the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity and mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of*

[7] 21 USC §355 (d).

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alternative treatments."[8] Such evidence may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers or other scientific methods or tools.[9] For vaccines, which require BLA licensure, the Public Health Service Act requires only the biological product to be "safe, pure and potent", detailed standards on data and information is deferred to the FD&C Act.[10]

A brief and blunt comparison of the three different approval pathways can be made from the regulations itself. In terms of efficacy, adequate and well-controlled investigations are mandatory for traditional approvals, but not for EUAs. Furthermore, traditional approvals can be made only when experts conclude "fairly and responsibly" that the product is effective for its purported use. Accelerated approval requires the product to show the same efficacy on surrogate markers, but state that surrogate markers only need to be "reasonably likely" to reflect clinical benefit. As for EUAs, the regulations require "reasonable belief" that the product "may be" effective. In terms of safety, traditional approval requires the sponsors to demonstrate that the product is safe for use under its applied indication, while the Secretary is directed to implement the risk-benefit assessment framework for new drug approvals. No specific clause addresses the safety standards for accelerated approval. While there is also no particular regulation on the safety of EUA products, the FD&C Act does mandate a risk and benefit analysis for both known and potential risks and benefits that would include safety analysis. To sum up, the EUA regulations loosened the standards for quality of evidence, standard of efficacy, as well as

[8] 21 USC §356 (b)(1)(A).
[9] 21 USC §356 (b)(1)(B).
[10] 42 USC §262(a)(2).

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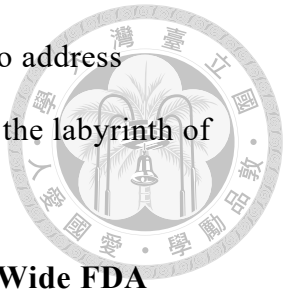
standard of safety for medical products, undoubtedly hoping to address emergencies as quickly as possible, and not to be hindered by the labyrinth of US FDA approvals.



B. FDA Guidance on EUAs: A Focus on Procedure, and Wide FDA Discretion on Standards

Based on the authorization from the FD&C Act emergency use authorization clause, the US FDA has issued guidance documents on EUAs. In January 2007, the FDA published the Emergency Use Authorization of Medical Products and the Emergency Use Authorization Questions and Answers in 2009. When the PAHPRA amendments were made in 2013, the FDA issued a new set of guidance documents with a better focus on public health needs in April, 2016 to replace to previous two guidance documents, and finalized the guidance document Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders.[11] This guidance served as the procedural basis for US EUAs, and was not amended even to the end of the pandemic.

The guidance first clarifies that the EUA is separate from the use of medical products under investigative applications or expanded access, and that it is within the Commissioner's purview to make individual authorizations once the EUA declaration has been made by the HHS Secretary. The guidance document also emphasize the authorizing criteria for medical products. It interprets the FD&C Act to mean that targets of the medical product seeking EUA must be causing a serious or life-threatening disease or condition,

[11] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS AND RELATED AUTHORITIES: GUIDANCE FOR INDUSTRY AND OTHER STAKEHOLDERS (2017).

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confirming the narrow circumstances for which EUAs can be granted. It also identifies that the "may be effective" standard is lower than that for traditional or accelerated approval processes, and that the US FDA will assess this criteria on a case-by-case basis, utilizing a risk-benefit analysis. To perform the risk-benefit analysis, the FDA will look at the "totality of scientific evidence" to make an overall determination, which may include but is not limited to: clinical trials conducted both domestically and abroad, and even animal study data for efficacy. On top of that, the guidance document explains what constitutes adequate or available in the "no alternatives" requirement. Insufficient supplies of other products may be deemed "unavailable"; indication not including certain populations would make the medical product "inadequate"; and resistance developed against existing approved products would also satisfy the requirement.[12]

Going into specific instructions of EUA application procedures, the US FDA encourages cooperation strategies that were not included in the federal regulations. Firstly, the US FDA indicates that an IND or IDE (investigational process license) is not warranted for products aimed at an EUA submission. Secondly, the US FDA dedicates a large section to describing pre-EUA activities that would facilitate the subsequent submissions, urging sponsors to engage with the US FDA early in development, and to confirm trial and analyses strategies in the advance stages of development, so that developments will not be impeded by rapidly changing circumstances. Pre-EUA discussions may range from determining suitable approval pathways to appropriate trial protocols to obtain authorization. However, the guidance document insists that

[12] *Id*. at 4-8.

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these discussions do not indicate US FDA qualifications, and that US FDA decisions at this stage would be based on a number of factors unrelated to the clinical characteristics of the medical product, including competing US FDA obligations and government stockpile needs.[13]

The guidance document also outlines the information and/or data that sponsors of an EUA should prepare for submission. The summary of scientific evidence should include information on the product's safety and effectiveness, risk and benefit assessments (which should include an adverse event profile), and approved alternatives to the product. For safety information, which was not mentioned at all in the federal regulations, the US FDA states its preference for safety data from controlled clinical trials, but will also consider data from other clinical experience and even non-clinical data if controlled clinical trials are not available. Rigorous safety data would be required of unapproved products, compared to approved products seeking authorization for unapproved use. In comparison, only very large strokes were made for efficacy data instructions. In addition to emphasizing efficacy standards would be made on a case-by-case basis, the US FDA recommends sponsors to describe the product's mechanism of action, preclinical testing data, animal testing data, any evidence from human experience, and data supporting dosing decisions. As for risk and benefit analysis, which the federal regulations specifically asked for, the guidance vaguely describes items that might be needed, such as risk mitigation or benefit optimizing measures, limitations and uncertainties, contraindications, and anticipated effect of the product on the agent it is intended for. Conditions necessary or appropriate to protect public health may be imposed on an EUA,

[13] *Id*. at 9-10.

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and monitoring and reporting of adverse events is mandatory according to the federal regulations for unapproved products.[14]

In short, the US FDA guidance document on EUAs is more of a procedural manual and a reinstatement of the agency's wide discretion for safety and efficacy standards in EUA programs. As stated multiple times throughout the guidance document, safety and efficacy standards will be decided on a case-by-case basis. This is understandable, as emergencies can be very different in nature, and different products with varying goals that cannot be easily summarized in a single guidance document. As we can see in the following section, for the same emergency, the COVID-19 pandemic, it was necessary to develop different standards for diagnostics, drugs, and vaccines.

II. The COVID-19 Pandemic: Racing by Rolling

The COVID-19 virus was not entirely and utterly novel to the human society. The SARS virus that created chaos in the densely populated Asian region in 2003 was also a coronavirus, both viruses were transmitted similarly, and even developed similar symptoms. Although the deadly SARS epidemic died down mysteriously within months before vaccines could be fully developed, it was clear that this sort of miracle could not be banked on when a new coronavirus hit. Therefore, when the COVID-19 pandemic unraveled, in addition to churning out reliable diagnostic tests and protective equipment, the sense that COVID-19 vaccines would be necessary to end the pandemic gradually took shape. The problem was more of how and when it could be achieved.

[14] *Id*. at 11-25.

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Numerous developments that occurred across the span of two decades contributed to an sturdy foundation for COVID-19 vaccines to build upon. First of all, new vaccine technologies were already being experimented with that allowed rapid manufacturing. Secondly, with the isolated and preserved SARS virus, we have gained a better understanding of the coronavirus, which made early identification of potential targets for vaccine design possible. Thirdly, a matured scheme for reviewing vaccine efficacy and safety is familiar to both the reviewing agency US FDA and to vaccine manufacturers. In other words, the common language spoken between the industry and the governmental authorities facilitated development of standards and procedures. The US FDA began by communicating with vaccine developers, and publishing guidance documents for COVID-19 related medical products. As vaccine development progressed, the US FDA also issued guidance documents specifically for vaccines, amending them on the way.

A. Declaration of Health Emergency

Even though the virus was not completely unfamiliar, the speed with which it spread throughout the globe was unprecedented. With first cases identified in China in mid-December 2019, the virus spread across the Pacific to USA in mid-January, and was transmitting domestically by the end of the same month. With the global epidemic and quick spread of the virus in mind, the US Secretary of Department of Health and Human Services announced a public health emergency. Nevertheless, the virus continued to spread across the country, necessitating emergency authorization schemes for medical products. On February 4, 2020, the Secretary of HHS determined that the public health emergency has posed a significant threat to national security, or the health and

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security of citizens living abroad, and that circumstances justify the authorization of emergency use of diagnostics for the detection and diagnosis of the COVID-19 virus.[15] On March 27, 2020, the Secretary of HHS further extended the emergency use authorization scope to use of drugs and biological products during the COVID-19 pandemic.[16]

With the declarations under their belts, the FDA first began issuing a number of EUAs, including the first diagnostics tests on February 4, and the first drugs to be used against COVID-19: hydroxychloroquine sulfate and chloroquine phosphate products, on March 28, 2020. The first EUAs appeared to be trouble-ridden and several were revoked after more evidence became available. In May 2020, the FDA began publishing guidance documents for different types of medical products applying for emergency use authorization and approvals. These included a guidance on drugs and biologics aimed at treating the disease, a guidance on developing diagnostic kits for diagnosing the disease, a guidance on monoclonal antibody products for treatment and prevention of the disease, and obviously, one for the development of COVID-19 vaccines. The guidance document on COVID-19 vaccines continued to be revised throughout the public health emergency according to the existing knowledge of the disease, as well as the availability of new products.

B. COVID-19 Vaccine Guidance Documents: Trial Design, Efficacy Cutoffs, and Safety Requirements

[15] DEPARTMENT OF HEALTH AND HUMAN SERVICES, DETERMINATION OF PUBLIC HEALTH EMERGENCY, FR85(26) 7316-7317 (2020).
[16] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION DECLARATION FR 85(63) 18250-18251 (2020).

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A COVID-19 vaccine development guidance document was first published in June 2020, followed by the a guidance document specifically for emergency use authorizations in October 2020. Considering the fact that early human trials commenced in the United States in March 2020,[17] the guidance documents seemed to have arrived a bit late. However, the document still serves as important guidance for vaccine development in terms of phase II and III trial protocol design, safety evaluation, statistical analysis, and evidently, emergency use authorization standards.

The guidance document "Development and Licensure of Vaccines to Prevent COVID-19" (hereinafter the Licensure Guidance Document) published in June 2020 focuses on the data needed to achieve BLA licensure for COVID-19 vaccines, including clinical and non-clinical items for review. For the purposes of this thesis, only the clinical parts of the guidance documents will be reviewed here. The Licensure Guidance Document states first and foremost that it is principle for sponsors to apply via the traditional approval route, since no surrogate markers exist. The Licensure Guidance Document also opens the possibility for adaptive and/or seamless clinical trial designs for more rapid progression through clinical trial phases, given sponsors discuss trial directions with the US FDA as soon as possible. In terms of safety, sponsors are required to act upon preliminary safety data that inform on the risk of vaccine-associated enhanced respiratory disease, a vaccine risk identified during the development of other coronavirus vaccines, as a safeguard for study participants.[18] In terms

[17] Center for Disease Control and Prevention, *CDC Museum COVID-19 Timeline* (March 15, 2023), https://www.cdc.gov/museum/timeline/covid19.html (last accessed April 3, 2023).
[18] DEPARTMENT OF HEALTH AND HUMAN SERVICES, DEVELOPMENT AND LICENSURE OF VACCINES TO PREVENT COVID-19 (JUNE 2020) 9 (2020).

