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CURRENT REGULATIONS AND EVOLVING LEGISLATION FOR VACCINE APPROVAL AND MONITORING PROGRAMS IN THE UNITED STATES

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ABSTRACT

This analysis looks at recent amendments to laws and regulations and offers a thorough summary of the current vaccination laws in the US. The Food and Drug Administration (FDA) is principally overseeing the regulatory framework for vaccinations, which guarantees the efficacy, safety, and quality of vaccines before and after their release onto the market. Important components include clinical trials conducted prior to licensure, post-marketing surveillance programs like the VAERS, and particular regulations mandated by the 1986 National Childhood Vaccine Injury Act (NCVIA). The FDA evaluates vaccines for safety and efficacy via several stages of clinical trials as part of its stringent pre-licensure procedure. The post-marketing surveillance system, which includes the Vaccine Safety Datalink (VSD) and VAERS, is essential for tracking side effects and maintaining public safety after licensure.

New public health needs and improved vaccination safety monitoring have been addressed by recent legislative and regulatory revisions. These include revised procedures for the expedited consideration of vaccines during public health emergencies, such as the COVID-19 pandemic, improvements to the VICP, and adjustments to reporting requirements. The FDA Reauthorization Act (FDARA) and the 21st

Century Cures Act feature provisions that simplify the vaccine research and clearance process by using cutting-edge clinical trial designs and real-world evidence.

Keywords: Vaccine, Vaccine Adverse Event Reporting System (VAERS), CDC, CBER

INTRODUCTION

The FDA's vaccination approval rules and regulations have changed dramatically during the last few decades. Title 21 of the Code of Regulations mandates that the FDA enforce strict standards for the safety, effectiveness, and potency of vaccinations. The FDA's efforts to improve the approval process are shown in the significant increase in new biological product approvals from 1994 to 2024. The CBER of the FDA has been in charge of overseeing the safety, efficacy, and purity of vaccines in the US through the implementation of laws that cover things like clinical trial criteria and vaccine manufacturing.

The FDA is committed to upholding high standards in the vaccine industry, as evidenced by its strict testing and oversight procedures throughout the vaccine development lifecycle.

The FDA's vaccination approval regulations have changed significantly since 1994. The FFD&C Act was significantly modified by the FDAA Act of 2007, which affected vaccination regulation. Furthermore, the FDA's approval process for novel medications, including vaccines, has changed, with a focus on expediting the procedure and expanding access to experimental therapies, particularly in critical circumstances like the AIDS epidemic. The FDA has been modifying its review procedures to guarantee stringent guidelines and evidence-based decision-making, as seen by the latest events concerning the approval of COVID-19 vaccinations. The aforementioned modifications signify an ongoing progression in FDA guidelines, propelled by the imperative to tackle nascent health issues, augment security, and expedite the availability of therapies that can save lives.

In 2014, the US CDC stated that about 75 percent of premature deaths and over 21 million hospital admissions were avoided during the course of a 20-year immunization campaign (1994–2013). In spite of these advantages for public health, vaccinations are frequently taken for granted, and a campaign against them has been stoked by false information.

Passive immunotherapies from immunized livestock were used as early treatments for infectious illnesses. However, a 1901 incident involving tetanus-infected horses giving tainted diphtheria antitoxin resulted in multiple infant deaths and brought attention to the importance of regulatory supervision. The Biologics Control Act of 1902, which assigned the Hygienic

Laboratory (later NIH) the responsibility of supervising biological medicines, was inspired by this event.

Through a number of legislative initiatives, such as the "Pure Food and Drugs Act" and the "Federal Food, Drug, and Cosmetic Act", the NIH managed biological treatments. The FDA took over responsibility for biologics in 1972 and established the Center for Drugs and Biologics. In order to create the CDER and CBER, this center was divided in 1987. Recombinant monoclonal antibody management and a few other biologicals were moved from CBER to CDER in 2002 **[1]**.

USE OF NEW APPROVAL PROGRAMS AND STANDARDS

The review team "intends to make every effort to conduct an expedited review and act early on the application" for applications that the FDA determines address a significant public health need. Throughout the review process, the FDA staff and the applicant will communicate often as part of expedited evaluations.

Fast Track

In an effort to provide patients with novel and possibly better medicines more quickly than with traditional techniques, the "Fast Track" system expedites the study and assessment of drugs for serious illnesses with urgent medical requirements. This entails developing novel medicines in situations where none now exist or providing treatments that may be superior to those that are already available.

A Fast Track medication needs to demonstrate a benefit over current treatments, like

1. Greater efficacy
2. Preventing major side effects
3. Improving diagnosis for improved results;
4. Decreased substantial toxicity that leads to treatment cessation;
5. Meeting new or expected public health demands

Fast Track designation has several advantages, such as:

1. More regular meetings and written correspondence with the FDA
2. Qualification for Priority Review and Accelerated Approval
3. Rolling Review: This process enables the Biologic License Application (BLA) to be submitted in chunks and evaluated as it is finished.

The pharmaceutical business may apply for Fast Track designation at any point during the development process. Based on the medication's potential, the FDA evaluates the request and decides within 60 days **[2]**.

