Use of Real-World Evidence in Regulatory Decisions: Emergency Use Authorization, Accelerated Approval

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REDI 2024: Regulatory education for Industry. May 30, 2024, College Park, MD

Informal Communication Disclaimer

This presentation and comments represent the author's own best judgement as a scientist. They do not bind or obligate FDA.

Learning objective

- To improve the understanding of potential uses of real-world evidence (RWE) in FDA's regulatory decisions

Outline

- Regulatory Framework to Make Vaccines Available
- Emergency Use Authorization (EUA) of the first COVID-19 Vaccine
- Accelerated approval of a Chikungunya vaccine
- Summary
- Challenge questions
- Acknowledgements

Regulatory framework for vaccines

Licensure

"Traditional" Approval

Accelerated Approval

"Animal Rule" Approval

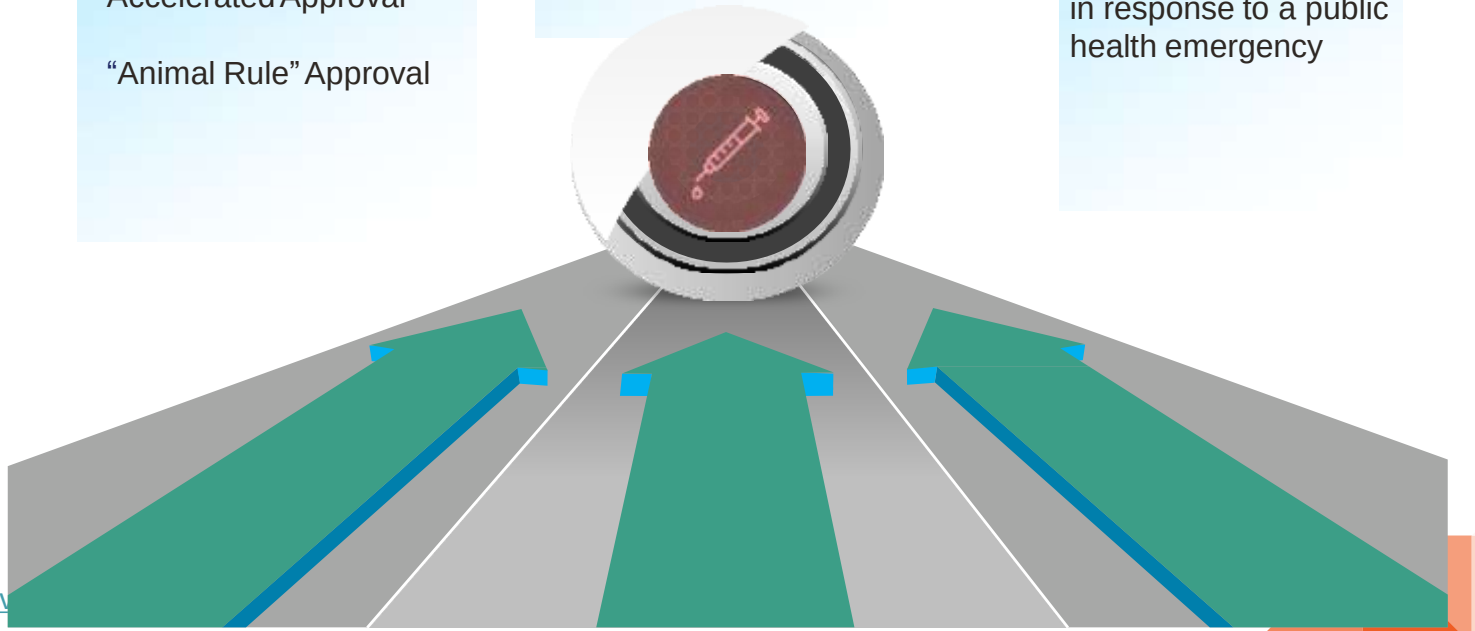
IND

Investigational product with no, or limited, human safety and effectiveness data

Expanded access use options

EUA

Investigational product, or unapproved use of an approved product, in response to a public health emergency



