Different FDA standards for EUA and full BLA approval?

Supplemental information to the question posed by Chairman Wenstrup at the hearing of the Select Subcommittee on the Coronavirus Pandemic, March 21, 2024.

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Chairman Wenstrup, Ranking Member Ruiz, members of the House Select Subcommittee on the Coronavirus Pandemic

Please accept into the official record this supplemental information to the answer given by witness Dr. David Gortler to a question posed by Chairman Wenstrup at the hearing of the Select Subcommittee on the Coronavirus Pandemic, on March 21, 2024. Please note that as Dr. Gortler kindly referred to me in connection with some of the information provided in his answer, I am providing this supplemental information. Dr. Wenstrup's question was [1]

Does the FDA have different standards for EUA and full BLA approval? Could you explain the difference if there is one?

Summary:

Yes, the FDA does have different standards. For this discussion, there are three standards.[2]

1. A higher *"established as safe and effective"* standard applied to a conventional BLA.
2. A lower *"believes may be effective"* standard applied to an EUA.
3. A lower *"reasonably likely to predict"* standard applied to an "accelerated approval" BLA used to approve seasonal influenza and updated COVID-19 vaccines and which relies on surrogate endpoints whose establishment does not require the "substantial evidence" standard.

These standards differ concerning the quality and quantity of scientific data required as well as the degree of certainty with which the FDA makes its determination. A comparison of the conventional BLA and EUA standards is shown in Table 1.

Therefore, it is incorrect and misleading to state that the FDA has established EUA products to be "safe and effective" when they only meet the "believes may be effective" standard. The assertion by the FDA that the EUA standard, as applied to the COVID-19 vaccines, is *"near or equal"* to the conventional BLA standard, is inaccurate. Further, it is incorrect and misleading to imply that data underlying "accelerated approval" BLA products establish them to be "safe and effective" with the same rigor and confidence as those approved under a conventional BLA.

[1] https://www.youtube.com/live/GtENpB5Axqg?si=x4OUbI3N-Nm4F5iN&t=3776
[2] The descriptive terms coined here are based on terms employed in statute or regulation.

Table 1: Summary of differences between conventional, full BLA product approval and EUA

	Conventional BLA	Emergency- EUA
Overall description	"established as safe and effective" [3]	"believes may be effective" (1)
Depth of review by FDA.	Comprehensive	More abbreviated than for BLA. Data summary taken "more at face value" than BLA. [4]
EFFECTIVENESS		
Strength of evidence for effectiveness.	FDA assesses if sponsor has established that the product is safe and effective for its proposed uses.	FDA determines if it is *"reasonable to believe"* that the product "may be effective"
Quality/ quantity of evidence.	*"substantial evidence" "consisting of adequate and well-controlled investigations including clinical investigations."*	*"the totality of scientific evidence available* […] *including data from adequate and well-controlled clinical trials, if available."*
SAFETY	Small, if any, component of potential risks and benefits applicable.	*"known and potential benefits of the product outweigh the known and potential risks of the product"* Includes potential risks and benefits. Overestimated nature of emergency threat will overestimate potential product benefit. A higher level of product-related safety risk will be accepted in the face of a speculatively higher product benefit.
MANUFACTURING	Good Manufacturing Practices (GMPs) required.	GMPs may be waived.
	Lot release testing by FDA may be required	Regulations for lot release do not apply to investigational or EUA products (2) Limited stability may be available.

Note that the same evidentiary standards governing drugs[5] apply to biological products, including vaccines. [6]

Further Detail

Introduction: We have heard the term "safe and effective" applied to the COVID-19 vaccines by FDA and CDC. Recently, on February 15th 2024, FDA's Dr. Peter Marks testified before this committee that the *"American public can be assured of the simple fact that FDA-approved and authorized vaccines are high quality, effective, and safe."* (3) and that for the initial EUA, the standard for effectiveness applied was *"near or equal"* to that required for a conventional approval.

For this discussion, FDA has three regulatory standards applying to the COVID-19 vaccines.

1. A higher *"established as safe and effective"* standard for a conventional BLA.
2. A lower *"believes may be effective"* standard for an EUA.
3. A lower *"reasonably likely to predict"* standard applied to an "accelerated approval" BLA. This is applied to the approval of seasonal influenza and updated COVID-19 vaccines which rely on surrogate endpoints whose establishment does not require the "substantial evidence" standard.

These standards differ concerning the quality and quantity of scientific data required as well as the degree of certainty with which the FDA makes its determination.

Conventional BLA - "Established as safe and effective" This is the high standard for full approval via a conventional Biological License Application (BLA). "Safe and effective" is a term defined by law and regulation. For a drug to be fully approved, it must be established as safe and effective by data of a high quality that constitutes *"substantial evidence" "consisting of adequate and well-controlled investigations including clinical investigations."*

[3] 21 USC section §355 (d) https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355&num=0&edition=prelim
[4] https://www.youtube.com/watch?v=43XAc5iDN9k
[5] Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.
[6] 42 USC §262 (j) https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section262&num=0&edition=prelim

This was NOT the standard applied to the EUA products.

EUA - "Believes may be effective" This lower standard applies to products under Emergency Use Authorization (EUA). To meet this standard, FDA merely must assess that it is *"reasonable to believe"* that the product *"may be effective"* based on *"the totality of scientific evidence available."* This evidentiary standard does not need to include clinical studies.