Table 1: Approval of vaccines through fast-track designation

Vaccine	Approval Year	Applicant
Comirnaty	**2020**	**Pfizer-BioNTech**
Spikevax	**2020**	**Moderna**
Vaxchora	**2016**	**Bavarian Nordic**

Breakthrough Therapy

Medications aimed to treat serious conditions that show promise in improving key medical metrics above current treatments might be named breakthrough medicines based on preliminary clinical evidence. The purpose of this classification is to expedite the process of
their creation and regulatory evaluation.

The patient will determine whether there has been a noticeable improvement over existing therapy. Important factors are the therapy's duration and impact as well as the importance of the documented clinical result. First clinical evidence should typically show an obvious benefit above presently suggested therapy.

When a medication is designated as Breakthrough Therapy, it can be used for the following:

1. Every characteristic of the Fast Track designation.
2. Thorough instruction on a productive drug development approach, starting with Phase 1.
3. Senior managers' dedication to the organization.

If any requirements for the designation are to be fulfilled, a request for Breakthrough Therapy designation must be sent to the FDA before the end of phase II meetings. After an initial BLA or supplement filing, the FDA expects that no requests will be made because the primary objective of the designation is to expeditiously obtain the necessary evidence for approval. Requests for designation as a Breakthrough Therapy will receive a response from the FDA within 60 days of filing. Breakthrough Therapy Designations are non-refundable within the fiscal year in which they are conferred after they are approved by CBER **[3]**.

Table 2: Approval of Vaccines through Breakthrough Therapy

Vaccine	Approval Date	Applicant
Ixchiq	**09-NOV-2023**	**Valneva Austria GmbH**
Abrysvo	**21-AUG-2023**	**Pfizer, Inc**
Vaxneuvance	**16-Jul-2021**	**Merck Sharp & Dohme Corp**
Prevnar 20	**08-Jun-2021**	**Wyeth Pharmaceuticals, Inc**
Ervebo	**19-Dec-2019**	**Merck Sharp & Dohme, Corp.**
Bexsero	**23-Jan-2015**	**GlaxoSmithKline Biologicals**
Trumenba	**29-Oct-2014**	**Wyeth Pharmaceuticals, Inc**

Accelerated Approval Program

The FDA launched the Accelerated Approval Program in order to expedite the approval of medications to treat serious disease and to address medical needs that aren't currently met, using surrogate

endpoints. These endpoints are indicators believed to predict clinical benefit but are not direct measures of it, such as physical signs, imaging results, or lab tests. Using surrogate endpoints can significantly shorten the time required for FDA approval. Pharmaceutical companies must conduct further research to confirm the anticipated clinical benefits. If a confirmatory trial shows the medication genuinely provides therapeutic benefits, it can receive traditional FDA approval. However, the FDA has regulatory mechanisms in place to potentially remove the drug from the market if the confirmatory trial fails to demonstrate its clinical benefits.

Included in this section are accelerated approvals (AAs) for infectious disease indications for which traditional approval has been later given for the particular indication and postmarketing trials have confirmed therapeutic benefits **[4]**.

Table 3: Approval Of Vaccines through Accelerated Approval Program

Vaccine	Approval Date	Applicant
Audenz	31/01/2020	Seqirus Inc
Flucelvax Quadrivalent	23/05/2016	Seqirus, Inc
Trumenba	14/04/2016	Wyeth Pharmaceuticals, Inc
Flublok	29/10/2014	Protein Sciences Corporation
Fluzone High Dose	27/06/2012	Sanofi Pasteur
Prevnar 13	30/12/2011	WYETH
Flulaval Quadrivalent	09/06/2011	ID Biomedical Corporation of Quebec
Agriflu	27/11/2009	Seqirus Inc

APPROVAL OF VACCINES

Early on in the vaccine development process, a decade or more of intensive laboratory study is usually conducted by researchers to investigate prospective vaccinations. Collaboration between researchers from universities and the corporate sector is common during this time. To improve the vaccine's efficacy, scientists first see how well it works in mice and other small animals to see if it can elicit an immune response. The effectiveness of a vaccination is determined by how well it guards against infection, disease symptoms, hospitalization, and mortality. The vaccine moves on to human clinical trials for testing if encouraging outcomes are seen **[5]**.

Stage of Clinical Development

The vaccine moves onto the clinical development phase, commonly referred to as a clinical trial, following the FDA's receipt of an Investigational New Drug (IND) application that contains details about vaccine quality, manufacturing technology, and data from animal studies. There are three phases at this stage, and a fourth one could come if the FDA approves the vaccine. Phase 1 has between 20 and 100 participants. Evaluate immunological response, safety, and side effects. Phase 2 has between 100 and 300 people. Offers

more safety information and assesses the immunological response in a bigger, more varied population. Phase 3 has approximately 1,000–3,000 people. Verifies the effectiveness of vaccines, tracks adverse effects, and collects information for safe use. Phase 4 (after FDA approval) has thousands of people. Ongoing research to assess efficacy and safety over the long term **[5]**.

