U.S. FOOD & DRUG ADMINISTRATION

FDA Drug Topics: Development and U.S. Regulation of Preventive Vaccines

CAPT Julienne Vaillancourt, RPh, MPH

Center for Biologics Evaluation and Research

My comments are an informal communication and represent my own best judgement.
These comments do not bind or obligate FDA.

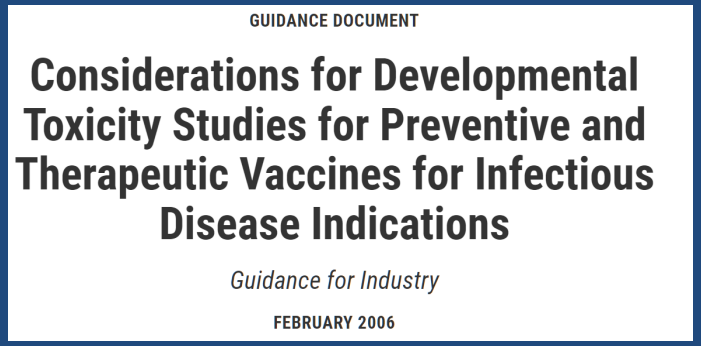
Learning Objectives:

- Identify the legislative Acts leading to and authorizing FDA to regulate preventive vaccines and discuss the historical context of each
- List basic regulatory requirements and types of data needed to support vaccine licensure and marketing approval
- Outline the usual vaccine development process from conception to marketing and explain key regulatory milestones during the process

FDA's Legal Framework

- Constitution
- Legislation
- Regulations
- Guidance

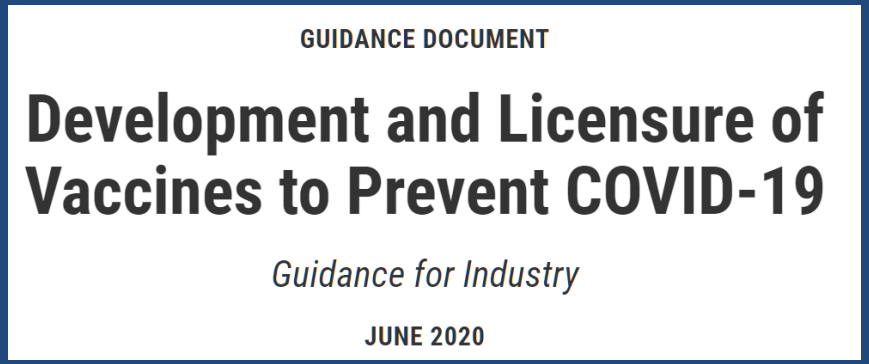
Vaccine-specific Guidance Documents Examples