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of efficacy, details are given on trial population selection, requiring early phase human trials to enroll healthy adults with low risks of severe COVID-19, dose finding, and collecting immunogenicity data.[19]

For later phase clinical trials, the Licensure Guidance Document emphasizes that the enrollment of "many thousands" of participants would be necessary, and at this stage, participants should include those with comorbidities, those with previous COVID-19 infections, as well as diverse ethnic and racial populations. Later phase efficacy trials should all be randomized, double-blinded, and placebo-controlled, with 1:1 randomization between vaccine and placebo groups. Once a safe and effective vaccine becomes available, this vaccine should be used as the control group intervention in subsequent efficacy trials, and that trials shall be prepared in advance for this circumstance. Multiple vaccines can be tested in the same clinical trial, and lot-to-lot consistency trials could be included in the efficacy trials. Safety follow-up durations should be extended as long as possible, with one to two years as the minimum. Several suggestions were given for clinical endpoints: while preferring virologically confirmed SARS-CoV-2 infection with one or two clinical symptoms as the primary endpoint, endpoints without clinical symptoms are also accepted. However, the US FDA further advises sponsors to include analysis of asymptomatic and severe versus mild COVID-19 in efficacy trials, and defines severe COVID-19 as patients with positive PCR results, and exhibiting any of the following: clinical signs of severe systemic illness (respiratory rate > 30 per minute, heart rate >125 per minute, SpO2< 93% on

[19] *Id*. at 10.

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room air at sea level or PaO2/FiO2<300mmHg), respiratory failure, evidence of shock, significant organ failure, admission to ICU or death.[20]

The efficacy cutoff numbers were given as statistical considerations in the Licensure Guidance Document. By setting the point estimate for placebo-controlled efficacy trials at 50%, the US FDA is basically drawing the approval line at vaccine efficacy of 50%. The US FDA further requires that the alpha-adjusted confidence interval lower bound be greater than 30%, and emphasizes that the same standards apply to interim analyses aimed at early detection of efficacy, implying the same standards would be used in in EUA reviews. The Licensure Guidance Document also points out that should COVID-19 vaccines be licensed for use, subsequent non-inferiority trials using licensed vaccines as control group should set the primary relative efficacy point estimate at ≥10%, which can be roughly understood to mean the trial vaccine should at least be 90% as effective as licensed vaccines.[21]

The safety evaluation guidance was similar to that of the influenza vaccine guidance: solicited local and systemic adverse events should be recorded at least 7 days after vaccination, unsolicited adverse events in all study participants for at least 21-28 days after vaccination, serious adverse events to be evaluated for at least 6 months for all study participants, though longer follow-up periods may be necessary for vaccines using novel platforms, and constant monitoring of balance of randomization ratio and adverse events ratio is necessary. The minimum size of the safety database was set to be 3000, but if significant safety signals arise during the trial phases, further evaluation might

[20] *Id*. at 10-14.
[21] *Id*. at 14.

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be needed. Unlike most traditional approvals, the US FDA envisions it to be necessary for post-licensure safety monitoring and pharmacovigilance activities to take place, and did not rule out supplementary safety investigations for specific concerns. Although the EUA process and future approvals based on surrogate markers are contemplated in the Licensure Guidance Document, nothing concrete was stipulated at that time.[22] The Licensure Guidance Document has not been amended to date.

Building on the Licensure Guidance Document, the US FDA rolled out the "Emergency Use Authorization for Vaccines to Prevent COVID-19 - Guidance for Industry" (hereinafter the EUA Vaccine Guidance Document) in October 2020. Unlike the Licensure Guidance Document, the EUA Vaccine Guidance Document is only meant for the duration of the public health emergency, which is in conformance with the FD&C Act. Sponsors applying for EUAs are still expected to complete phase III trials with clinical endpoints and file for traditional approval once there is "substantial evidence" that the vaccine is effective and safe. Early communication with the US FDA is again encouraged with the sponsors, and sets rare communication requirement: chemistry, manufacturing and controls information and data for IND should be submitted at least one month before EUA application, and notifying the US FDA at least 24 hours before any interim analysis is completed.[23] The safety and effectiveness information part of the EUA Vaccine Guidance Document is a compilation of requirements for typical IND applications and the continuous stages of the clinical trials. Details on the bioassays used for clinical endpoint

[22] *Id*. at 15-19.
[23] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION FOR VACCINES TO PREVENT COVID-19 -GUIDANCE FOR INDUSTRY (OCTOBER 2020) 4 (2020).

doi:10.6342/NTU202302527

determination, and a list and summary of all relevant nonclinical studies were also required. The utility of interim analysis from Phase III efficacy studies with a clinical endpoint is also recognized.

Considering the short time for development of the vaccine, safety data for all phases of clinical trials be collected and submitted for review, and phase III clinical trials should include median follow-up duration for at least two months. The safety data must include local and systemic solicited adverse reactions, severe adverse events and adverse events of special interests data up to at least one month for more than 3000 vaccine recipients, and at least 5 severe COVID-19 cases in the placebo group to support a favorable benefit-risk profile for vaccine-induced ERD.[24] Furthermore, active follow-up for safety for all those that receiving the vaccine under the EUA would be mandatory, and sponsors must propose strategies on how to continue with clinical trials after the EUA has been granted.[25] This shortened safety follow-up period is generally undisputed, as it is inevitable that rare adverse events arise only after medical products are applied on a wider population. However, it will be important to deal with new or known adverse events (such as hypersensitivity) that arise after the EUA is granted to ensure a balance between vaccine coverage and safety.[26]

Procedural-wise, the US FDA announces in the guidance document that a designated VRBPAC session will be held openly to discuss the safety and efficacy of each and every vaccine EUA application that has, "on its face", submitted all information under Section 564 of the FD&C Act and the Vaccine

[24] *Id*. at 10.
[25] *Id*. at 11.
[26] Mariana C Castells & Elizabeth J Phillips, *Maintaining Safety with SARS-CoV-2 Vaccines*, 384 N ENGL J MED 646-648 (2021).

doi:10.6342/NTU202302527

EUA document. The FDA also aims to make briefing material for the VRBPAC available online at least two days before the meeting is scheduled. Only manufacturing information that is considered confidential commercial or trade secret will be discussed in closed meetings, and not subject to public disclosure. The Vaccine EUA guidance further explains that information availability shall be subject to relevant FDA guidance, but would not be limited by the time frame given in those guidance documents.[27]

After the first EUAs, the FDA revised the Vaccine EUA Guidance Document in both February and May 2021. In February, the FDA added Appendix 2 to the Vaccine EUA Guidance Document, which elaborated on adjustment of prototype vaccines for SARS-COV-2 variants.[28] In May, the US FDA added a passage explaining its prioritizing rationale for COVID-19 vaccines. The US FDA references the Emergency Use Authorization of Medical Products and Related Authorities Guidance Document to stress that decisions on EUAs factor in public health needs, availability and adequacy of the information concerning the safety and efficacy of the product, whether the product will be included in government stakeholder stockpiles. However, for a stringent review on product quality and evaluation of clinical trials, early interaction with the US FDA is crucial. Thus, the US FDA is inclined to not review or process future EUA requests from vaccine developers that have not been engaging with the US FDA in an ongoing manner regarding the development of their product. The US FDA believes that this would enhance the

[27] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 23, at 10-11.
[28] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION FOR VACCINES TO PREVENT COVID-19 -GUIDANCE FOR INDUSTRY (FEBRUARY 2021) 18 (2021).

doi:10.6342/NTU202302527

integrity as well as speed up the authorization process.[29] No changes were made to trial design, safety requirements, and efficacy cutoffs for new submissions of EUAs throughout the public health emergency.

C. Interim Analysis –An Additional Role?

One of the greatest efforts offered by the guidance document aimed at accelerating the COVID-19 vaccines authorization is the use of interim analysis for efficacy evaluation. The EUA Vaccine Guidance Document did not elaborate on the definition and extent of interim analysis, but it is actually a concept and method that has been well-developed and incorporated into clinical trial design for more than four decades.[30] It is commonly used to determine whether the clinical trial in question is still worth continuing and occasionally to adjust the proceedings of a clinical trial,[31] and has been recognized by the US FDA as an important statistical tool in clinical trials as early as 1998.[32] In fact, the US FDA issued guidelines on how to use interim analysis to determine or adjust clinical trial size, and even under some circumstances to adjust study design.[33] Interim analysis has also been useful in ending clinical trials early and achieving an earlier traditional approval, in which case the US FDA still determines that there is substantial evidence supporting the product's efficacy.[34]

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[29] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION FOR VACCINES TO PREVENT COVID-19 -GUIDANCE FOR INDUSTRY (MAY 2021) 5 (2021).
[30] For one of the earliest guidelines on interim analysis in clinical trials, see: Nancy L Geller & Stuart J Pocock, *Interim Analyses in Randomized Clinical Trials: Ramifications and Guidelines for Practitioners*, 43 BIOMETRICS 213 (1987).
[31] A. Kumar & B. S. Chakraborty, *Interim Analysis: A Rational Approach of Decision Making in Clinical Trial*, 7 J ADV PHARM TECHNOL RES 118 (2016).
[32] DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDANCE FOR INDUSTRY: E9 STATISTICAL PRINCIPLES FOR CLINICAL TRIALS 24-26 (1998).
[33] DEPARTMENT OF HEALTH AND HUMAN SERVICES, ADAPTIVE DESIGNS FOR CLINICAL TRIALS OF DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY (NOVEMBER 2019) (2019).
[34] An example of a cancer drug achieving traditional approval with early stoppage in phase III trial with favorable interim analysis, *see* Robert C Kane et al., *United States Food and Drug Administration Approval Summary: Bortezomib for the Treatment of Progressive Multiple Myeloma after One Prior Therapy*, 12 CLIN CANCER RES 2955 (2006).

doi:10.6342/NTU202302527

However, can interim analyses results be used in accelerated approvals and EUAs as well?

First clues can be found in the definition of interim analysis. The US FDA guidance document on adaptive clinical trial design defines interim analysis as: "*any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial.*"[35] The adaptive trial guidance document recognizes that early stoppage of trials can be due to the following results in interim analysis: clear establishment of superiority, unlikeliness of trial demonstration of treatment difference, and apparent unacceptable adverse effects observed from the trial. Based on this description, it seems the US FDA is open to approving drugs and biologics whose clinical trials were completed early, because interim analysis showed apparent benefits of the "treatment" under trial. Does this mean the US FDA has been using interim analysis as a tool to accelerate approval? The answer is yes, and no. Since accelerated approval was established in 1992, many drugs and biologics have attempted to test the limits of the US FDA approval standards. Soaring incidents and mortalities of various cancers drove scientists and pharmaceuticals on a spree for developing cancer treatments, coming up with second, third, fourth, and even more advanced lines of treatment for patients that fail the first line or classic treatment schemes. Understandably, clinical trials for advanced treatments were more difficult to complete due to the shrinking number of patients and unpredictability of treatment responses. Thus, cancer treatments have been applying for accelerated approval based on one large single-group study, and then conducting randomized controlled trials post-

[35] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 32, at 25.