Accepting the Vaccine

The FDA receives Biological License Applications (BLAs) from companies prior to vaccination approval in the United States. Clinical and pre-clinical data are included in the BLA.

1. Details about the manufacturing process
2. Details concerning the production plant

To make sure the vaccination is both safe and effective, the FDA examines the data from clinical trials. Additionally, the BLA includes prescription details that are subject to change based on usage, dose, and administration. The FDA determines whether to approve the vaccine for use based on this review **[5]**.

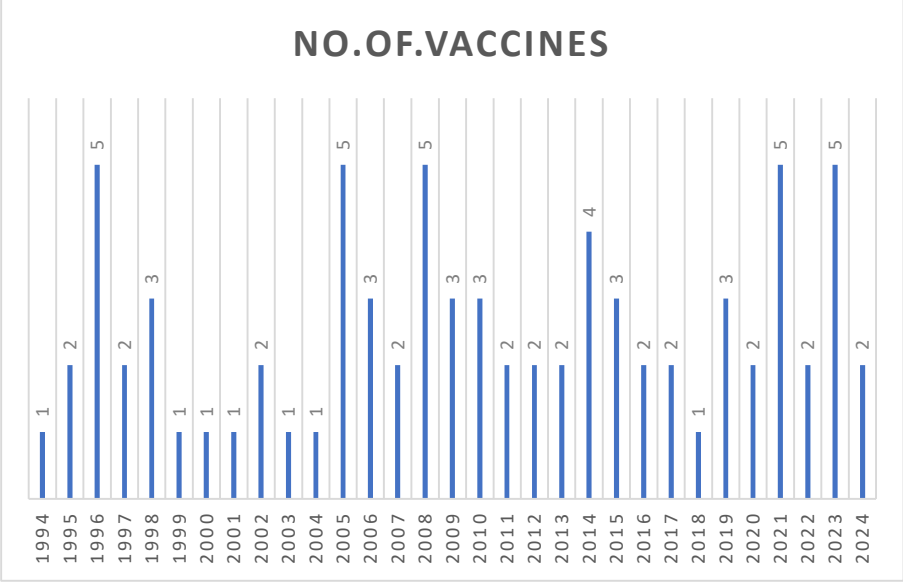

Figure 1: Changes in the Number of Vaccines Approved 1994-2021

Table 3: Year of Approval of Vaccines and their Manufacturer.

Year	Brand Name	Company
1994	Typhim Vi	Aventis Pasteur
1995	Havrix	Smithkline Beecham
	Varivax	Merck
1996	Acel-Imune	Lederle
	Comvax	Merck
	Trihibit	Aventis Pasteur
	Tripedia	Aventis Pasteur
	Vaqta	Merck

1997	**Rabavert**	**Chiron Behring**
	Infanrix	**Smithkline Beecham**
1998	**Lymerix**	**Smithkline Beecham**
	Rotashield	**Wyeth**
	Certiva	**North American Vaccine**
1999	**Tripedia**	**Connaught**
2000	**Prevnar**	**Wyeth**
2001	**Twinrix**	**Smithkline Beecham**
2002	**Pediarix**	**Glaxosmithkline**
	Daptacel	**Aventis Pasteur**
2003	**Flumist**	**Medimmune**
2004	**Decavac**	**Aventis Pasteur**
2005	**Proquad**	**Merck**
	Fluarix	**Glaxosmithkline**
	Adacel	**Sanofi Pasteur**
	Tdap: Boostrix	**Glaxosmithkline**
	Menactra	**Sanofi Pasteur**
2006	**Gardasil**	**Merck**
	Zostavax	**Merck**
	Rotateq	**Merck**
2007	**Afluria**	**Seqirus Inc.**
	H5n1 Avian Influenza Vaccine	**Sanofi Pasteur**
2008	**Dtap-Ipv Vaccine**	**Kinrix**
	Pentacel	**Sanofi Pasteur**
	Tenivac	**Sanofi Pasteur**
	Kinrix	**Glaxosmithkline**
	Pentacel	**Sanofi Pasteur**
	Rotarix	**Glaxosmithkline**
2009	**Fluzone Quadrivalent**	**Sanofi Pasteur**
	Cervarix	**Glaxosmithkline**
	Hiberix	**Glaxosmithkline**
2010	**Prevnar 13**	**Wyeth**
	Menveo	**Novartis**
	Agriflu	**Seqirus Inc.**
2011	**Boostrix**	**Glaxosmithkline**
	Menactra	**Sanofi Pasteur**
2012	**Flucelvax**	**Novartis**
	Menhibrix	**Glaxosmithkline**
2013	**Flulaval**	**Id Biomedical Corporation of Quebec**
	Fluzone Quadrivalent	**Sanofi Pasteur**
2014	**Rapivab**	**Biocryst**
	Gardasil 9	**Merck**
	Trumenba	**Wyeth**
	Flublok	**Protein Sciences Corporation**
2015	**Fluad Quadrivalent**	**Seqirus Inc.**
	Quadracel	**Sanofi Pasteur**
	Bexsero	**Glaxosmithkline**
2016	**Vaxchora**	**Bavarian Nordic**
	Flucelvax Quadrivalent	**Seqirus Inc.**
2017	**Heplisav-B**	**Dynavax Technologies Corporation**
	Shingrix	**Glaxosmithkline**
2018	**Vaxelis**	**Msp Vaccine Company**
2019	**Jynneos**	**Bavarian Nordic**
	Dengvaxia	**Sanofi Pasteur Inc**
	Ervebo	**Merck Sharp & Dohme Corp**
2020	**Menquadfi**	**Sanofi Pasteur**
	Audenz	**Seqirus Inc**
2021	**Prehevbrio**	**Vbi Vaccines**
	Comirnaty	**PFIZER-Biontech**
	Ticovac	**Pfizer**