GUIDANCE DOCUMENT

Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications

Guidance for Industry

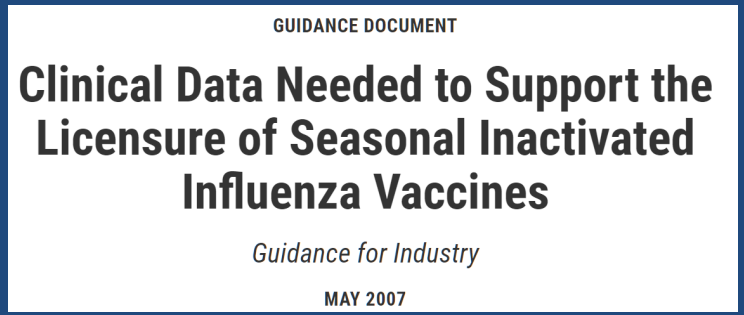
FEBRUARY 2006


GUIDANCE DOCUMENT

Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

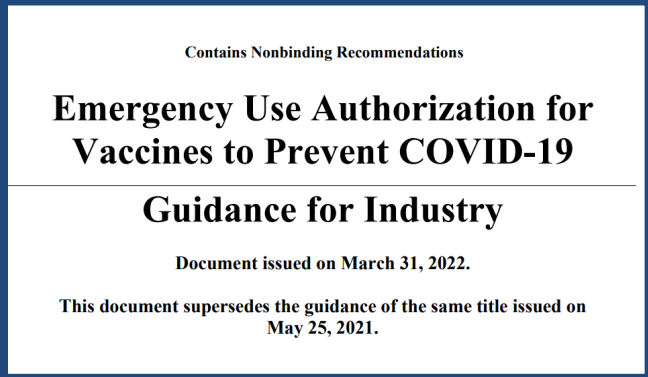
JUNE 2020


GUIDANCE DOCUMENT

Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

Guidance for Industry

MAY 2007


Contains Nonbinding Recommendations

Emergency Use Authorization for Vaccines to Prevent COVID-19

Guidance for Industry

Document issued on March 31, 2022.

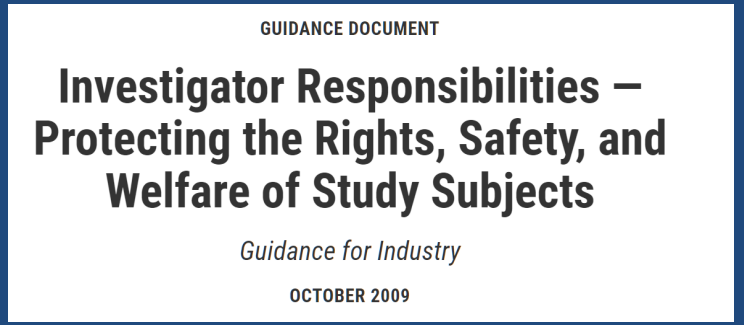
This document supersedes the guidance of the same title issued on May 25, 2021.

General Topics Guidance Examples


GUIDANCE DOCUMENT

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry

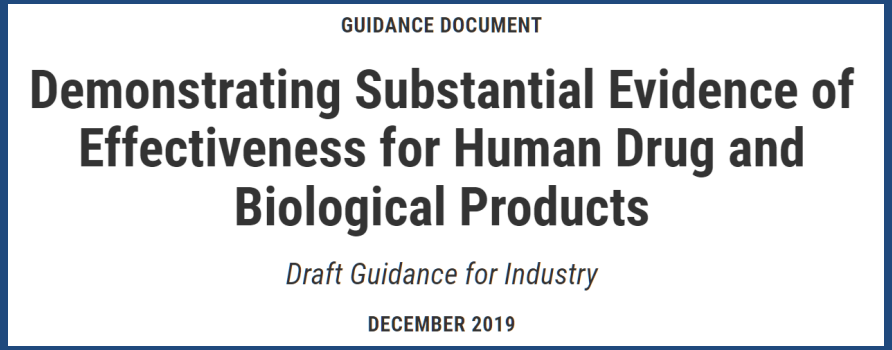
DECEMBER 2017


GUIDANCE DOCUMENT

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

Guidance for Industry

OCTOBER 2009


GUIDANCE DOCUMENT

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Draft Guidance for Industry

DECEMBER 2019

Legal Authority to Regulate Vaccines

Federal Food, Drug and Cosmetic Act
(FD&C Act)

Public Health Service Act
(PHS Act)

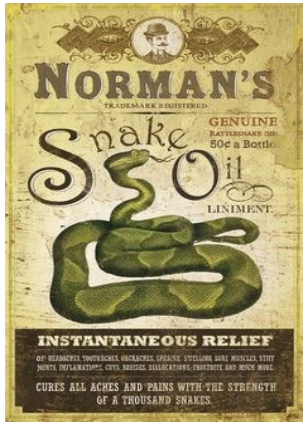
Vaccines & Related Biologics in Worldwide Use in the 1890s

- Live vaccines:
  - smallpox and rabies
- Heat-killed vaccines:
  - cholera, typhoid, and plague
- Anti-toxins:
  - diphtheria and tetanus
- Dramatic impact on rates of disease & deaths
- By 1895 laws regulating biologics were enacted
  - France, Germany, Italy and Russia

1902: Biologics Control Act

1905: Significant Publications

- *The Great American Fraud* (Samuel Hopkins Adams)
- *The Jungle* (Upton Sinclair)