doi:10.6342/NTU202302527

approval, or so called confirmatory trials, to evaluate treatment efficacy.[36] The drawback of this approach is that once treatments are approved based on accelerated approval, it becomes even more difficult to recruit subjects for the ongoing clinical trials, often resulting in confirmatory trials taking longer to complete, or even could not be completed. Ultimately, the clinical benefit of the cancer treatment could not be verified timely by controlled clinical trials, leading to drawn out verification or withdrawal, which poses risks to patients either way. To address the issue with uncertainty caused by accelerated approvals for oncology treatments, the US FDA has proposed, albeit unofficially, that oncological treatment sponsors base accelerated approval applications on interim analyses of phase III trials rather than final analyses of phase II trials as early as 2003.[37] In other words, the US FDA encouraged cancer treatment developers to design phase III trials with interim analyses even when they are aiming for accelerated approval, and to carry on with the same trial after accelerated approval has been granted to subsequently obtain traditional approval. The US FDA has since handed out accelerated approvals to several cancer treatments based on such clinical trial designs, including oxaliplatin for metastatic colorectal cancer in 2004,[38] and ado-trastuzumab emtansine for metastatic breast cancer in 2013.[39] Thus, incorporating interim analysis into accelerated approvals was not solely for the purpose of making accelerated approval even faster, but more to enhance the integrity of the

[36] Lola A. Fashoyin-Aje et al., *The On- and Off-Ramps of Oncology Accelerated Approval*, 387 N ENGL J MED 1439,1440 (2022).
[37] E. A. Richey et al., Accelerated Approval of Cancer Drugs: Improved Access to Therapeutic Breakthroughs or Early Release of Unsafe and Ineffective Drugs?, 27 J CLIN ONCOL 4398,4404 (2009).
[38] Amna Ibrahim et al., *FDA Drug Approval Summaries: Oxaliplatin*, 9 THE ONCOLOGIST 8 (2004).
[39] Laleh Amiri-Kordestani et al., *FDA Approval: Ado-Trastuzumab Emtansine for the Treatment of Patients with Her2-Positive Metastatic Breast Cancerfda Approval Summary for T-Dm1 for Her2+ Mbc*, 20 CLIN CANCER RES 4436 (2014).

doi:10.6342/NTU202302527

pathway, and deliver a swifter confirmation. That being said, accelerated approvals based on interim analysis has mostly been granted for cancer treatments, where trial subjects are patients hoping extend their lives by years or month, but not vaccines, which are directed for large healthy populations.

An important feature of interim analysis established its unique presence in modern day clinical trials and approvals. By US FDA definition, which reflects the consensus of biostatisticians, interim analyses need to be conducted by an independent body unrelated to trial operations, and are strongly encouraged to be pre-planned and predesignated in trial designs.[40] This means that interim analyses would not and should not affect the still ongoing trial, and prevents the interim analyses from contaminating study results. Only under this critical premise, may alterations to trial operation and design be feasible. Otherwise, an analysis conducted before the conclusion of the trial that unblind trial designation would effectively call an end to the trial, regardless of the interim analysis results. If interim analyses is so neutral and beneficial, why has it not been applied to vaccine development? In fact, it has. Vaccine clinical trials have been designed with interim analysis.[41] It is just that the US FDA has yet to recognize it as a valid approval endpoint. And yet, under the COVID-19 emergency, the US FDA has decided that the time has come for it to open the gates, at least temporarily.

Seeing as the Vaccine EUA Guidance Document was published after several COVID-19 vaccine trials have begun, and only preceded the first

[40] Kumar & Chakraborty, *supra* note 31, at 119.
[41] Dipika Sur et al., *Efficacy and Safety of a Modified Killed-Whole-Cell Oral Cholera Vaccine in India: An Interim Analysis of a Cluster-Randomised, Double-Blind, Placebo-Controlled Trial*, 374 THE LANCET 1694 (2009).

doi:10.6342/NTU202302527

COVID-19 vaccine approval by about 2 months, it is reasonable to assume that many of the trial designs, efficacy cutoffs, and safety standards were developed through private discussions with sponsors well before they submitted their EUAs, based on past experience in vaccine development and approvals on both sides. This can be confirmed by the US FDA repeatedly asking vaccine developers to facilitate early communication regarding trial design and manufacturing considerations in the guidance documents. Even so, we can observe from these guidance documents the US FDA's thinking on EUAs, as well as a clear standard for EUA set by the US FDA. If we make a simple comparison of the COVID-19 vaccine EUA guidance standards to that of influenza vaccines, we can see that some compromises the US FDA had decided to make. Efficacy wise, the EUA guidance standards require only a 50% point estimate for clinical efficacy at interim analysis, while influenza vaccines require 70% and completion of phase III trials. In terms of safety, the US FDA was ready to consider just a median of two months of safety follow up data as opposed to the standard 6-month follow up period for both traditional and accelerated approvals for influenza vaccines. On the other hand, the US FDA mandated COVID-19 vaccine EUA sponsors to complete clinical trials amidst the EUA, as well as post-market monitoring of adverse events to confirm safety. I will now turn to the earliest COVID-19 vaccine EUAs, to see whether the standards set out by the guidance documents were implemented in EUA approvals.

III. COVID-19 Vaccine Approvals by the US FDA

As stated before, within 300 days of declaring the public health emergency, the US FDA had authorized the first COVID-19 vaccine, BNT (by

doi:10.6342/NTU202302527

Pfizer and BioNTech), on December 11, 2020 for emergency use. A few days later, on December 18, Moderna's Moderna TX was also granted an EUA. Two months later, on February 27, 2021, Janssen's COVID-19 vaccine also obtained its EUA in the US. All authorizations were made within one month of submission, in fact, Moderna was found eligible within 20 days of officially sending its application. The speed with which the EUAs were possible was particularly astounding if one considered that all sponsors put their stakes on newly developed vaccine production techniques, using viral mRNA or vectors as the major vaccine content. This part will look at the authorizations for these three vaccines, to gain a comprehensive picture of how the US FDA processed COVID-19 vaccine EUAs in the early stages of the pandemic.

A. Trial Designs: Reflecting the Unknown

All three vaccines sponsors conducted several clinical trials, and large, randomized, blinded, placebo-controlled phase III trials were conducted by all three sponsors. All trials were designed to be case-driven efficacy studies. Event-driven efficacy study design is actually the most straightforward vaccine efficacy trial design statistically, but because it may result in uncertainty of trial duration and cost, scientists have since developed various methods to determine sample size based on known or estimated prevalence rates in recent decades.[42] However, when infection rates are undetermined, an event-driven design with pre-planned interim analysis is the feasible and reasonable option. While not many infectious diseases are so elusive, this method has still been used in developing vaccines for rarely occurring diseases. Incidentally, when Merck

[42] Joseph Heyse & Ivan Chan, *Review of Statistical Innovations in Trials Supporting Vaccine Clinical Development*, 8 STAT BIOPHARM RES 128,133 (2016).

doi:10.6342/NTU202302527

developed the human papillomavirus (HPV) vaccine against the relatively rare cervical cancer, it encountered two major challenges: the long but poorly described natural history of HPV infection, and its undetermined prevalence. Unfortunately, this makes conducting clinical trials under normal standards extremely risky for the developers, and thus extraordinarily costly. To overcome these difficulties, the biostatisticians of Merck developed a two stage case-driven vaccine efficacy study to evaluate the efficacy of the HPV vaccine.[43] These vaccine development considerations for rare and evasive diseases eventually paved the way for the COVID-19 vaccines. Although the COVID-19 disease evidently had a high prevalence, little was confidently construed of its nature and no one could say for sure exactly how high its prevalence was in the early stages of the fierce pandemic, thus necessitating the event-driven design. On the other hand, the high prevalence of the disease made it easier to accumulate the number of confirmed cases needed to overcome the null hypothesis of the vaccine trial at adequate power. In sum, the classic form of vaccine efficacy trial design worked decidedly well in this rapidly developing pandemic.

Leading the race from the beginning, BNT utilized multi-phase clinical trial designs. The major clinical trial, Study C4591001, commenced in late April 2020, and accrued up to 43651 participants by the time BNT submitted the EUA.[44] The study was first designed to be a phase I and II trial for dosage selection and immunogenicity, but was modified in July 2020 to expand the

[43] Keaven M Anderson et al., *An Adaptive Design for Case-Driven Vaccine Efficacy Study When Incidence Rate Is Unknown*, 5 STATISTICS AND ITS INTERFACE 391 (2012).
[44] BioNTech SE, *Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of Rna Vaccine Candidates against Covid-19 in Healthy Individuals,* CLINICALTRIALS.GOV (February 28, 2023), https://clinicaltrials.gov/ct2/show/NCT04368728 (last accessed April 8, 2023).

doi:10.6342/NTU202302527

study into a mixed phase II and III study to evaluate clinical efficacy.[45] Based on the phase I dose escalation results, the selected dose was determined for the subsequent phase II/III trial. BNT set two primary clinical endpoints for its phase III evaluation: both for COVID-19 diagnosis after 7 days of completion of two-dose vaccination, but first in subjects that did not have COVID-19 diagnosis history, and the second regardless of whether subjects have COVID-19 history. Secondary clinical endpoint was for COVID-19 diagnosis after 14 days of completion of two-dose vaccination, while also recording severe COVID-19s and US CDC defined COVID-19s. COVID-19 diagnosis required at least one clinical symptom and a positive nucleic acid amplification test (NAAT). According to calculation based on the null hypothesis that the point estimate of vaccine efficacy be at least 30%, interim analyses should be performed when a total of 62, 92, and 120 cases of COVID-19 were confirmed, and a final efficacy analysis when at least 164 confirmed COVID-19 cases have been identified.[46] Statistical considerations aside, this means the duration of the study was unspecified at the start of the trial.

Trailing behind, Moderna officially submitted its EUA on November 30, 2020. Moderna conducted traditional step-wise clinical trials, with one phase I, one phase 2a, and the pivotal phase III trial. The phase III study, study mRNA-1273-P301, was designed almost perfectly in line with US FDA's Vaccine EUA Guidance Document.[47]It is a phase III, randomized, double-blinded and placebo controlled trial, and enrolled 30,400 participants from 99 sites all in the United

[45] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION (EUA) FOR AN UNAPPROVED PRODUCT REVIEW MEMORANDUM: APPLICATION NUMBER 27034 (PFIZER BIONTECH) 12 (2020).
[46] *Id*. at 13-14.
[47] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION (EUA) FOR AN UNAPPROVED PRODUCT REVIEW MEMORANDUM: APPLICATION NUMBER 27073 (MODERNA) 13 (2020).

doi:10.6342/NTU202302527

States. The primary clinical endpoint of the study was the efficacy of the vaccine to prevent protocol-defined COVID-19 at least 14 days after completing the vaccinations in subjects without a history of confirmed COVID-19 disease. Protocol-defined COVID-19 was defined as at least two systemic symptoms, plus at least one respiratory signs/symptoms, and an nasopharyngeal swab, nasal swab or saliva sample positive for SARS-CoV-2 by RT-PCR. The study was also powered to test secondary efficacy endpoints of the vaccine's ability to protect against severe COVID-19, death due to COVID-19, the protection of a single dose of vaccination, and COVID-19 of a less restrictive definition. It was also a case-driven study, which planned to perform two interim analyses when 53 and 106 confirmed COVID-19 have been accrued, and required 151 COVID-19 cases for final analysis. This design allowed the sponsor to test the null hypothesis of vaccine efficacy being smaller than 30% at a one-sided alpha of 0.0047.[48]

Following the path of the two novel vaccines, Janssen's COVID-19 vaccine took a bit more time. Even though two EUAs have been previously given, the US FDA determined that EUA vaccines were unapproved products, and that current supplies of those vaccines were insufficient to vaccinate the population for which they are indicated, thereby declaring the statutory requirement of emergency use authorization still in place.[49] The Janssen vaccine utilizes yet another novel technique there is well known in gene therapies and gene function studies research, but has nevertheless never been approved for use

[48] *Id*. at 14-15.
[49] DEPARTMENT OF HEALTH AND HUMAN SERVICES, EMERGENCY USE AUTHORIZATION (EUA) FOR AN UNAPPROVED PRODUCT REVIEW MEMORANDUM: APPLICATION NUMBER 27205 (JANSSEN) 9 (2021).