	Vaxneuvance	**Merck**
	Prevnar 20	**Wyeth**
2022	**Priorix**	**Glaxosmithkline**
	Spikevax	**Moderna Tx Inc.**
2023	**Ixchiq**	**VALNEVA AUSTRIA Gmbh**
	Cyfendus	**Emergent Biosolutions**
	Abrysvo	**Pfizer**
	Arexvy	**Glaxosmithkline**
	Penbraya	**Pfizer**
2024	**Capvaxive**	**Merck**
	Mrsevia	**Moderna Tx Inc.**

From 1994 to 2024, approximately 78 vaccines have been approved **[6], [7]**.

VACCINE PRICE

Vaccine costs differ, with different costs for adult and pediatric vaccinations. The pricing details are listed in tabular form below **[8]**.

Table 4: Prices of Pediatric Vaccines and their Manufacturer

S. No.	Brand Name	Cost/Dose (CDC)	Cost/Dose (Private Sector)	Manufacturer
1.	Abrysvo	$221.2	$295.00	Pfizer
2.	Acthib	$11.1	$12.9	Sanofi Pasteur
3.	Adacel	$37.0	$47.8	Sanofi Pasteur
4.	Afluria Tiv	$15.9	$21.59	Seqirus USA, Inc
5.	Afluria Tiv	$15.7	$19.96	Seqirus USA, Inc
6.	Bexsero	$150.02	$223.74	GlaxoSmithKline
7.	Beyfortus (100mg)	$395.00	$519.7	Sanofi Pasteur
8.	Beyfortus (50mg)	$395.00	$519.7	Sanofi Pasteur
9.	Boostrix	$37.01	$47.39	GlaxoSmithKline
10.	Covid-19 Vaccine	$85.9	$128.00	Moderna
11.	Daptacel	$21.68	$29.31	Sanofi Pasteur
12.	Dengvaxia	$65.9	$66.00	Sanofi Pasteur
13.	Engerix B	$17.37	$28.42	GlaxoSmithKline
14.	Flucelvax Tiv	$21.4	$32.44	Seqirus USA, Inc
15.	Flucelvax Tiv	$20.2	$32.44	Seqirus USA, Inc
16.	Flulaval Tiv	$15.21	$19.7	GlaxoSmithKline
17.	Flumist Tiv	$20.23	$24.7	AstraZeneca
18.	Fluzone Tiv	$15.07	$19.29	Sanofi Pasteur
19.	Fluzone Tiv	$15.07	$20.67	Sanofi Pasteur
20.	Gardasil	$240.30	$287.53	Merck
21.	Havrix	$23.89	$38.008	GlaxoSmithKline
22.	Hiberix	$11.07	$12.80	GlaxoSmithKline
23.	Infanrix	$21.65	$28.79	GlaxoSmithKline
24.	Ipol	$16.4	$42.63	Sanofi Pasteur
25.	Jynneos	$229.5	$270.00	Bavarian Nordic
26.	Kinrix	$48.27	$61.07	GlaxoSmithKline
27.	Menquadfi	$111.0	$166.98	Sanofi Pasteur
28.	Menveo (One-Vial)	$108.74	$157.35	GlaxoSmithKline
29.	Menveo (Two-Vial)	$108.74	$157.35	GlaxoSmithKline
30.	M-M-R Ii	$25.68	$92.49	Merck
31.	Pediarix	$66.06	$97.96	GlaxoSmithKline
32.	Pedvaxhib	$16.13	$29.70	Merck
33.	Penbraya	$189.3	$230.7	Pfizer
34.	Pentacel	$70.18	$114.52	Sanofi Pasteur
35.	Pneumovax 23	$65.8	$117.08	Merck
36.	Prevnar 20	$185	$261.5	Pfizer
37.	Priorix	$25.67	$92.49	GlaxoSmithKline
38.	Proquad	$178.34	$270.14	Merck
39.	Quadracel	$47.90	$62.20	Sanofi Pasteur
40.	Recombivax Hb	$14.58	$27.11	Merck