Evidence required for vaccines

Evidentiary effectiveness standard

- Traditional Approval ← *Substantial evidence in humans*
- Animal Rule ← *Substantial evidence in animals*
- Accelerated Approval ← *Reasonably likely to predict*
- Emergency Use Authorization ← *Reasonable to expect*
- Expanded Access Program
- Investigational New Drug application

Approved

Investigational

Emergency use authorization of COVID-19 vaccines during pandemic

- February 4, 2020: HHS Secretary declared a COVID-19 public health emergency
- March 27, 2020: HHS Secretary declared that circumstances justified authorization of emergency use of drugs and biologics, further indicating that the FDA may issue an EUA to allow unapproved medical products/unapproved uses of approved medical products/ to be used in an emergency to diagnose, treat, or prevent COVID-19 when there are no adequate, approved, and available alternatives.
- June 2020: FDA issues guidance for industry: “Development and licensure of vaccines to prevent COVID-19”, which indicates that, for an EUA, FDA must determine that the known and potential benefits outweigh the known and potential risks.
  - Once a manufacturer submits an EUA request for a COVID-19 vaccine to FDA, the agency evaluates the request and determines whether the relevant statutory criteria are met, taking into account the totality of the scientific evidence about the vaccine that is available to FDA.

Emergency use authorization (EUA) of the first COVID-19 vaccine

- December 11, 2020:
  - Citing the totality of the available data, which provided “clear evidence that the vaccine may be effective in preventing COVID-19”, and supported that “the known and potential benefits outweigh the known and potential risks”, FDA issued an EUA for Pfizer-BioNTech COVID-19 mRNA Vaccine, as a two-dose series for persons ages 16 years and older administered 3-weeks apart
  - Safety data included 37,586 randomized, placebo-controlled trial participants followed for a median of two months after second dose.
  - Effectiveness data included analysis of 36,523 participants
  - Available data did not allow a “determination about how long the vaccine will provide protection..” However, durability assessment, while desirable, is NOT an EUA requirement.
  - Participants continued to be monitored for up to 6 months after the last vaccination for serious adverse events.
- May 10, 2021: EUA expanded to include those 12 through 15 years of age

Licensure of the first COVID-19 vaccine under priority review*:

- August 23, 2021**: FDA approved Comirnaty, the first COVID-19 vaccine, for the prevention of COVID-19 disease in individuals 16 years of age and older.
  - Substantial evidence of efficacy and safety demonstrated by:
    - Effectiveness data from approximately 20,000 vaccine and 20,000 placebo recipients ages 16 and older, safety data from approximately 44,000 people
      - Approximately 12,000 vaccine recipients had been followed for at least 6 months
  - Additionally, FDA conducted a rigorous evaluation of post-EUA safety surveillance data pertaining to myocarditis and pericarditis and determined that the data demonstrate increased risks, particularly within the seven days following the second dose. This safety risk was added to the Fact Sheets.
  - The vaccine continued to be available under EUA for individuals 12 through 15 years of age and for administration of a third dose to certain immunocompromised individuals.

*Priority review justification: Drug that treats a serious condition AND would provide significant improvement in safety/effectiveness
**https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine

Emergency use authorization (EUA): Third dose* (1)

- Pfizer submitted data, including RWE, to support a third dose of COMIRNATY
  - Referenced several observational studies suggesting waning of protection during the Delta variant surge among 2-dose vaccinees
  - Included safety/immunogenicity data against the reference (Wuhan-Hu-1) strain from approx. 300 adults
  - Effectiveness was based on immunobridging analyses.

EUA of third dose (2): RWE also considered during VRBPAC

- September 17, 2021: VRBPAC met to discuss booster dose*
  - Presentations also included CDC data on vaccine effectiveness* and data from observational studies in Israel on waning of protection from primary vaccination and effectiveness of third dose vaccination*
  - VRBPAC members voted 16-2 against third dose licensure for ages 16 years and older, citing insufficient data**
  - FDA asked the committee to vote on whether the available data would support an EUA, VRBPAC members voted 18-0 in favor of EUA for 18 years and older with high risk of exposure**
- On September 21, 2021, based on the HHS emergency declaration, considering the totality of data available to support effectiveness of the third dose and the known and potential benefits and known and potential risks, FDA authorized the booster dose under EUA for individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional/occupational exposure**