doi:10.6342/NTU202302527

in a vaccine in the United States against an infectious disease.[50] This technique, compared to the mRNA vaccine method, has been tested in vaccines for multiple diseases since almost 20 years ago,[51] and an adenovirus vector based vaccine is under clinical investigation for HIV AIDS.[52] It is reasonable to say that the technique is much more mature than mRNA, and vaccine developers have already had human experience with vaccines of the same technique. One of the vaccine's greatest strengths is that it was designed to require a single dose, compared to that of Pfizer/BNT and Moderna, which both require two-doses at least two weeks apart. Results from 5 trials were submitted to the US FDA for the Janssen application, including two phase I trial, 1 phase 2a trial, and two phase III trials. The two phase III trials evaluated the safety and efficacy of one dose and two doses of the Janssen vaccine, the former recruiting 40,000 subjects, and the latter 30,000 subjects. The single dose phase III trial, Study 3001, is a randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of a single dose of the Janssen vaccine in subjects 18 years old and older. The trial involved a staged enrollment strategy, which enrolled healthy young and healthy participants first, and after the independent Data Safety monitoring Board's evaluation of safety data Day 3 post-vaccination, the trial proceeded to recruit a batch of participants between the ages 18 to 59 years regardless of comorbidities, and a batch of participants older than 60 years old without comorbidities. Finally, after another independent evaluation, the trial began enrolling those older than 60 years regardless of comorbidities. When

[50] It has however, been used in an Ebola vaccine that was approved by the European Medicines Agency in 2020. See *id*. at 13.
[51] Nia Tatsis & Hildegund CJ Ertl, *Adenoviruses as Vaccine Vectors*, 10 MOL THER 616 (2004).
[52] Fuminori Sakurai et al., *Adenovirus Vector-Based Vaccine for Infectious Diseases*, 42 DRUG METAB PHARMACOKINET 100432 (2022).

doi:10.6342/NTU202302527

study participants experienced COVID-19 symptoms, they were to obtain a nasopharyngeal swab for PCR test, and a molecular confirmation by a central lab would be done. There were two primary endpoints: the efficacy of a single dose of the target vaccine to protect against moderate to severe/critical COVID-19, after 14 days and 28 days of vaccination. Study 3001 was also an event-driven study, whose final analysis was planned to be conducted when at least 42 moderate to severe cases of COVID-19 occurring after 28 days of completing vaccination were accrued, when at least 6 cases of COVID-19 occurring after 28 days of completing vaccination were accrued in the over 60 years population, at least 5 severe/critical cases of COVID-19 in the placebo group with a favorable vaccine-to-placebo split, and also, safety-wise, when the first 50% of participants have at least 2 months of follow up after vaccination. Moderate and severe COVID-19 were defined by a number of symptoms, and severe COVID-19 cases were to be judged by a blinded clinical severity adjudication committee. The designs were used to reject the null hypothesis that vaccine efficacy ≤30% for each co-primary endpoint at a 2.5% one- sided significance level and a VE point estimate ≥50% for each co-primary endpoint. There is an additional condition that vaccine efficacy point estimate against severe COVID-19 be at least 50%. Study 3001 was conducted in 8 countries across 3 continents.[53]

Of note, COVID-19 vaccines developers did not disclose all details of clinical trials on the official trial publication website until the public applied considerable pressure. While the FD&C Act requires all clinical trial protocols to disclose certain information on clinicaltrials.gov, there is no obligation for

[53] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 49, at 15-22.

doi:10.6342/NTU202302527

sponsors to do so before trials commence, and there is no requirement to disclose trial amendments and reasoning. In view of increasing the credibility of FDA EUA decisions, some have suggested the FDA to require EUA sponsors to update protocol changes and trial status details.[54] Considering the increasingly important role of adaptive trial designs as described above, enhancing disclosure falls in line with facilitating trust through promoting transparency.

B. Efficacy in Excellence

In BNT's pivotal trial, the predesignated 162 COVID-19 confirmed cases was achieved on November 14, 2020, about 7 months after the phase II/III trial officially began enrolling subjects. For the final analysis, the sponsor set a criterion for success at the posterior probability that vaccine efficacy exceeds 30% was >99.5%. On analysis, the BNT vaccine met the predetermined criterion with ease. For the first primary efficacy endpoint, evaluating confirmed cases after 7 days of completing vaccination, vaccine efficacy was 95.0%, with a 95% confidence interval of 90.3% to 97.5%. For the second primary efficacy endpoint, evaluating confirmed cases after 14 days of completing vaccination, vaccine efficacy was 94.6%, with a 95% confidence interval of 89.9% to 97.3%. Subgroup analyses showed consistent performance of the vaccine across different age, ethnicity and underlying medical conditions groups, and the cumulative incidence rate of COVID-19 along the duration of the study was indicated the vaccine provided protection against the disease.[55] This showed that even though the sponsor's predetermined criterion for success differed from that of the US FDA Vaccine EUA Guidance Document, the final

[54] Aris Angelis & Jonathan Darrow, Safeguarding Evidence-Based Decision Making in the FDA for Covid-19 Vaccines, 39 VACCINE 2329 (2021).
[55] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 45, at 23-29.

doi:10.6342/NTU202302527

efficacy evaluation of the BNT vaccine met both the US FDA and sponsor efficacy standards. The secondary endpoint was not as successful, with only a small number of severe COVID-19 cases (a total of 4 occurring in all subjects completing 2 doses, and after 7 days of completing vaccine schedule), but the US FDA reviewers still commented that the case split favored the vaccine protected against severe COVID.

In Moderna's pivotal efficacy trial, mRNA-1273-P301, the preplanned interim analysis conducted when 95 cases were confirmed for COVID-19 (for some reason not conducted at the prespecified 53% cases or 106 cases, presumably due to the pace with which confirmed cases were identified), the vaccine efficacy was 94.5%, with a lower bound of the 95% confidence interval at 86.5%, and one-sided p-value <0.0001 for rejecting the null hypothesis that vaccine efficacy would be lower than 30%. Subgroup analyses was also conducted according to the Vaccine EUA Guidance Document, and revealed that the efficacy was observed evenly across all populations (except those where there were too few cases). Since only 2.2% of the participants had history of prior COVID-19 disease, it was impossible to evaluate whether the vaccine was effective for people who had prior infection at this point. Protection for severe COVID-19 was also tricky to interpret due to the small number of severe cases, but no severe cases occurred in the vaccine group. The cumulative incidence curves mapped at interim analysis also showed that the incidence rate of both groups overlapped, before the Day 14 of the trial, but began to diverge afterwards. Final analysis was conducted on November 21, 2020, which was when a total of 196 confirmed cases were identified from the trial participants. Final analysis showed that the vaccine efficacy against COVID-19 starting 14

doi:10.6342/NTU202302527

days after completing the vaccine schedule was 94.1%, with a lower bound of the 95% confidence interval at 89.3%, which was slightly lower than that observed in the interim analysis two weeks before. Similar results were seen in the over 65 years old group. Again, all severe COVID-19 cases occurred within the placebo group. No subpopulation or other secondary endpoint analyses were made for the final analysis. The US FDA did not have sufficient time to evaluate the final analysis data independently, but verified that it did not jeopardize the outstanding interim analysis.[56]

For the Janssen vaccine, the pivotal trial Study 3001 showed that a single shot of the vaccine demonstrated vaccine efficacy against moderate to severe COVID-19 for subjects older than 18 and not tested positive for COVID-19 at vaccine administration was 66.9% (lower bound of the 95% confidence interval 59.03%) at least 14 days after vaccination, and 66.1% (lower bound of the 95% confidence interval 55.01%) at least 28 days after vaccination. Due to the protocol's requirement that case confirmations were to be done by the central lab, the slight delay in the central lab confirmations slowed down analyses. However, Janssen presented later data in multiple amendments, which were found to be consistent with that of the initial submitted data. The efficacy results were also found to be consistent across age groups, ethnicity, race, sex, and country. In the case of comorbidities, it was observed that vaccine efficacy was lower in the group without comorbidities, especially in the older age group. However, the US FDA explains that the confidence intervals are wider, which is probably because of a shorter follow up period and the interference of prior EUAs, which led to loss of participants. The US FDA based its explanation on

[56] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 47, at 24-33.

doi:10.6342/NTU202302527

its comparison between the data of earlier central lab confirmed cases, and latter numbers, which included more cases and thereby exhibited a higher vaccine efficacy and narrower confidence interval. A cumulative incidence graph also showed moderate to severe/critical COVID-19 numbers began to diverge after 14 days of receiving vaccine or placebo, generating a favorable pattern. The study also evaluated vaccine efficacy for any symptomatic COVID-19, which was similar to that for moderate to severe COVID-19. For severe COVID-19, vaccine efficacy was 76.7% for those occurring at least 7 days after vaccination, and 85.4% for those occurring at least 14 days of vaccination, and appeared to be slightly lower in participants older than 60-years-old. All 7 COVID-19-related deaths occurred in the placebo group, suggesting the vaccine's protection against COVID-19 deaths. They study also set out to test the vaccine's efficacy against asymptomatic COVID-19, by obtaining serology results from a group of participants regardless of their symptoms (though those with symptoms were ruled out from analysis), at Day1 (pre-vaccination), Day 29, and Day 71, but no statistically significant results were seen at the time of the EUA submission. The efficacy study also allowed an exploration into the different strains circulating the globe at the time, which revealed variation in different countries that did not result in difference of vaccine efficacy.[57]

It can be seen that all three vaccines met their pre-specified criteria easily and rapidly, with rapid recruitment and equally rapid case development. Also of interest, is how later trials proved appeared to be more difficult to conduct once vaccine EUAs have been dished out and the general population

[57] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 49, at 27-39.

doi:10.6342/NTU202302527

had access to an authorized vaccine. The speed with which both the interim and final analyses time points were achieved is simply unprecedented.

C. Safety in Short

In the pivotal BNT study, safety evaluation was conducted in a manner similar to that of influenza vaccines. Reactogenicity was under close follow-up for up to 6000 participants who received the trial vaccine for 7 days after each dose, all adverse events monitored for all subjects for up to a month, serious adverse events monitored for all subjects for up to 6 months, and a prolonged 2-year follow up period for related serious adverse events. However, in accordance with the FDA Vaccine EUA Guidance Document, safety data submitted for the EUA was only up to a median follow-up period of 2 months. Although strictly speaking, the median follow-up period fell short of two months at the EUA cutoff date, November 14, 2020, due to a gap in enrollment, the US FDA explained that median follow-up period was achieved before the cutoff date, and that a larger safety database was preferable and accepted the safety data up to November 14, 2020. There was also the important design of having an independent but unblinded Data Monitoring Committee to review severe COVID-19 cases with the objective of screening for vaccine-enhanced disease by a predesignated stoppage rule.[58] Solicited, unsolicited, and serious adverse events were evaluated qualitatively and somewhat statistically, in a manner similar to that for influenza vaccines (see figure 2).

[58] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 45, at 15-17.