41.	**Rotarix**	**$108.4**	**$138.74**	**GlaxoSmithKline**
42.	**Rotateq**	**$81.59**	**$95.96**	**Merck**
43.	**Spikevax**	**$85.9**	**$128.00**	**Moderna**
44.	**Tenivac**	**$24.30**	**$37.10**	**Sanofi Pasteur**
45.	**Trumenba**	**$135.9**	**$190.2**	**Pfizer**
46.	**Twinrix**	**$73**	**$126.19**	**GlaxoSmithKline**
47.	**Vaqta**	**$23.97**	**$37.73**	**Merck**
48.	**Varivax**	**$144.2**	**$174.32**	**Merck**
49.	**Vaxelis**	**$100.58**	**$150.8**	**Merck**
50.	**Vaxneuvance**	**$168.73**	**$222.54**	**Merck**

Table 5: Prices of Adult Vaccines and their Manufacturer

S. No.	Brand Name	Cost/Dose (CDC)	Cost/Dose (Private Sector)	Manufacturer
1.	**Abrysvo**	**$195.8**	**$295.00**	**Pfizer**
2.	**Adacel**	**$28.60**	**$47.83**	**Sanofi Pasteur**
3.	**Afluria Tiv**	**$15.5**	**$21.59**	**Seqirus USA, Inc**
4.	**Afluria Tiv**	**$14.3**	**$19.96**	**Seqirus USA, Inc**
5.	**Arexvy**	**$175.04**	**$280.00**	**GlaxoSmithKline**
6.	**Bexsero**	**$128.35**	**$223.74**	**GlaxoSmithKline**
7.	**Boostrix**	**$28.86**	**$47.39**	**GlaxoSmithKline**
8.	**Engerix-B**	**$34.97**	**$69.4**	**GlaxoSmithKline**
9.	**Engerix-B**	**$36.22**	**$69.4**	**GlaxoSmithKline**
10.	**Fluarix Tiv**	**$13.91**	**$19.7**	**GlaxoSmithKline**
11.	**Flucelvax Tiv**	**$19.7**	**$32.44**	**Seqirus USA, Inc**
12.	**Flucelvax Tiv**	**$19.2**	**$32.44**	**Seqirus USA, Inc**
13.	**Flumist Tiv**	**$17.6**	**$24.70**	**AstraZeneca**
14.	**Fluzone Tiv**	**$13.92**	**$19.29**	**Sanofi Pasteur**
15.	**Fluzone Tiv**	**$14.3**	**$20.67**	**Sanofi Pasteur**
16.	**Gardasil 9**	**$182.79**	**$287.53**	**Merck**
17.	**Havrix**	**$39.5**	**$82.86**	**GlaxoSmithKline**
18.	**Heplisav-B**	**$77.9**	**$147.6**	**Dynavax**
19.	**Ipol**	**$24.04**	**$42.63**	**Sanofi Pasteur**
20.	**Jynneos**	**$229.5**	**$270.0**	**Bavarian Nordic**
21.	**Menquadfi**	**$81.72**	**$166.98**	**Sanofi Pasteur**
22.	**Menveo One-Vial**	**$90.3**	**$157.35**	**GlaxoSmithKline**
23.	**M-M-R Ii**	**$62.69**	**$92.49**	**Merck**
24.	**Penbraya**	**$171.9**	**$230.7**	**Pfizer**
25.	**Pneumovax23**	**$82.31**	**$117.08**	**Merck**
26.	**Prehevbrio**	**$33.8**	**$65.50**	**VBI**
27.	**Prevnar 20**	**$181.1**	**$261.5**	**Pfizer**
28.	**Priorix**	**$62.7**	**$92.49**	**GlaxoSmithKline**
29.	**Recombivax Hb**	**$32.67**	**$66.82**	**Merck**
30.	**Shingrix**	**$124.89**	**$197.89**	**GlaxoSmithKline**
31.	**Spikevax**	**$81.6**	**$128.00**	**Moderna**
32.	**Tenivac**	**$22.34**	**$37.10**	**Sanofi Pasteur**
33.	**Trumenba**	**$111.9**	**$190.2**	**Pfizer**
34.	**Twinrix**	**$77.80**	**$126.19**	**GlaxoSmithKline**
35.	**Vaqta**	**$48.79**	**$78.97**	**Merck**
36.	**Varivax**	**$108.04**	**$174.32**	**Merck**
37.	**Vaxneuvance**	**$149.62**	**$222.54**	**Merck**

PRESCRIPTION DRUG USER FEES

PDUFA was initially enacted by Congress in 1992 in an effort to facilitate prompt evaluation of novel medications and biologics. Every five years since then, PDUFA has been reauthorized by Congress. The "Program for Enhanced Communication and Review Transparency for New Molecular Entity (NME) New Drug Applications (NDAs) and Biologics License Applications (BLAs)" (abbreviated "the Program") was introduced by the FDA

under PDUFA V. This included forming a team dedicated to fostering effective communication with sponsors. PDUFA VI (2018–2022) further emphasized improved communication and provided more detailed guidelines on special meeting types, meeting requests, and packages.

PDUFA IV expanded the use of fees to support post-market safety activities and removed the previous three-year restriction on these activities. The FDA's usage of prescription medicine user fee revenue was expanded by PDUFA III to encompass a three-year postapproval and marketing term. This permitted the FDA to double its staff dedicated to monitoring medication side effects and create databases to track drug usage through fee collection.