1906: Federal Food and Drugs Act

- A.k.a. the Pure Food and Drugs Act
- Prohibited interstate commerce in misbranded and adulterated foods, drinks, and drugs
- Criminal penalties
- Product seizures

1937: Elixir Sulfanilamide

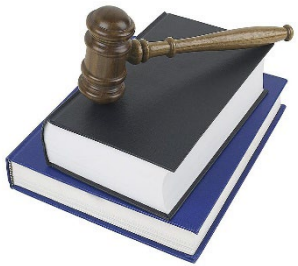
107 people died after a chemist used a poisonous solvent in a new liquid preparation of sulfanilamide for treating streptococcal infections

1938: Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Required basic safety testing of medicines
- Inspections
- Injunctions
- Cosmetics and therapeutic devices

1944: Public Health Service Act (PHS Act)

- Consolidated several laws, including the Biologics Control Act
- Provisions relevant to regulation of biologics
  - Licensure of biologics
  - Control of communicable diseases



Late 1950s/Early 1960s: Thalidomide Tragedy

1962: Kefauver-Harris Drug Amendments to the FD&C Act

- Manufacturers now had to prove that a drug was not only safe, but also effective before marketing
- Regulation of clinical investigations, adverse events, Rx advertising

PHS Act

Section 351(i)(1)

As amended by the BPCI Act and the FCA Act, a **"biological product"** is defined as

- a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)
- applicable to prevention, treatment, or cure of a disease or condition of human beings "

https://www.federalregister.gov/documents/2020/02/21/2020-03505/definition-of-the-term-biological-product

PHS Act

Section 351

- Need **license** to distribute in interstate commerce
- Product must be safe, pure, potent
- Facility – meet appropriate standards
- Consent to inspection
- Suspension/revocation power
- Recall authority

Vaccines are Biological Products and Drug Products

- As biologics, vaccines are licensed under PHS Act
- Vaccines are also subject to certain provisions of the FD&C Act

Vaccine Licensure

- Biologics Licensing Regulations: 21 CFR 601
- Licensed Biologics must be:
  - Safe, Pure and Potent
  - Manufactured consistently according to Current Good Manufacturing Practices (cGMPs) to ensure continued safety and effectiveness

21 CFR 600.3(p)

- The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

21 CFR 600.3(r)

- *Purity* means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. *Purity* includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

21 CFR 600.3(s)

- The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

IND Regulations
21 CFR 312

- FD&C Act prohibits introduction of unapproved drugs into interstate commerce

- Investigational New Drug Application (IND)
  - request for exemption from the statute based in the CFR
  - Primary function is protection of human research subjects
  - Required for clinical investigations of unapproved drugs in the U.S.

Contents of an IND
21 CFR 312.23

- Cover Sheet (Form 1571)
- Introductory statement and general investigational plan
- Investigator's Brochure
- Protocol(s), including investigator information
- Chemistry manufacturing, and controls data
- Pharmacology and toxicology information, including non-clinical data (animal studies)
- Previous human experience with the investigational drug

Primary Objectives of IND Review 21 CFR 312.22(a)

- In all phases of the investigation, to assure the safety and rights of subjects
- In Phase 2 and 3, to help assure that the quality of the scientific evaluation is adequate to permit an evaluation of effectiveness and safety

An IND application may go into effect:

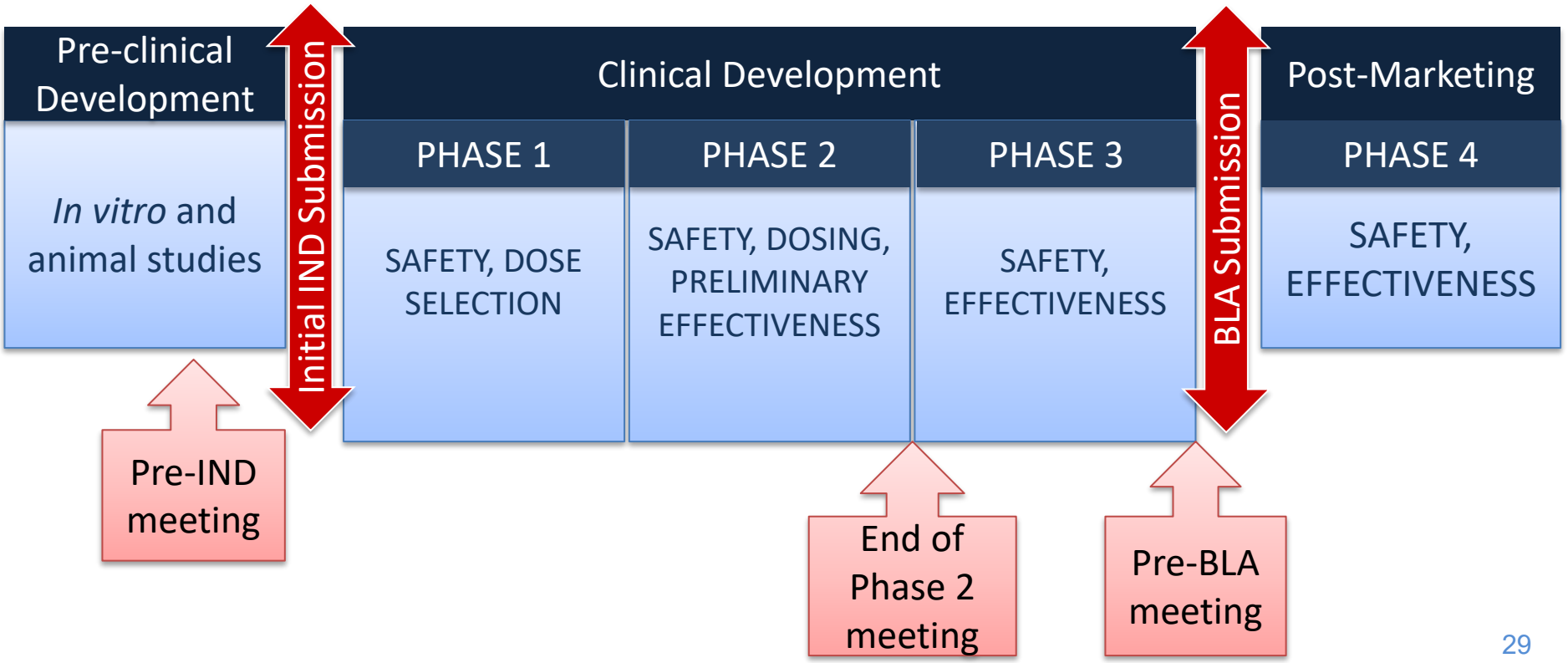
- 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigations described in the application are subject to a **Clinical Hold**; or

- on earlier notification by FDA that the clinical investigations in the IND may begin.