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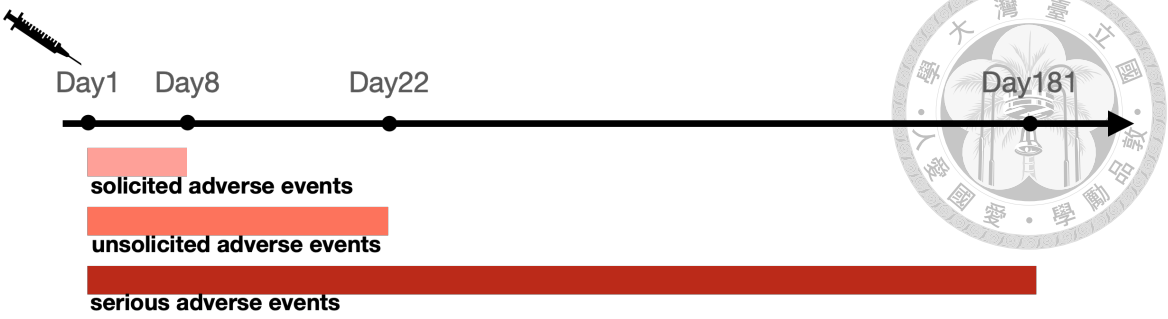

Figure 2: Vaccine Adverse Event Recording Timeline

Two unsolicited adverse events were given special attention: lymphadenopathy and Bell's palsy. The former was judged to be related to the vaccine, while the latter, though not exceeding background population incidences, would be surveilled after authorization.[59] Additionally, the US FDA performed MedDRA queries (SMQs) independently on the safety database, and found that there was slight increase of hypersensitivities in the vaccine group. On top of this, the US FDA took note of 2 anaphylactic reactions occurring in subjects who received the Pfizer/BNT vaccine outside of the clinical trial, which was in UK where authorization was granted a few weeks earlier. In describing serious adverse events, only 2 of the 6 deaths occurred in the vaccine arm. Although the US FDA reviewers did not make the direct conclusion that the deaths were unrelated to the vaccine, it was noted that the events were in line with the incidence rates in general populations. In sum, the US FDA concludes that the safety database of over 18,800 subjects meets the expectation of the Licensure Guidance Document, and that the safety follow-up time of a median of 2 months met that of the Vaccine EUA Guidance Document. There were no notable imbalances or patterns in the various adverse events analyses apart from lymphadenopathy and Bell's palsy, and though not observed in the clinical trial,

[59] *Id*. at 37.

doi:10.6342/NTU202302527

anaphylactic reactions to the vaccine. Additionally, safety results from BNT162-01, a first-in-human phase I trial showed that the immunological results of vaccine receivers, namely Th1 and Th2 ratios, showed that there was no noticeable risk for vaccine-induced enhanced disease.[60]

Moderna submitted its safety data and analyses to the US FDA on a rolling basis, with the first interim analysis efficacy and safety cutoff sat November 7 and 11, 2020, respectively, and then the second efficacy and safety cutoffs at November 21 and 25 of the same year respectively. The final efficacy analysis was submitted on December 4, 2020, and the final safety analysis 4 days later. Since the US FDA did not find significant differences between the first and second sets of data upon preliminary analyses, the US FDA was satisfied that Moderna had met the requirement of median follow-up period of 2 months.[61] Moderna's vaccine safety evaluation was mostly based on the interim analysis with a cutoff date on November 11, 2020. Final analysis, which was conducted with a cutoff date on November 25, 2020, was only party evaluated independently by the US FDA, where no additional concerns compared to the interim analysis. The parts of the final analysis that were evaluated independently, new deaths, serious adverse events, unsolicited adverse events of interest, and pregnancies, reflected the US FDA's priority on safety assessment under time constraint. Moderna's safety data underwent the standard analysis, in which the US FDA found the solicited adverse event type and rate in the vaccine group to be similar to that of vaccines that stimulate immune responses. Unsolicited adverse events were similar between the vaccine group and the

[60] *Id*. at 39-42.
[61] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 47, at 14-19.

doi:10.6342/NTU202302527

placebo group, though slightly higher in the vaccine group, it was not found statistically significant. The MedDRA queries were also conducted on the unsolicited adverse events, which revealed imbalance in lymphadenopathy, hypersensitivity, and Bell's palsy, leading to individual analysis of the cases. None of the deaths observed throughout the trial was found to have causal relationship to the vaccine, and overall the rates and events was similar to general populations. Serious adverse events that could not be ruled out to have relationships with the vaccine were: facial swelling, intractable nausea/vomiting, rheumatoid arthritis, peripheral edema with exertion, and autonomic dysfunction. Safety follow-up from subjects of the phase I and phase II trials did not reveal any alarming signals.[62]

Janssen's safety population was much smaller than its study population. In the pivotal phase III study, Study 3001, only a subset of 6736 subjects at the cutoff date of January 22, 2021, from 45 sites in three countries, the US, Brazil and South Africa,[63] were followed for 7 days post vaccination for local and systemic reactions, and another 28 days for unsolicited adverse events. Medically attended adverse events were collected for the entire study population for 6 months after vaccination. The staged enrollment strategy led to a lower percentage of participants over 60 years old being followed for the US FDA required 2 months (or 8 weeks, as in this study).[64] Solicited adverse event and unsolicited adverse events did not reveal surprises, unsolicited adverse events were balanced across the vaccine and control arm, while unsolicited adverse events related to study vaccine was higher in vaccine recipients. MedDRA

[62] *Id*. at 33-49.
[63] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 49, at 23.
[64] *Id*. at 17-18.

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Queries were also conducted by the US FDA on the safety database, which identified embolic and thrombotic events to be slightly higher in the vaccine group, thus clinical histories of the thromboembolic events relationship were scrutinized individually. Although ultimately all cases were judged to be unrelated to vaccine, the numerical imbalance cautioned the US FDA to surveil for future events after authorization. Angioedema, wheezing, arthritis and peripheral neuropathy were identified to be related to vaccine reactogenicity. Of the 25 deaths reported in throughout the trial, 2 in the vaccine group were due to respiratory infection unrelated to COVID-19. Relationship to the vaccine with serious adverse events including Pericarditis, Bell's palsy and Guillain-Barre Syndrome could not be excluded.[65] Overall, the US FDA was satisfied that the safety population met requirements by the Vaccine EUA Guidance Document, and apart from the adverse events whose relationship with the vaccine could not be excluded, no remarkable signals were noted.

In the intense race to be authorized for use, the vaccine sponsors put in their best to meet the two-month median follow-up period, and it appears the US FDA welcomed these attempts as along as the sponsors brought in complete follow-up data afterwards. On the other hand, the US FDA did not simply rely on the sponsor's own safety analyses, but utilized the MedDRA Queries system to conduct a comprehensive and independent investigation of the safety database that was submitted. Safety analyses were pulled off neatly with the sponsor's cooperation to provide access to safety databases, and the US FDA's streamlined analysis system already in place. Also of note, the US FDA did not

[65] *Id*. at 43-52.

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limit its safety analysis to the sponsor's data, but also evaluated incidents of adverse events that occurred outside of clinical trials.

D. Benefit/Risk Assessment and VRBPAC Meetings: Balancing the Stakes

Under the mandate of the federal law, all sponsors conducted benefit/risk assessment for their EUA submissions, and though not mandated by federal law, all cases were reviewed by VRBPAC meetings that were open to the general public or observation.

The BNT/Pfizer vaccine came on strong in the benefit part of the benefit/risk assessment, with its significant reduction in risk of contracting COVID-19 disease. Although there were several unknowns about the vaccine, including duration of protection, efficacy in certain populations, efficacy under changing pandemic characteristics, protection against asymptomatic infection and long-term effects of the disease, the fact that it demonstrated excellent efficacy in the general population signaled it was ready for use in the pandemic. Known risks included those observed in safety assessment, while safety in certain populations, extremely uncommon adverse events and risk of vaccine-enhanced diseases are still among the unknown. In the VRBPAC Meeting on December 10, 2020, the center of discussion revolved around the need for long-term safety data. Balancing the public health and ethical need to vaccinate study subjects that received placebos and the need for long-term safety data, the sponsor maintained that loss of up to 20% of placebo recipients would still result in adequate post-authorization efficacy study and safety study. The anaphylactic cases that occurred outside clinical studies also attracted interest, and the US FDA reassured that the fact sheet and prescribing information for the Pfizer-BNT vaccine would warn against usage by individuals with serious

doi:10.6342/NTU202302527

allergic histories. The US FDA also provided the extrapolation that vaccines that have been shown to be effective against mild diseases have never been shown to be not effective against severe diseases, and thus, although there is limited direct data to support protection against severe disease for the Pfizer/BNT vaccine, it is reasonable to guess that it would still be effective against severe diseases. After discussions concluded, the committee members voted on whether the totality of available scientific evidence supported that the benefits of the Pfizer-BNT COVID-19 vaccine outweighed the risks for its target population. 17 members voted yes, 4 voted no and 1 abstained, giving the green light for the Pfizer-BNT vaccine's EUA.[66]

Moderna's vaccine also gave powerful benefit statements, with reduction in both confirmed COVID-19 and severe COVID-19. The unknown benefits were the same as those for Pfizer-BNT vaccines. The known risks were either low in incidence or considered tolerable, and no specific safety concerns were identified. The VRBPAC Meeting was held on December 17, 2020. The concerns brought up by members included the collection of blood specimen to understand immunogenicity generated by the vaccine better, as well as the need for long term and special population efficacy and safety data. There was also the issue of whether unblinding and vaccinating placebo group participants would taint the follow-up data from the pivotal trial, and there were suggestions to proceed with vaccination according to CDC prioritization as a compromise. After discussions, all but 1 of the 21 members voted in favor of granting the

[66] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 45, at 50-54.

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Moderna vaccine EUA for individuals 18 year of age and older. The single member that did not support the submission abstained.[67]

Janssen's vaccine efficacy was also rendered a significant known benefit. The unknown benefits, known risk and unknown risks were same as the above two vaccines. VRBPAC Meeting was held on February 26, 2021. At the outset, the committee members were concerned with whether the ongoing trial evaluating the two-dose option would affect the current EUA submission, to which the US FDA responded that amendments would be contemplated should the trial revealed better efficacy. Members also took issue with Janssen's definition for the disease, which did not fit perfectly with that set out in the FDA guidance documents. However, the US FDA was happy with the definition, especially since the definition evidently captured most US FDA-defined COVID-19 cases. The lack of analysis on participants with past COVID-19 history also drew some attention, and the discussions reflected growing concern for strain variation. As for the older population with comorbidities, for whom the US FDA applied additional analysis, comparing between initially submitted confirmed cases and supplemented cases, the committee members did not express much interest. The committee members thus voted an overwhelming 22 yeses, with no one against or abstaining.[68]

With little ambiguity in efficacy and safety results, the VRBPAC members were most concerned about the ethical issues and the feasibility of completing safety follow-up. This is a reasonable apprehension for EUAs, since follow-up periods were allowed to be shortened and vaccines would be

[67] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 47, at 55-59.
[68] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 49, at 60-63.

doi:10.6342/NTU202302527

administered on large health populations. Interestingly, only 4 votes against the vaccine EUA were casted for the first vaccine, the following two vaccines won overwhelming support of the VRBPAC. The success of the previous vaccine EUAs may have nudged the members to say yes.

Due to the ongoing pandemic, it is still important to have as many of the population as possible to received effective vaccines. Thus, all sponsors proposed to vaccinate all study participants after the EUA by unblinding participants upon request or after their 6-month follow-up period, and offering those who received placebos the study vaccine. Although safety monitoring was important, this was a compromise made by the US FDA in face of the pandemic.[69] A rigorous pharmacovigilance plan was endowed upon the sponsors. Sponsors were required to report vaccine administration issues, serious adverse events, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death in all vaccinated cases following the EUA. Periodic safety reports with descriptions on the adverse events are also required. Existing databases, such as COVID-19 HERO registry, Department of Defense Health System Databases, and the Veteran Health Administration electronic medical record database, are also utilized for observational studies for vaccine safety[70]. Moderna proposed a Real World Effectiveness Study as part of their post-authorization observational study commitment.[71] A newly established v-safe program, a smartphone-based

[69] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 45, at 43. DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 47, at 50. DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 49, at 54.
[70] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 45, at 45.
[71] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 47, at 51.

doi:10.6342/NTU202302527

program implemented by the CDC is also incorporated into vaccine safety monitoring.[72]

E. Success With Surprise

A brief overview of the characteristics and results of the COVID-19 EUAs can be seen in Table 2.