From FY1998 to FY2002, known as PDUFA II, the FDA gained expanded flexibility in using prescription drug user fees, including funding preclinical and clinical trial stages of drug development. During the initial PDUFA period from FY1993 to FY1997, "Activities necessary for the review of human drug applications and supplements" could be funded using fee money under PDUFA I. This encompassed not only the review process itself but also activities like facility inspections, FDA correspondence addressing application errors, and research oversight crucial for application assessment.

Each five-year reauthorization of PDUFA sets an initial cap on fee revenue for the first year, adjusting annually based on workload changes and inflation. Until PDUFA VI, fees were divided into three categories annually to contribute one-third of total revenue: fees for application, establishment, and product.

In order to generate 80% of the overall fee revenue, PDUFA VI creates a new user charge structure that does away with the product and setup costs and adds a program fee. PDUFA VI eliminates the fee for a supplemental application while maintaining the application fee, which will account for 20% of the overall fee income.

Application fee: Each time an NDA or BLA is submitted, the application sponsor—typically the manufacturer must pay a charge to the FDA for review.

Program fee: The sponsor must cover the yearly program fee for each prescription pharmaceutical product included in an application **[9]**.

PRE-APPROVAL

PDUFA's effectiveness in reducing the time from when a manufacturer submits a BLA to when the FDA makes an approval decision is measured by the approval times for NDAs and BLAs. Under PDUFA I, the FDA implemented two categories of review times: Standard and Priority Review, and committed to achieving specific goals for shortening the drug review process.

Priority and Standard Review

From 1992 to 2023, the FDA reviewed priority applications with the aim of

completing 90% of these reviews in less than six months. Nonetheless, there have been significant alterations to the normal application review timeline. 90% of standard applications were to be reviewed in a year at the beginning, from 1992 to 1997. After that, the deadline was decreased, with the objective being to finish 90% of standard application evaluations in 10 months or less between 1998 and 2023.

Original Efficacy Supplements

From 1992 until 2007, the FDA set a target of finishing 90% of reviews of original efficacy supplements in less than six months. 2008 saw the implementation of priority-based differentiation in the review goals. Within ten months of delivery, 90% of standard efficacy supplements and 90% of priority efficacy supplements were to be reviewed, according to the redesigned objectives.

Resubmissions

The objectives for resubmitting work have also changed. The FDA set a goal to complete 90% of all resubmissions, regardless of classification, within six months between 1992 and 1997. When the FDA set separate objectives for Class 1 and Class 2 resubmissions in 1998, this was altered. Between 1998 and 2023, the goal was to review 90% of the Class 1 resubmissions in two months and 90% of the Class 2 resubmissions in six months.

Manufacturing Supplements

The objectives of the review timeline for the production of supplements have also changed significantly. The FDA set a goal to conduct 90% of reviews in six months or less between 1992 and 1997. The objectives were changed in 1998 to distinguish between supplements with prior approval and supplements that were considered standard. The new targets were to finish 90% of standard supplement reviews in six months and 90% of prior approved supplement reviews in four months.

Resubmission of Efficacy Supplements

The review of resubmitted efficacy supplements from 1992 to 1997 started out without a clear objective. This was altered in 1998 when the FDA announced that 90% of these resubmissions would be reviewed in six months. The targets were adjusted in 2003 and were set at 90% of the Class 1 resubmissions in two months and 90% of the Class 2 resubmissions in six months. These targets were in place until 2023 **[10], [11], [12]**.

The FDA will evaluate proprietary names that are submitted in conjunction with the NDA/BLA procedure and during medication development to mitigate medication errors linked to similar-sounding or similar-looking names, unclear abbreviations, acronyms, dose designations, and packaging designs prone to errors, within agreed-upon timelines.

In case disagreements arise over scientific or procedural problems that cannot be settled at the "signatory authority level," the Agreement permits written appeals to the subsequent two levels based on predetermined standards. 90% of these appeals will receive a response from FDA within 30 days of receipt **[9]**.

THE PROGRAM

A review framework, known as "the Program," will be put into place by the FDA and will be applicable to all original Biologics License Applications (BLAs) filed between October, 2012, and September, 2017, including those that are resubmitted after a Refuse-to-File decision. The objective of this program is to improve communication and transparency between applicants and FDA review teams.

Its objective is to expedite patient access to new medications and biologics that meet rigorous standards of safety, effectiveness, and quality. It aims to improve the efficiency and efficacy of the first review process and decrease the number of review rounds required for approval. An independent contractor specializing in evaluating regulatory review effectiveness and biopharmaceutical development programs will assess the Program **[10]**.

"The Program" will be implemented by the FDA throughout the review process for all initial BLAs, including resubmissions made in response to rejections. The Program has the following parameters:

1. Pre-submission meeting.
2. Original application submission.
3. Day 74 letter.
4. Review performance goals.
5. Mid-cycle communication.
6. Late-cycle communication and advisory committee meetings.
7. Inspection.