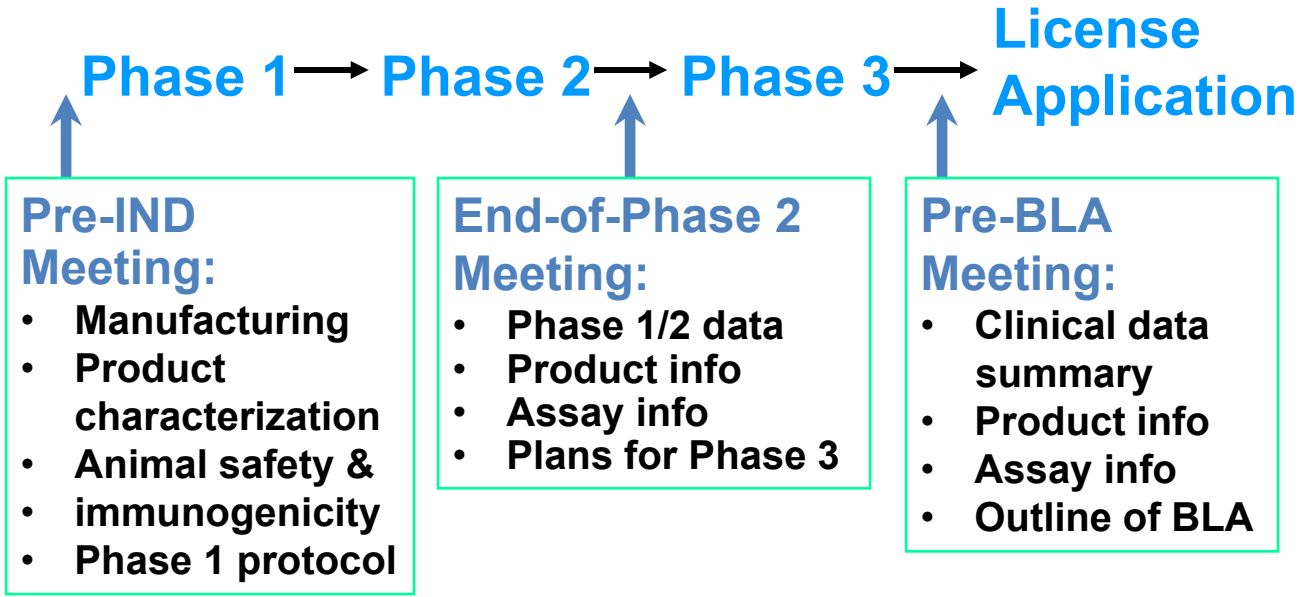
Biologics Regulations
21 CFR 600-680

- Biologics License Application (BLA)
  - A request for permission to introduce, or deliver for introduction, a biological product into interstate commerce (21 CFR 601.2)
  - Requires data from non-clinical and clinical studies demonstrating that the manufactured product meets prescribed requirements of safety, purity, and potency
  - 12-month for standard reviews and 8-month for priority reviews from the date of receipt of the application

Vaccine Clinical Development



Vaccine Development: Meetings with FDA



IND = Investigational New Drug Application
BLA = Biologics License Application

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

- Composed of experts external to FDA, convened upon request by FDA
- Evaluates data and advises FDA on the safety, effectiveness, and use of vaccines and related biological products prior to certain regulatory decisions (e.g., licensure or emergency use authorization of new vaccines)
- Also advises FDA on more general topics critical to advancing regulatory science
- Recommendations are non-binding but usually followed by FDA

Regulatory Definition of Safety

21 CFR 600.3

“relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time”

Approaches to safety assessments

~0-14 days

Solicit (ask about) local and systemic reactions, such as injection site reactions, fever, headache, joint/muscle aches, etc. for at least 7 days after each vaccination

~0-28 days

Unsolicited adverse events collected for at least 21-28 days after each study vaccination

Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations

Safety Database* Considerations

- Characteristics of the vaccine
- Review of early phase safety data
- Any safety signals or theoretical safety issues (may require larger database)
- Target population
- Seriousness of disease targeted for prevention
- For preventive vaccines, assessment of uncommon adverse reactions typically requires a safety database of ≥3,000 subjects followed for *at least* 6 months after completion of vaccination regimen
  - Database size provides adequate power to detect events that occur at a rate of 1/1,000 subjects or higher

**# of subjects vaccinated with the final formulation, dose, and regimen*

Evaluation of Vaccine Effectiveness

- Expectation of “substantial evidence of effectiveness” from adequate and well-controlled clinical studies
- Gold standard is randomized controlled trial (RCT)
  - Mitigate risk of bias by balancing potentially confounding factors across treatment groups
  - Typically, double-blinded to further mitigate risk of bias
- For vaccines, a single large, multi-center (multi-regional) trial may provide sufficient evidence of effectiveness.

FDA Licensure Pathways

- Licensed vaccines must be safe, effective, and manufactured consistently to ensure continued safety and effectiveness
- Three licensure pathways are available, each with different approaches for demonstration of effectiveness with the same requirements for demonstrating safety and manufacturing consistency across these approaches:
  - Traditional Approval
  - Accelerated Approval
  - Animal Rule Approval

Traditional Approval

Endpoint that directly demonstrates clinical benefit

- Field trial: protection against natural disease
  Examples: Rotavirus vaccines and COVID-19 vaccines
- Challenge trial: protection against infection under controlled conditions
  Example: Cholera vaccine to prevent cholera (human challenge trial)
- Trial showing vaccine elicits an immune response, or impacts an intermediate clinical endpoint, that has been **scientifically established to predict protection against the disease of interest**
  Examples: Hepatitis B vaccines: anti-HBsAg IgG concentration ≥10 mIU/mL
  And HPV vaccines: prevention of pre-cancerous lesions (necessary precursor to cancer)