Table 2: COVID-19 Vaccine EUAs

	Pfizer/BNT	Moderna	Janssen
Submission date	2020/11/20	2020/11/30	2021/02/04
EUA date	2020/12/11	2020/12/18	2021/02/27
Mechanism	mRNA	mRNA	Adenovirus vector
Trial subjects	44,000	30,400	39,321
Efficacy data	confirmed COVID-19 7 days after vaccinations	confirmed COVID-19 7 days after vaccinations	mod-sev. COVID-19 14 or 28 days after vaccination
Vaccine efficacy	Final analysis 95%	Interim analysis 94.5% Final analysis 94.1%	Final analysis 66.9%-85.4%
Safety database size	38,000	30,350	43,783

Source: compiled from FDA authorization documents.

As the pandemic sprawled out across the globe in 2020, there were many speculations as to how vaccines development and approval could be accelerated. The abundance of literature was at least partly reflected in the FDA Vaccine EUA Guidance Document, which was prepared under the backdrop of the US FDA being caught in bipartisan politics. On the one hand, it did not wish to lose public trust by adhering to the Trump administration's wishes; on the other hand, if it did not answer to the administration's deeds it could be further marginalized and struggle to deliver much needed guidance under the

[72] DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 45, at 46. DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 47, at 51; DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 49, at 56.

doi:10.6342/NTU202302527

emergency status.[73] The Vaccine guidance documents reflected the US FDA's effort to operate on a evidence-based basis, by incorporating and citing relevant past guidance and new literature.

Of course, other factors were predicted to contribute immensely to the rapid development of COVID-19 vaccines. The arrival of mRNA vaccines was expected to facilitate faster and less costly manufacturing,[74] and some even considered the use of master protocols to evaluate multiple vaccines or doses in one or several trials, which is another experience derived from oncological treatment development.[75] Various adaptive trial designs were also considered, including utilizing interim analyses for population selection or even sample size adjustment, and variations of Bayesian designs that incorporate information from historical trials.[76] Others feared that phase III trials would have difficulty recruiting subjects, and brought up the issue of human challenge trials.[77]

However, as we can see from the above observations from the first three EUAs handed out by the US FDA, none of these, and many concepts that the FDA's Vaccine EUA Guidance Document mentioned, came to be of concern to the sponsors or the US FDA. While the Vaccine EUA Guidance Document rightly predicted that there would be a need for adaptive trial designs with interim analyses, it was wrong in assuming that vaccine developers would make attempts at the EUA with interim results. The rapid recruitment of subjects and

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[73] *See e.g.* Lawrence O Gostin, Science, Leadership, and Public Trust in the COVID-19 Pandemic, MILBANK QUARTERLY OPINION 1-2 (2020); Jonathan L Iwry, *FDA Emergency Use Authorization from 9/11 to Covid-19: Historical Lessons and Ethical Challenges*, 76 FOOD & DRUG LJ 362 (2021).
[74] Nicholas AC Jackson et al., *The Promise of mRNA Vaccines: A Biotech and Industrial Perspective*, 5 NPJ VACCINES 11 (2020).
[75] Jie Chen & Naitee Ting, *Design Considerations for Vaccine Trials with a Special Focus on COVID-19 Vaccine Development*, 18 Journal of Data Science 550,558 (2020).
[76] Mengya Liu et al., *Innovative Trial Designs and Analyses for Vaccine Clinical Development*, 100 CONTEMP CLIN TRIALS 106225 (2021).
[77] Nir Eyal et al., *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, 221 THE JOURNAL OF INFECTIOUS DISEASES 1752 (2020).

doi:10.6342/NTU202302527

accumulation of confirmed cases, and perhaps even more important, the astoundingly high vaccine efficacy, made it possible for final analyses to be made within 6 months of the trials being commenced.

Obviously, however, the COVID-19 vaccine EUAs were not without downfalls. Despite the US FDA's effort to make science-based and regulated decisions, EUA decisions are, even more so than their regular approval decisions, undeniably political decisions that reflect that values and needs of the nation at that time. This is clear from the huge amount to financial and other resources devoted to developing and manufacturing COVID-19 vaccines before the applications for EUA reached the US FDA, and also the permeating concern for vaccine hesitancy after the EUAs were authorized and vaccines rolled out for administration.[78] Considering the reviews themselves, it was inevitable that some high-risk populations were initially excluded from trials and subsequent vaccination programs.[79]

I would also like to take a moment to highlight the role of the disease itself that resulted in the unprecedented success of vaccine development. The COVID-19 pandemic emergency sets itself apart from past emergencies or need for acceleration in that it is not only a great threat to human health, but that it is also of such wide scale, and such high incidence rate. Therefore, while measures to streamline clinical trials and shorten safety follow-up periods significantly reduced trial and review timeline, concepts and methods developed specifically to make efficacy trials easier to complete did not exactly came into use for the

[78] See e.g. Michael Daly & Eric Robinson, *Willingness to Vaccinate against COVID-19 in the U.S.: Representative Longitudinal Evidence from April to October 2020*, 60 AM J PREV MED 766 (2021); Jagdish Khubchandani et al., *Covid-19 Vaccination Hesitancy in the United States: A Rapid National Assessment*, 46 J COMMUNITY HEALTH 270 (2021).
[79] Monika Kumari et al., *A Critical Overview of Current Progress for COVID-19: Development of Vaccines, Antiviral Drugs, and Therapeutic Antibodies*, 29 J BIOMED SCI 68 (2022).

doi:10.6342/NTU202302527

first three COVID-19 vaccines approved by the United States. For example, all of the pivotal efficacy trials went overboard to recruit 10 times the Vaccine EUA Guidance Document's minimal requirement of 3000 subjects, and none of them needed any help facilitating this recruit or completing the trial within 6 months. Neither was there the need to cut trials short and make determinations based on interim analyses. Instead, the classic even-driven design was undertaken, and even though interim analyses were planned, they were not used to alter trial design or be used as the basis to adjust sample size. The scale, severity and speed of the pandemic made conducting clinical trials so much more easier and faster to complete clinical trials compared to those for cancer treatments, non-communicable diseases (remember dabigatran?), treatments for diseases that take long to take effect (remember Sofosbuvir?), or even a similar viral infection that simply did not affect as many people (the flu). Therefore, despite being relatively less familiar, the novel virus' quick spread and moderate mortality rate became an advantage for vaccine EUAs.

The pandemic, as we know, didn't just end with the vaccine EUAs. Many researchers were still rightly concerned with the safety of the vaccines,[80] while others observed vaccine hesitancy due to EUAs as opposed to traditional approvals.[81] In response, the US FDA published monthly safety monitoring results of the EUA vaccines. For example, in the first month, more than 13 million shots were administered (either Pfizer/BNT or Moderna), but no unexpected safety issues were identified in the nearly 7000 reported adverse

[80] Qianhui Wu et al., *Evaluation of the Safety Profile of COVID-19 Vaccines: A Rapid Review*, 19 BMC MED 1 (2021).
[81] *See e.g.* Jagdish Khubchandani et al., *COVID-19 Vaccination Hesitancy in the United States: A Rapid National Assessment*, 46 J COMMUNITY HEALTH 270 (2021).

doi:10.6342/NTU202302527

events (including reports from the v-safe system).[82] The vaccines were also compared alongside other vaccine candidates globally.[83] Researchers pointed out the need for harmonized and transparent approval processes, in addition to follow-ups on efficacy and development of vaccines that could address variants.[84] Overall, the COVID-19 vaccine EUAs were quickly embraced by scientists and policy-makers around the world, and eventually contributed to bringing down the pandemic.

What the US FDA has successfully achieved with the COVID-19 vaccine EUAs, however, is confirming the efficacy of vaccines through large-scale and organized trials with streamlined, or to some extent, synchronized, trial execution and review. While the US FDA has been inching its value-based decision-making process earlier in the recent decade, from involving advisory committees for boundary work in later phases of approvals to dabbling in academic forums and generating guidance with both academic and pharmaceutical input, the EUA review apparently has thrusted its political needs further upstream. This is not to say that the EUA decisions lacked scientific basis or are skewed to favor certain sponsors; however, we must admit that the standards set forth within the guidance documents or even those communicated in more detail between the US FDA and vaccine developers are designed for the purpose of ending the pandemic as quickly as possible. Therefore, even though the results of the EUAs are often presented in numbers that resemble a scientific process, it would be imprudent to dismiss the political nature of the process.

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[82] Julianne Gee et al., *First Month of COVID-19 Vaccine Safety Monitoring—United States, December 14, 2020–January 13, 2021*, 70 MORBIDITY AND MORTALITY WEEKLY REPORT 283 (2021).
[83] Edouard Mathieu et al., *A Global Database of COVID-19 Vaccinations*, 5 NATURE HUMAN BEHAVIOUR 947 (2021).
[84] Rebecca Forman et al., *COVID-19 Vaccine Challenges: What Have We Learned So Far and What Remains to Be Done?*, 125 HEALTH POLICY 553,555-556 (2021).

doi:10.6342/NTU202302527

IV. COVID-19 Vaccine Approvals by the TFDA

I will now turn to a brief introduction and analysis of the decision making and legal framework of the COVID-19 vaccine approvals by the FDA in Taiwan (TFDA), where I reside, and where very different political concerns exist. The operations of the TFDA is highly influenced by the US FDA, not only are review tracks similar (there is also fast track, breakthrough therapy designation, accelerated approval), the decisions of the US FDA often play an important role in TFDA's approval decisions. During the pandemic, the TFDA was perhaps not under as much pressure to bring COVID-19 vaccines to the market. Due to aggressive border control, quarantine requirements, and social solidarity expressed by the citizens, the impacts of the pandemic was not fully felt on the island until May 2021.[85] Taiwanese vaccine developers eager to develop their own vaccines also caused a frenzy during the pandemic, and although one vaccine was approved for use in Taiwan, it was not widely distributed globally. The following section will give a brief introduction of the legal framework of the TFDA approvals and expeditions, review the timeline of COVID-19 vaccine approvals, and a short analysis on the Taiwan-based Medigen COVID-19 vaccine.

A. Vaccine Approval Regulations and Expedition Programs

The authority to review and approval new drugs and vaccines is vested in the TFDA, under the Ministry of Health and Welfare by Article 39 of the Pharmaceutical Affairs Act.[86] While the legislation itself does not require the

[85] Po-Han Lee et al., *'The Future of Taiwan Studies in the Post-Covid World': Online Series on 'Covid and Governance: Global and Social Solidarity', 31 July 2020*, 5 INTERNATIONAL JOURNAL OF TAIWAN STUDIES (2022).