The following are the program's parameters:

Pre-submission meeting

The applicant is advised to engage in discussions with the appropriate FDA review division regarding the application's content at a pre-BLA meeting.

a) The meeting must occur at least two months before the planned application submission to ensure constructive FDA input.

b) During the pre-BLA meeting, both the applicant and the FDA will collaborate on defining the comprehensive application content, including initial talks on Risk Evaluation and Mitigation Strategies (REMS). The FDA review team and senior staff will attend, and the meeting's agreement and discussion will be summarized.

c) If agreed upon, the applicant and the FDA may decide to submit specific application components within 30 days after the initial submission, provided it does not hinder the review team's ability to commence their

assessment. Such agreements will also be recorded in the FDA meeting minutes.

Original application submission

Applications must be complete at the time of submission, as agreed upon at the pre-BLA meeting. If no pre-BLA meeting occurs, the submission must still be complete. Applications should include a comprehensive list of all manufacturing facilities and clinical sites. Any agreed components to be submitted post-original application must be received within 30 days.

c) Incomplete applications, or those missing components after 30 days, may face a Refuse-to-File.

Day 74 Letter

The FDA will get in touch with applications that are enrolled in "The program" within 74 calendar days of receiving the initial submission. The recommended review schedule, including the internal mid-cycle discussion meeting, will be outlined in the Day 74 letter for these applications. The letter will also include preliminary thoughts on whether an Advisory Committee (AC) meeting to examine the application could be necessary **[10], [11]**.

Review performance goals

For New Molecular Entities (NMEs) New Drug Applications (NDAs) and original Biologics License Applications (BLAs) submitted under the Program, the PDUFA review timeline starts after the 60 calendar-day period for filing review, which begins upon FDA receiving the original submission.

Mid-Cycle communication

The FDA Regulatory Project Manager (RPM) and pertinent team members will get in touch with the applicant to discuss the application review status within a fortnight of the FDA's internal mid-cycle review meeting. The applicant and the RPM will schedule the time of this correspondence

a) The update will cover important findings, requests for information, key safety considerations, initial considerations regarding risk management, proposed dates for late-cycle meetings, updates on potential Advisory Committee (AC) meetings, and other anticipated review milestone dates.

Late-cycle meetings and advisory committee meetings

a) Supervisors from disciplines addressing major issues, the signature authority, and pertinent members of the review team will be among the FDA representatives present at the late-cycle conference.

b) A minimum of 12 days prior to the AC meeting, if an application is subjected to one, the late-cycle meeting will be arranged. Final questions are sent out two days prior to the meeting, and AC sessions are normally scheduled no later than three months (regular review) or two months (priority review) prior to the goal date.

c) The late-cycle meeting for applications that do not require an AC meeting will

happen no later than three months (regular review) or two months (priority review) ahead to the goal date of PDUFA.

d) The late-cycle meeting agenda may cover major deficiencies identified, issues related to the AC meeting (if applicable), evaluations of REMS or other risk management measures, requests for additional information, and any supplementary data or analyses. The topic of whether further data will be examined in the present cycle and whether it calls for an extension of the PDUFA goal date will also be discussed **[10], [11]**.

Inspection

The FDA intends to finish all GMP, GCP, and GLP inspections in six months for priority applications and ten months for regular applications. Any problems will have two months to be fixed at the conclusion of the review period.

As part of the quality system, the FDA will use a tracking system to document key review milestones for applications. These milestones include:

1. Pre-BLA meeting and consent to the full text of the application.
2. Submission of components within 30 days of the original submission.
3. The 74-day letter's issuance.
4. Mid-cycle correspondence.
5. Initial and follow-up evaluations.
6. DR letters.
7. late-cycle meeting.

An unbiased third-party analysis and review management will benefit from this tracking data. The PDUFA annual performance report will include a summary of performance data.

An independent contractor with expertise in biopharmaceutical development and regulatory review will continuously evaluate the Program.

Clinical holds

A clinical hold is an order issued by the FDA to delay or suspend a clinical trial. This action is taken when there are concerns about participant safety, inadequate design, or insufficient data to support the trial's progression. Clinical holds ensure that potential risks are adequately addressed before the trial can proceed.

The FDA promises to reply to 90% of the entire responses to clinical holds submitted by sponsors within 30 days of receiving them **[10]**.

Responses to meeting requests

Upon receiving a formal meeting request, the FDA notifies the requester about the time, location, and Date of the meeting and the anticipated Center participants.

Previously, the response time for meeting requests was approximately 14 calendar days. Currently, meetings have been classified into four types with specified response times.

1. Type A meetings are essential for advancing stalled drug development

programs or addressing significant safety concerns, including those requested within three months following an FDA's action other than approval.

2. Pre-IND and pre-NDA/BLA sessions are included in Type B meetings.
3. Particular End of Phase 1 and End of Phase 2/pre-Phase 3 conversations, as well as meetings on post-marketing or REMS requirements beyond the framework of marketing application evaluations, are reserved for Type B (EOP) meetings.
4. Type C meetings include all other types of meetings.