Accelerated Approval

Surrogate endpoint that is reasonably likely to predict clinical benefit

- A drug that treats a serious condition AND
- Provides a meaningful advantage over available therapies AND
- Demonstrates an effect on a surrogate endpoint that is reasonably likely, but not scientifically established, to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)
  - Example: opsonophagocytic antibody response for prevention of pneumococcal pneumonia in elderly

Animal Rule

Product is being developed to ameliorate or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling biological, chemical, radiological, or nuclear toxic substances

Product cannot be approved based on other efficacy standards (i.e., "traditional" or accelerated approval)

- Adequate and well-controlled field trials are not feasible
- Human efficacy studies are not ethical

Evidence from animal studies can provide substantial evidence of effectiveness only when four specified criteria are met

Required post-licensure confirmatory studies:

- Must be conducted when such studies are ethical and feasible
- May be uncontrolled observational field studies

Example of vaccine approved under the "Animal Rule":
Post-exposure prophylaxis use of anthrax vaccine

Emergency Use Authorization (EUA)

Established in Section 564 of the Federal Food, Drug, and Cosmetic Act

Allows for FDA authorization of unapproved medical products (or unapproved uses of approved medical products) to address public health emergencies related to biological, chemical, radiological, or nuclear agents

Requires prior determination of a threat, and declaration of circumstances justifying need for EUA to address that threat, by the Secretary of Homeland Security, Defense, or Health and Human Services

- The agent referred to in the EUA declaration can cause a serious or life-threatening disease or condition
- The medical product may be effective to prevent, diagnose, or treat the serious or life-threatening condition caused by the agent
- The known and potential benefits of the product outweigh the known and potential risks of the product
- No adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition

Summary

- Vaccines are biological products and drug products
- The FD&C Act and the PHS Act authorize FDA to regulate vaccines
- Regulations for vaccine development and licensure are found in the 300s and the 600s of Title 21 of the Code of Federal Regulations (CFR)
- The development and licensure pathway of each preventive vaccine follows a basic course from the pre-clinical phase to the post-licensure phase with unique features throughout that are based on several factors and considerations

References

1) *Science and the Regulation of Biological Products - From a Rich History to a Challenging Future.* US Food and Drug Administration, Center for Biologics Evaluation & Research. September 2002 (https://archive.org/details/scienceregulatio00cent/page/n11/mode/2up)
2) Baylor, Norman and Midthun, Karen. "Regulation and testing of vaccines", Chapter 73 in *Vaccines, Fifth Edition.* Plotkin, SA, Orenstein, WA, and Offit, PA. Philadelphia: Elsevier (2008)
3) Shapiro, Stuart Z., The HIV/AIDS vaccine researchers' orientation to the process of preparing a US FDA application for an investigational new drug (IND): what it is all about and how you start by preparing for your pre-IND meeting. *Vaccine* 20:1261-1280, 2002.
4) Federal Food Drug and Cosmetic Act (FD&C Act), June 25, 1938. Codified at 21 U.S.C. Ch. 9 (http://uscode.house.gov/browse/prelim@title21/chapter9&edition=prelim)
5) Public Health Service Act, July 1, 1944. Codified at 42 U.S.C. Sec. 262. (https://uscode.house.gov/view.xhtml?req=(title:42%20section:262%20edition:prelim)
6) Code of Federal Regulations, Title 21, Food and Drugs, Parts 312 and 601 Washington, DC, Office of the Federal Register, National Archives & Records Administration, 2021. (https://www.ecfr.gov/current/title-21).

Thank you!

Acknowledgements and gratitude to the staff and leadership of the Office of Vaccines Research and Review and the Policy Staff in the Office of the Director in FDA's Center for Biologics Evaluation and Research (CBER)!


FDA
U.S. FOOD & DRUG
ADMINISTRATION