[86] Pharmaceutical Affairs Act Article 39: For the manufacturing and import of drugs, information concerning the ingredients, source of active pharmaceutical ingredients, specifications, functions, summary of manufacturing process, and the specification and method of testing, as well as other related

doi:10.6342/NTU202302527

TFDA to review the efficacy and safety of drug applicants, other provisions of the same act have stated that approved drugs must be effective and safe, and that unsafe drugs may be pulled off the market after warning.[87] With the authorization of Article 39(4) of the Pharmaceutical Affairs Act, the Ministry of Health and Welfare published the Regulations for Registration of Medicinal Products. The regulations are the basis of new drug application procedures and standards. The regulations state the type of information and forms that sponsors have to submit for new drug applications, requires the drugs to be effective and safe,[88] and specifically states that drugs that have already obtained Certificate of Pharmaceutical Product from the listed reference countries may undergo an adjusted review process.[89]

In addition to the Pharmaceutical Affairs Act and the Regulations for Registration of Medicinal Products, the TFDA has also issued guidance on expedited programs for new drug applications. There is abbreviated review, priority review, accelerated approval, breakthrough therapy designation, and Pediatric and Rare Severe Disease Priority Review Voucher Program. Each expedition scheme has its own criteria, features, and review timeline.[90]

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information and certificates, accompanied by labels and use instructions in the original and Chinese languages, and samples, together with the fee paid, shall be filed with the central competent health authority for registration and market approval. No manufacturing or importation of such drugs shall be allowed until a drug permit license is approved and issued.

[87] Pharmaceutical Affairs Act Article 5, 45, 48.

[88] Regulations for Registration of Medicinal Products Article 25: "In any of the following situations, applications will be rejected:….. 3.The major efficacy of the applied drug is unclear or insignificant; or the drug fails the drug re-evaluation; 4.The applied drug has severe side effects or safety concerns;……."

[89] Regulations for Registration of Medicinal Products Article 38: "(1)The FSC from the country of origin and the CPP are not required for the application of NCE (New Chemical Entity) drugs. (2)In cases where the FSC from the country of origin and CPP are submitted for the aforementioned application, the central health competent authority may adjust the review process according to the actual situation……."

[90] Taiwan Center for Drug Evaluation, *New Drug Application (NDA),* CENTER FOR DRUG EVALUATION, TAIWAN, https://www.cde.org.tw/eng/drugs/med_explain?id=39 (last accessed May 21, 2023).

doi:10.6342/NTU202302527

For public health emergencies, the Pharmaceutical Affairs Act stipulates in Article 48 that a "special case" for manufacturing and import shall be established. In such a special case, the TFDA has the authority to annul the approval if the drug has obtained approval, the emergency has ended, or there are safety concerns for the drug. The TFDA published the Regulations for Approval of Special Medicinal Products' Manufacturing or Importing as a Special Case, which mandates the approval of such special case be made on the risk/benefit analysis of the drug.[91]

B. The COVID-19 Vaccine Approvals

A number of COVID-19 vaccines have been approved for import and use in Taiwan since 2021. The first batch of AstraZeneca vaccines arrived in Taiwan on March 3, 2021,[92] and the TFDA announced about 2 weeks later that the Advisory Committee on Immunization Practices (ACIP) has deemed the benefits of the AstraZeneca vaccine outweighed its risks, and has approved it for use.[93] When the Moderna and Pfizer/BNT vaccines arrived in Taiwan later that year, respectively in June and September, the TFDA gave similar announcements. In other words, it was unclear whether the vaccines underwent the "special case" review. While chemistry and manufacturing examinations

[91] Regulations for Approval of Special Medicinal Products' Manufacturing or Importing as a Special Case Article 3(1): "Centers for Disease Control or pharmaceutical firms may submit the following documents when applying to the central competence authority for approval of specific medicinal products' manufacturing or importing as a special case in accordance with Subparagraph 2 of Paragraph 1 of Article 48-2 of the Act: 1. A complete prevention or therapy protocol. 2. Related science evidence or references to show the benefits will greater than the risks. 3. Instructions of the drug. 4. The drug's certificates of the market approval in foreign countries or a photocopy of the reference country's pharmacopeia; and 5. Treatment plan in the event of severe adverse reaction."

[92] Ministry of Health and Welfare, News, First Batch of AstraZeneca COVID-19 Vaccines Arrive in Taiwan, March 3, 2021, available at: https://www.mohw.gov.tw/cp-5014-58437-1.html (last accessed: May 25, 2023).

[93] Ministry of Health and Welfare, News, AstraZeneca COVID-19 Vaccines Will Begin Administration on March 22, 2021, March 19, 2023, available at: https://www.mohw.gov.tw/cp-5014-58733-1.html (last accessed: May 25, 2023).

doi:10.6342/NTU202302527

were conducted, there is no information on whether the importer submitted risk/benefit analysis information, and was reviewed by the TFDA. Although according to the Regulations for Registration of Medicinal Products, vaccines that have been approved in used in the listed ten countries may undergo an alternative review route, the Taiwan authorities failed to publish relevant information on drug reviews, and only announced ACIP policies for vaccination recommendations. Even though the TFDA claims to have held expert committee meetings to discuss the approval for imports and manufacturing of COVID-19 vaccines, the TFDA has failed to reveal the meeting records, minutes, results to the publics, and even refused to reveal the composition of the committee, leading to various speculation from outside the agency.[94]

C. The Medigen Vaccine (MVC COVID-19 Vaccine)

On the other hand, more than one Taiwanese pharmaceutical aimed to bring a COVID-19 vaccine onto the market. In August 2020, the TFDA held a conference for the facilitation of COVID-19 drug and vaccine development. Following that conference, the TFDA issued conditional approval for phase I clinical trials for two pharmaceuticals developing COVID-19 vaccines in the same month, and even established an online platform for the recruitment of trial participants in November. By the end of that year, the TFDA approved Medigen's application for phase II trial of its vaccine, the MVC COVID-19 vaccine. After a significant lapse of time, the TFDA published a comparison of the phase I and II trials conducted for the AstraZeneca, Moderna and

[94] Taiwan Food and Drug Administration, Announcements, TFDA Announces VRBPAC Members Selection Procedures and Calls for End of Misinformation, June 25, 2021, available at: https://www.fda.gov.tw/tc/newsContent.aspx?cid=4&id=t600410 (last accessed: May 25, 2023).

doi:10.6342/NTU202302527

Pfizer/BNT COVID-19 vaccines in June, 2021,[95] and subsequently the TFDA published its EUA standards for domestically made COVID-19 vaccines.[96] On July 19, the TFDA announced that MVC COVID-19 vaccine has reached the standards for EUA, and is approved for use.[97] Sadly, another vaccine failed the review.[98]

The EUA standards published on July 19, 2021, is also of interest to this thesis. According to the two-page powerpoint document in huge block letters, the TFDA announces that domestically made COVID-19 vaccines can achieve approval through immunobridging evaluations, and comparing the domestically made vaccines with foreign vaccines that have already been approved. The TFDA elaborates that the study vaccine should be compared alongside the AstraZeneca vaccines, and the study vaccine should achieve both a 50% seroconversion rate, and the lower bound of the 95% confidence interval for the geometric mean titer ratio must be greater than 0.67 on Day 28 after completion of vaccination. For safety, the TFDA requires a safety database of at least 3000 subjects with at least one month follow-up, with a median 2 month follow-up for all subject.

[95] Taiwan Food and Drug Administration, News, TFDA Explanations on the Phase I and Phase II Trial Size Comparison Charts Given on Central Epidemic Command Center Press Conference, June 1, 2021, available at :https://www.fda.gov.tw/tc/newsContent.aspx?cid=4&id=t600352 (last accessed: May 25, 2023).
[96] Taiwan Food and Drug Administration, News, TFDA Publishes EUA Review Standards for Domestically Made COVID-19 Vaccines with Expert Advice and Reviews Cautiously to Ensure Vaccines are Effective and Safe, June 10, 2021, available at: https://www.fda.gov.tw/tc/newsContent.aspx?cid=4&id=t600385 (last accessed: May 25, 2023).
[97] Taiwan Food and Drug Administration, News, MoHW Approves Medigen MVC-COV1901 COVID-19 Vaccine for Special Case Manufacturing, July 19, 2021, available at: https://www.fda.gov.tw/tc/newsContent.aspx?cid=4&id=t600452 (last accessed: May 25, 2023).
[98] Taiwan Food and Drug Administration, News, TFDA Holds VRBPAC Meeting for Review of UbiAsia UB-612 COVID-19 Vaccine, August 16, 2021, available at: https://www.fda.gov.tw/Tc/newsContent.aspx?cid=4&id=t600499 (last accessed: May 25, 2023).

doi:10.6342/NTU202302527

The TFDA EUA standard is clearly a mixture of different approval standards. First of all, it utilizes the accelerated approval concept of using surrogate markers as endpoints instead of clinical endpoints. This is based on the WHO's publication of antibody titers and seroconversion rate elicited by COVID-19 vaccines. On the other hand, it still requires the study vaccine to be compared with an approved and available vaccine, the AstraZeneca vaccine. Finally, the safety data follow-up period and database size borrows some numbers from the US FDA, but also created significant leeway in both size and duration. For the two vaccine candidates that submitted for approval through this route, the COVID-19 vaccine reviewing committee followed this standard. The TFDA published the meeting results, which are both one page announcements that the vaccines have met the standards, and recorded the voting results of the meeting. No further revelation on the meeting proceedings, including questions that were brought up for discussion or post-marketing requirements were included in the announcements. The MVC COVID-19 vaccine, which achieved approval, was welcomed by the Taiwanese population and contributed to increasing vaccine coverage on the island.

D. Emergency Considerations with a Local Touch?

The TFDA's decision making process reveals how the TFDA has referenced the US FDA, and dealt with obstacles that the US FDA clearly did not encounter in its EUA approvals. In a more general context, it is important to note that unlike the US, Taiwan does not boast of a world-leading pharmaceutical industry, and its pharmaceutical market is severely restricted by its population and national health insurance policies. Therefore, while Taiwan has endeavored to establish a consistent and applicable drug and biologics

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review program under constraints, its local and unique political considerations have guided its way.[99] This is also clearly observed in how the TFDA dealt with COVID-19 vaccines during the pandemic.

Interesting aspects directly relating to Taiwan's status during the COVID-19 pandemic were observed. In addition to following the US FDA's authorization decisions for Moderna and Pfizer/BNT, the TFDA developed its own methods for domestically made vaccines. The major reason, interestingly, is the lack of the COVID-19 epidemic in Taiwan in the early stages of the pandemic. Without the high incidence rate and mortality rate, it was impossible to conduct clinical trials with clinical endpoints in Taiwan. Even when the pandemic finally hit Taiwan in May 2021, three imported vaccines have already made it difficult to conduct clinical endpoint based phase III trials in Taiwan. Therefore, the TFDA chose to wait for the WHO's publication of surrogate endpoints to set its standards for domestically developed COVID-19 vaccines. This also reflects on how not only technological advances and clinical trial adaptations were crucial to the rapid authorization of US EUAs, but that the nature of the pandemic itself played an important role in facilitating smooth and fast clinical trials that gained confidence for sponsors and reviewers.

V. Conclusion

The COVID-19 pandemic is the first global public health emergency to hit the US hard since the EUA program since it was established in 2004. Due to its little use, there were only very vague understandings of its scope and

[99] *See e.g.* Wen-Hua Kuo, The Voice on the Bridge: *Taiwan's Regulatory Engagement with Global Pharmaceuticals*, 3.1 EAST ASIAN SCIENCE, TECHNOLOGY AND SOCIETY: AN INTERNATIONAL JOURNAL 51-72 (2009); Joseph Wong, *Re-Making the Developmental State in Taiwan: The Challenges of Biotechnology*, 26.2 INTERNATIONAL POLITICAL SCIENCE REVIEW 169-191 (2005).

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limitations, despite the lengthy legal requirements. The COVID-19 pandemic has given the EUA program its first comprehensive examination. From the earliest drug and diagnostics EUAs that might be describe as reckless, the US FDA has approached the COVID-19 vaccine with much caution and deliberation.