Evidence required for vaccines

Approved

Investigational

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Accelerated approval: Qualifying criteria*

- Serious condition [21 CFR 312.300(b)(1)]
- Meaningful advantage over available therapies, and
- Demonstrates effect on surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (i.e., an intermediate clinical endpoint)
- Adequate and well controlled postmarketing confirmatory study(es), conducted with due diligence, to verify and describe the anticipated effect on IMM or other clinical benefit (may be ongoing at the time of approval)

* https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-E/section-601.41
** https://www.fda.gov/drugs/accelerated-approval-program/ongoing-infectious-disease-accelerated-approvals-vaccines

Recent accelerated approval example: Valneva's chikungunya vaccine live (IXCHIQ)

Approval: November 9, 2023

Dosage/Administration: For intramuscular use only; Administer IXCHIQ as a single approximately 0.5 ml dose

Indication: Prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at increased risk of exposure to CHIKV

Contraindications: Immunocompromised individuals, history of a severe allergic reaction (e.g., anaphylaxis)

Warnings: Severe or prolonged chikungunya-like adverse reactions , potential for vertical transmission of vaccine virus from pregnant individuals to fetus unknown, syncope

Clinical study (surrogate endpoint)

- IXCHIQ effectiveness against disease caused by CHIKV based on evaluation of seroresponse defined as anti-CHIKV neutralizing antibody level above threshold (μPRNT$_{50}$ titer ≥150).
  - Threshold derived from non-human primate model
- Seroresponse rates determined by μPRNT Assay among 266 vaccine and 96 placebo recipients:
  - 28 days after single dose of IXCHIQ: 98.9% (95% CI 96.7, 99.8)
    - 0% among placebo recipients
  - 180 days after single dose of IXCHIQ: 96.3% (95% CI: 93.1, 98.3)

Post-marketing confirmatory study 1

Test-negative, case-control observational study to assess effectiveness of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in the adolescent and adult population (12 years of age and older) in endemic areas of Brazil.

- Final Protocol Submission: May 31, 2025
- Study Implementation Readiness Verification Submission: June 30, 2025
- Study Initiation: March 1, 2026
- Study/Trial Completion: March 1, 2028
- Final Report Submission: September 30, 2028

Post-marketing confirmatory study 2

Pragmatic randomized controlled trial to assess the effectiveness and safety of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in adults in an endemic country.

- Final Protocol Submission: September 30, 2024
- Study Implementation Readiness Verification Submission: June 30, 2025
- Study Initiation: October 1, 2025
- Study/Trial Completion: July 31, 2029
- Final Report Submission: December 31, 2029

Summary

- FDA provides multiple pathways for vaccine access which may allow use of RWE.
- EUAs provide an expeditious pathway for larger access to investigational products (other options include expanded access programs and investigational new drug applications) to fill an unmet medical need
  - During the pandemic, under EUA, FDA was able to use real-world data to aid in decision-making for COVID-19 vaccines (i.e.third dose authorization)
- Accelerated approval: FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint. A confirmatory study is still required to confirm the anticipated clinical benefit.
  - FDA used accelerated approval to license a Chikungunya and other vaccines. The Sponsor proposed two postmarketing confirmatory studies with real-world evidence designs

Challenge question 1: Which answer is wrong regarding accelerated approval?

1. The condition needs to be serious

2. The vaccine provides a meaningful advantage only over existing vaccines (regardless of other existing treatments)

3. Demonstrates effect on a surrogate endpoint

4. Adequate and well controlled postmarketing confirmatory study(es)

Challenge question 2: Which answer is wrong regarding emergency use authorization (EUA)?

1. For an EUA, FDA must determine that the known and potential benefits outweigh the known and potential risks

2. FDA evaluates the request and determines whether the relevant statutory criteria are met, taking into account the randomized trial data submitted to FDA

3. FDA evaluates the request and determines whether the relevant statutory criteria are met, taking into account the totality of the scientific evidence available to FDA

Acknowledgements

- Kirk Prutzman
- Sudhakar Agnihothram
- Peter Weina
- Maria Allende
- Douglas Pratt
- David C. Kaslow
- Review teams, Office of Vaccines Research and Review, CBER