FDA acknowledges in its guidance documents (1) that the "believes may be effective" standard is lower than the conventional BLA "established as safe and effective" standard and the data supporting it do not need to include "*adequate and well-controlled clinical trials"* that meet the *"substantial evidence"* threshold otherwise needed for full conventional BLA approval.

As an indication of the paucity of the EUA's "believes may be effective" and "totality of scientific evidence" standard, even efficacy data concerning the Pfizer under-5 COVID-19 vaccine that FDA characterized are "preliminary, imprecise, and potentially unstable" were considered by FDA to meet this lower EUA evidentiary standard (p198/353 in (4)). [7]

Regarding safety, rather than the standard of "safe" required for full approval, the EUA standard requires that the *"known and potential benefits of the product outweigh the known and potential risks of the product,"* when considering the type of threat precipitating the emergency declaration. For a conventional approval, the word "*potential*," is omitted requiring[8] plainly that: "[t]*he Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks."*

Including the word "*potential*" lowers the quality of evidence acceptable for a risk-benefit analysis in an EUA. Firstly, because the nature of the threat posed by COVID-19 was poorly understood, assessment of potential benefit relied on speculation and yielded an overestimate of the threat posed by the novel pathogen. Secondly, because an entirely new class of therapeutics was being deployed for the first time with limited understanding of its pharmacology and toxicology, the potential benefits and harms were largely unknown.

The net effect in an EUA is to shift the risk-benefit balance in favor of apparent benefit for the same amount of absolute risk. A higher level of safety risk will be tolerated because a potential benefit has been overestimated.

Therefore, it is incorrect and misleading to imply that the EUA COVID-19 vaccines have been established as "safe and effective." Indeed, package inserts for the SPIKEVAX and COMIRNATY vaccines which are BLA-approved for those over 12 years of age state that *"safety and effectiveness" "have not been established"* in those under 12 years of age,(5,6) despite the availability of versions of SPIKEVAX and COMIRNATY under EUA.

Accelerated approval BLA - *"Reasonably likely to predict"*

There is an exception to the conventional BLA standard of "substantial evidence" within the "accelerated approval regulation"[9] which is applied to the full approval of annually updated seasonal influenza vaccines (7) and appears (8) to have been deployed for the recent XBB variant COVID-19 vaccines. "Accelerated approval" obviates the need for large trials that collect limited safety data and measure indirectly a clinical outcome such as disease reduction using a surrogate endpoint such as antibody levels in the blood. A surrogate endpoint, as FDA explains,(9) is a marker (e.g. a laboratory measurement) "*thought to predict clinical benefit but is not itself a measure of clinical benefit."*

The clinical studies in which blood is collected for antibody analysis must be *"adequate and well-controlled"* and conform to the *"substantial evidence"* standard. However, in an accelerated approval BLA this evidentiary standard is not required to establish the use of the surrogate endpoint in the first instance. Instead, such an endpoint is accepted after FDA assesses that it is *"reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit."* It is only after this sort of approval that the manufacturer may be required to study the product further and to describe its clinical benefit.

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[7] https://youtu.be/Ixm4UmldTGQ?t=14380
[8] https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section355&num=0&edition=prelim
[9] 21 CFR 601 Subpart E
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=601&showFR=1&subpartNode=21:7.0.1.1.2.5
Particularly 21 CFR 601.40 and 601.41
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=601.40
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=601.41

Given that an accelerated approval BLA requires only a *"reasonably likely to predict*" and not a *"substantial evidence"* standard to establish a surrogate endpoint, this lowered standard undermines the robustness of this type of BLA differentiating it from a classical BLA approval in terms of the quantity and quality of data FDA considers to render a decision.

Conclusion: It is incorrect and misleading to state that the FDA has established EUA products to be "safe and effective" when they only meet the "believes may be effective" standard. The assertion by the FDA that the EUA standard, as applied to the COVID-19 vaccines, is *"near or equal"* to the conventional BLA standard, is inaccurate. Further, it is incorrect and misleading to imply that data underlying "accelerated approval" BLA products establish them to be "safe and effective" with the same rigor and confidence as those approved under a conventional BLA.

References

1. FDA. Emergency Use Authorization of Medical Products and Related Authorities. 2017. 2022, at https://www.fda.gov/media/97321/download.)
2. Weir J. Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19: Chemistry, Manufacturing,and Controls (CMC) Considerations. Vaccines and Related Biological Products Advisory Committee (10/22/2020). 2020 Oct 22. at https://www.fda.gov/media/143353/download.)
3. Marks P. Testimony before the Select Subcommittee on the Coronavirus Pandemic Committee on Oversight and Accountability U.S. House of Representatives. 2024 Feb 15. at https://oversight.house.gov/wp-content/uploads/2024/02/FDA-SSCP-Vaccine-Safety-and-Surveillance-FDA-Written-Testimony-FINAL-Clean.pdf.)
4. FDA. Transcript 174th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting. 2022 June 15.
5. FDA. Spikevax Package Insert 2023-2024 Formula. 2023 Sep 11. at https://www.fda.gov/media/155675/download?attachment.)
6. FDA. COMIRNATY Package Insert 2023-2024 Formula. 2023 Sept 11. at https://www.fda.gov/media/151707/download?attachment.)
7. FDA. Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines 2007 May. at https://www.fda.gov/media/73706/download.)
8. Modjarrad K. Monovalent XBB.1.5 BNT162b2 COVID-19 Vaccine. ACIP 2023 Sep 12. at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-12/10-COVID-Modjarrad-508.pdf.)
9. FDA. Accelerated Approval Program. 2023 Nov 27. at https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program.)