Firstly, the US FDA issued two guidance documents focusing on COVID-19 vaccines, with one for licensure preceding the one specifically for EUAs. This shows that the US FDA was eager to establish a leadership role to coordinate vaccine development from the very start, and that the EUA program was simply a phase of vaccine development.

Secondly, from the standards given in the two guidance documents, we can see that the US FDA indeed intended on giving the vaccine developers some leeway in setting rules and goals for clinical trial. Although efficacy trial requirements and endpoint cutoffs appear to be the same, the US FDA distinctively allowed for interim analyses to be the basis of efficacy evidence. For safety, the US FDA cut the follow-up period short to only a median of two months to facilitate earlier submission. In order to expedite vaccine development and review, the US FDA brought out many of its treasured weapons: seamless or multiphase clinical trials, interim analysis, system-based review of safety data, and increased communication with sponsors.

Thirdly, in retrospect, while the US FDA's expediting schemes did not result in unacceptable risks, it appears that many were not warranted. All of the clinical trials for the first three COVID-19 vaccines recruited participants easily and swiftly, making early efficacy analysis possible, and fulfilling safety database size requirement simple. This was achieved by progress in vaccine

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technology, streamlined trial administration, and perhaps more importantly, the nature and extent of the disease itself. In other words, though past experience from various expediting programs were helpful, the size and severity of the pandemic itself still gave the COVID-19 EUAs a somewhat paradoxical edge.

Compared to the US FDA, Taiwan's FDA decision making on COVID-19 vaccines revealed both administrative and technical limitations. Depending heavily on review decisions of listed authorities from abroad, including the US FDA, it was relatively easy to approve Pfizer-BNT and Moderna COVID-19 vaccines (acquiring the vaccines proved to be much more difficult). However, when it came to domestically developed COVID-19 vaccines, the TFDA was first ironically hindered by the absence of the pandemic in Taiwan, and also struggled to implement a logical approval standard.

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Chapter 5 Conclusion: The Reference, Resilience, and Revelation of Evidence Review Under Emergency

When and how the COVID-19 pandemic will end, is the question that has been asked by everyone around the globe for more than a year, and there is no denying that the rapid emergence of COVID-19 vaccines comprised the crucial part of the answer. This thesis attempts to enrich this discussion by analyzing and comparing US FDA review of drugs and vaccines both before the pandemic and during, with a focus on the standard with which it reviewed the scientific evidence involved.

Starting with very basic understanding of the complicated review mechanisms reinforced by decades of trial and error, Chapter 2 of this thesis first outlines the various acceleration methods and the scientific evidence they considered. The chapter chronicles the reviews of the first successful new oral anticoagulant, dabigatran, and an iconic breakthrough hepatitis C drug, Sofosbuvir, with a focus on how the US FDA accepted and reviewed scientific evidence. From the dabigatran approval, we could see that the US FDA did not limit its approvals to clinical trials that adhered to the golden standard of double-blind randomized control trials, and that interpretation of efficacy could be messy even for well-designed trials. In the Sofosbuvir approval, we observed a concerted effort of the sponsor, academia and the US FDA, and flexible evidence review based on different circumstances. Chapter 2 constructed a baseline for standards and options for expediting of US FDA reviews.

Following the establishment of the US FDA expediting framework, and a recognition of its scope and elasticity, Chapter 3 of this thesis turned to the

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comparatively restrained and austere review of vaccines for infectious diseases similar to COVID-19. From influenza vaccines, the egg-based Agriflu and recombinant Flublok, we observed how the US FDA handled vaccines using familiar and unfamiliar vaccine techniques. Efficacy-wise, the US FDA was able to establish detailed review standards in advance based on decades of experience with influenza vaccines, and was comfortable with making extrapolations given the unpredictability of influenza epidemics. In terms of safety, however, the US FDA proceeded with intense caution, endorsing a standardized safety monitoring scheme in clinical trials and not relenting on safety follow-up periods and safety database size. It was clear that the US FDA held a tighter grip over vaccines compared to drugs even when public health needs were apparent.

Chapter 4 finally begins to analyze the US FDA reviews of COVID-19 vaccine EUAs. With the foundation built in the previous chapters, this chapter was able to truly evaluate the determination and innovation with which the US FDA reviewed the COVID-19 vaccine EUAs. There was a wide speculation over what standards the US FDA would hold the COVID-19 vaccines to for EUA, and even the guidance documents reflected a certain degree of flexibility clinical trial design. However, many of these accommodations proved to be unnecessary as the trials began rolling out, especially in consideration of efficacy, largely due to the nature of the pandemic itself. One feature that did significantly reduced trial duration was the short safety follow-up period. Compared to the 6 month follow-up period held so steadfastly by the US FDA in influenza vaccine approvals, the US FDA required only a median of 2 month follow-up period for COVID-19 vaccine EUAs. This is reasonable compromise,

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as most adverse events occur within 7 days of vaccination, and rare events require a much larger and longer safety evaluation that were never considered realistic in clinical trials. Therefore, even under immense time pressure, the US FDA did not, and was not obliged to, relent much on the quality and quantity of scientific evidence for COVID-19 vaccine EUAs. In comparison, Taiwan, where the pandemic hit late due to strict border and infection control, approving vaccines was much more problematic.

To elaborate on US FDA COVID-19 vaccine EUAs in detail, three features are central to the success of the EUA program in terms of scientific evidence review: reference, resilience, and revelation.

First of all, and surprising to a certain extent, the COVID-19 vaccine EUA reviews referenced past US FDA approval experience substantially, despite the unprecedented scale and severity of the pandemic in modern era. It is unsurprising that the EUA program would fall back on well-established approval processes: standard setting through guidance documents with an eye on rapidly progression academic development, review of efficacy and safety data by US FDA staff, and finally involving advisory committees for making first-in-history decisions. But the standards with which scientific evidence was to be reviewed adhered closer to that of the classical vaccine reviews than it was predicted to be: phase III, double-blind, randomized controlled trials involving thousands were required, with vaccine efficacy for trial endpoints, and decidedly similar safety follow-up protocols. Even the vaccine efficacy cutoff point at 30% referenced that of the lower bound for influenza vaccines. On the contrary, none of the anticipated novel or alternative scientific evidence review methods were experimented for the earliest EUAs: human challenging studies,

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real world evidence, master protocols or even surrogate markers were not given any attention in the US FDA's COVID-19 vaccine EUA reviews. Evidently, some of the expediting tools were also credited for the COVID-19 vaccine EUAs: procedurally there was the rolling review system and increased communications, and substantively, the use of the system-based review of safety data and utilization of post-marketing requirements. Furthermore, even though risk and benefit evaluation was mandated by the federal law and serves as a unique and compromising feature of the EUA, the advisory committee's review did not dwell of this analysis and was still more focused on the efficacy and safety analyses from the clinical trials. From the trials and reviews conducted, it seems that both the US FDA and the vaccine developers felt more comfortable with well-established methods and standards to validate scientific evidence in COVID-19 vaccine EUAs, hence we observed a good deal of referencing.

Secondly, profound resilience was reflected in the rapid and mass accrual of trial participants and the diversity of trial protocols, contrary to projections of limited trial capacity and need for uniformed trial guidelines at the beginning of the pandemic. From the guidance document and academic literature published before vaccines embarked on phase III trials voiced of eminent concern about conducting a clinical trial during the pandemic. US FDA vaccine guidance document required a minimum of 3000 for safety databases (admittingly not too small for even drugs and vaccines using a novel technique), and allowed for EUA submissions based on interim analysis results as opposed to final efficacy results so that drawn out trial duration would not hinder EUA reviews. While all vaccine sponsors programmed at least one interim analysis into their phase III clinical trials accordingly, eventually all efficacy final

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analyses data were submitted to the US FDA for review, because COVID-19 spread so fast that the number of confirmed cases to trigger interim and final analyses were both quickly achieved. Due to the case-driven approach of the trials, a logical strategy due to the vast unknowns of the virus and epidemic, recruitment surpassed the minimal safety database requirement of 3000 for all three pivotal vaccine trials by more than three-fold. Here, I would like to take a moment to appreciate the resilience of the people that participated in the clinical trials: regardless of their motive for adding themselves to the list, be it to make the world a better place or to increase self-protect, their actions in congregation has smoothed out wrinkles in the EUA review process. To be perfectly candid, many of the compromises the US FDA made for EUAs were taken out of expediting schemes to address unmet medical needs created by diseases and conditions distinctly disparate from that of the COVID-19 pandemic, and were therefore simply irrelevant. Thankfully, the vaccine sponsors departed from past drug and vaccine submissions by not limiting themselves to the capacities set by the US FDA. With the financial and technical aide of Operation Warp Speed, they absorbed the tumultuous waves of subjects and processed the bulk of data at unparalleled speed, defying ubiquitous doubt and exhibiting resilience.

Thirdly, the revelation of data and information played an important part in the US FDA review process, and was not compromised significantly during the COVID-19 pandemic. Under the FD&C Act, the US FDA is required to disclose submitted data and review memos for all drugs and vaccines that was approved for use. In practice, the US FDA makes not only the review memos of different divisions (including clinical, statistical, chemistry and manufacturing, reproduction toxicity studies, and more) available, but also revealed all

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communications records through emails and telephone calls between US FDA officers and the sponsor, in accordance with the Administrative Procedure Act. Advisory meeting summaries and minutes were also published accordingly, which included at least the discussion on major topics and voting records. For vaccine EUAs under the COVID-19 pandemic, a single review document was published for each vaccine, which combined clinical review, pharmacovigilance activities, chemistry, manufacturing and control (CMC) information, clinical assay information, and clinical study site inspections review, as well as the risk and benefit analysis results. Compared to drug or vaccine approvals in non-emergency conditions, the available information was brief but appears to have included all reviewed material. The VRPBAC meetings for COVID-19 vaccine EUAs were all announced in advance, materials were mostly made available before the meeting commenced such that any interested persons could submit comments for discussion, and the meetings were held completely in open sessions that were streamed online. Furthermore, the roster of voting members, temporary voting members and US FDA staff were also disclosed before the meeting, with a brief introduction of their current post, expertise, and representation status. Discussion and voting records were also viewable. Even under extreme time pressure, COVID-19 vaccine EUAs were subject to a high level of information disclosure, establishing decent accountability and trust at least among public health and medical experts, and eventually reflects in widespread vaccination worldwide. The TFDA evidently benefited fro the information disclosed by the US FDA, as the product information they published for Pfizer/BNT and Moderna vaccines relied highly on US FDA EUA summaries. On the other hand, the TFDA has yet declined to offer any

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information on the composition of the VRPBAC, and has never made review materials available before VRPBAC meetings for either imported or domestically-made COVID-19 vaccine EUAs. While due to heightened social solidarity vaccination needs were not significantly hindered, the lack of transparency was heavily criticized and crippled the vaccine sponsor's plans to expand abroad.

This thesis is obviously not the first nor the last to remark on how COVID-19 vaccine EUAs were possible, and definitely not the only one to examine the evidences it reviewed. However, it is my hope that readers of this thesis can appreciate how much of the EUA program, in particular for COVID-19 vaccines, is embedded in the decades of US FDA experience in reviewing scientific evidence. On the other hand, we should also keep in mind that a pandemic of this scale and severity is not just an escalated situation of past epidemics or unmet medical needs, and thus assessing and interpreting scientific evidence would be unprecedented in its own way. Therefore, should the next emergency approach some day in the future, we may be better prepared to tackle it conscientiously, referencing the past, maintaining resilience, and with adequate revelation.

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