For different types of meetings, the response times are as follows:

1. For a Type A meeting, the response time is 14 calendar days.
2. For a Type B meeting, the response time is 21 calendar days.
3. For a Type B (End-of-Phase) meeting, the response time is 14 calendar days.
4. For a Type C meeting, the response time is 21 calendar days.

For any meeting, the sponsor can request a written response instead of a teleconference, in-person meeting or videoconference. FDA evaluates this request and determines if a written response is suitable. If approved, the FDA notifies the requester about the response.**[11]**

Scheduling meetings

Taking into consideration the component's other obligations, the FDA schedules the meeting for the earliest day that works for all pertinent Center staff. The meeting should take place in accordance with the requested format. The meeting should be booked within fourteen calendar days. If it falls outside of the allotted time frame. The scheduling for different meeting types is as follows:

1. After receiving a meeting request, type A meetings are scheduled before 30 calendar days.

2. Type B meetings are set for 60 calendar days after the request is received.

3. After receiving the meeting request, Type B (End-of-Phase) meetings are planned before 70

Calendar days.

4. After the meeting request is received, type C meetings are scheduled before 75 calendar days.

Meeting minutes

Within 30 calendar days following the meeting, the Agency will compile the minutes and make them accessible to the sponsor. The main points of agreement, points of contention, topics for additional discussion, and action items from the meeting will be succinctly outlined in bullet points in these minutes. Extensive notes are

not required. Minutes of meetings are not necessary if the Agency responds in writing to any kind of meeting.

The issuance of meeting minutes has shown significant improvement over the years. In 1999, 70% of the minutes were issued within 30 calendar days. This increased to 80% in 2000, and from subsequent years onward, 90% of the minutes were issued within the same timeframe.**[11]**

POST-MARKETING SURVEILLANCE

Post-marketing surveillance is essential for monitoring vaccine safety. The manufacturer's label and product information are updated as significant adverse events, not identified during pre-licensure, are reported. Pre-licensure studies often have small sample sizes, thus rarer adverse effects or those affecting underrepresented populations (pregnant women, immunosuppressed patients, neonates, etc.) might not show up until after the vaccine is widely used. Post-marketing surveillance, in contrast to controlled pre-licensing trials, captures data from a broader, more diverse population.

The goals of PMS include identifying rare adverse events, monitoring known reactions, identifying risk factors, and spotting problematic vaccine lots. Surveillance is conducted through two main systems:

Active Surveillance

Links vaccination status to clinical outcomes, minimizing under-reporting but is expensive and may miss very rare events due to small sample sizes.

Passive Surveillance

Relies on voluntary reports from health professionals or vaccine recipients. It is simpler and less expensive, with a broad reporting base that can detect rare events, but is prone to under-reporting and reporter bias.

The observed incidents might be coincidental rather than the result of the vaccination, as both methods lack specificity. Carefully assessing the scientific evidence, data consistency, quality, and biological plausibility are necessary when establishing causality.**[13]**

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Vaccine safety surveillance

Health practitioners and vaccine producers are required by the "National Childhood Vaccine Injury Act" (NCVIA) of 1989 to notify the "Department of Health and Human Services" (DHHS) of particular adverse occurrences. The "Vaccine Adverse Event Reporting System" (VAERS) was created by DHHS in 1990, co-administered

by the FDA and CDC, to collect reports of adverse events following vaccination.

VAERS is a passive surveillance system accepting voluntary reports from health professionals, manufacturers, and the public. FDA regulations require manufacturers to report all adverse events occurring within the U.S., and serious, unexpected events from outside the U.S. These reports are evaluated case-by-case, considering the limitations of spontaneously reported data. The main goal of VAERS is to disseminate vaccine safety information to the public and scientific community.**[13]**

CONCLUSION

The regulatory landscape for vaccines in the United States has evolved significantly, driven by advances in scientific research, emerging public health challenges, and the need for robust safety monitoring. The introduction of new approval programs, such as Accelerated Approval and Breakthrough Therapy Designations, has expedited the availability of critical vaccines, particularly during public health emergencies like the COVID-19 pandemic. Changes in the number of vaccines approved reflect both advancements in vaccine technology and increased regulatory scrutiny to ensure safety and efficacy. The enactment of the PDUFA has further streamlined the approval process, providing additional resources for the FDA to expedite review times while maintaining rigorous standards.

Pre-approval clinical trials and post-marketing surveillance systems, including VAERS and the Vaccine Safety Datalink (VSD), have become essential components in monitoring vaccine safety. These systems have been enhanced through legislative updates and technological advancements, allowing for more comprehensive and real-time data collection and analysis. Despite these advancements, challenges remain, including the need for continued vigilance in post-marketing surveillance and addressing public misinformation about vaccine safety. The rising costs of vaccine development and pricing issues also require ongoing attention to ensure vaccines remain accessible and affordable. Overall, the evolving regulatory framework in the U.S. has successfully balanced the dual goals of protecting public health and fostering innovation in vaccine development. Continuous adaptation and improvement of these regulations will be crucial to addressing future public health needs and ensuring the safety and efficacy of vaccines for all populations.

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