Letters

RESEARCH LETTER

Speed, Evidence, and Safety Characteristics of Vaccine Approvals by the US Food and Drug Administration

There is an urgent need to develop a safe and effective vaccine to prevent coronavirus disease 2019 (COVID-19). However, recent surveys suggest that more than half of Americans are hesitant about receiving a potential COVID-19 vaccine, owing to concerns about adverse effects or lack of effectiveness.[1] There is also concern that the US Food and Drug Administration (FDA) might authorize a vaccine prematurely.[2] To understand the usual approval process followed by the FDA, we systematically evaluated all novel vaccines approved by the FDA over the last decade, characterizing the premarket development and regulatory review times, the clinical evidence on which approval was based, and the size and follow-up duration of the prelicensure safety database.

Methods | We identified all original biologics licensing applications (BLAs) for vaccines approved by the FDA between January 2010 and June 2020, excluding supplemental approvals of existing vaccines. Using publicly available FDA documents,[3] we identified 3 regulatory dates for each vaccine: investigational new drug submission (when human testing can begin), BLA submission, and FDA approval. We first identified all trials that provided safety and efficacy evidence for approval, characterizing them by study purpose and number of patients. Next, we identified all pivotal efficacy trials and determined the use of randomization, masking, comparator group, and primary end point using methods described previously.[4] For pivotal efficacy trials using a clinical primary end point, we collected vaccine efficacy. Finally, we estimated the total number of patients in the prelicensure safety database and determined the longest duration of follow-up for serious adverse events among all trials included in the safety database. The study did not require Yale University institutional review board approval or patient informed consent because it was based on publicly available information and involved no patient records.

Results | Between January 2010 and June 2020, the FDA approved 21 vaccines, most commonly for influenza (5 [23.8%]) and meningococcus (5 [23.8%]). Of these, 4 (19.0%) received Accelerated Approval. The median premarket clinical development period (investigational new drug submission to FDA approval) was 8.1 (interquartile range [IQR], 6.1-10.5) years, including a median FDA review period (BLA submission to FDA approval) of 12.0 (10.8-21.0) months (**Table 1**).

Each vaccine approval was supported by a median total of 7 (IQR, 5-13) clinical trials, including 2 (IQR, 1-3) pivotal efficacy trials and 1 (IQR, 1-1) trial considered essential to establishing lot-to-lot consistency. The median number of patients in the prelicensure safety database was 6710 (IQR, 4576-15 997), and the median follow-up for serious adverse events was 6 months (IQR, 6-12). The median aggregated number of patients enrolled among all pivotal efficacy trials supporting a given vaccine approval was 4961 (IQR, 3537-7775). All 21 vaccines were approved based on at least 1 randomized pivotal efficacy trial and 14 (66.7%) based on at least 2 pivotal efficacy trials. Among the 21 vaccines, 17 (81.0%) had at least 1 pivotal efficacy trial that used masking, 20 (95.2%) that used an active or placebo comparator group, and 8 (38.1%) approved based on a clinical primary end point; of these, the median vaccine efficacy was 91.9% (IQR, 79.6%-98.0%) (**Table 2**). Among the 5 vaccines for diseases for which no FDA-approved vaccine existed at time of approval, 4 (80%) used a clinical primary end point.

Discussion | Since 2010, most novel vaccines approved by the FDA required about 8 years of clinical development and were based on evidence from a median of 7 clinical trials, including at least 2 pivotal efficacy trials that were randomized, masked, and used a comparator group. These pivotal efficacy trials enrolled a median of 5000 patients, who were followed

Table 1. Characteristics of 21 Vaccines Approved by the FDA From 2010 to 2020

Characteristic	Median (IQR)
Indication, No. (%)	
Influenza	5 (23.8)
Meningococcus	5 (23.8)
DTaP[a]	2 (9.5)
Other[b]	9 (42.9)
Vaccines granted accelerated approval, No. (%)	4 (19.0)
Clinical development period, y[c]	8.1 (6.1-10.5)
FDA review period, mo[d]	12.0 (10.8-21.0)
No. of clinical trials supporting vaccine approval[e]	7 (5-13)
No. of pivotal efficacy trials	2 (1-3)
No. of trials considered essential to establish lot-to-lot consistency[f]	1 (1-1)
No. of patients in the safety database	6710 (4576-15 997)
Duration of follow-up for serious adverse events, mo	6 (6-12)

Abbreviations: BLA, biologics licensing applications; DTaP, diphtheria, tetanus, and acellular pertussis; FDA, US Food and Drug Administration; IND, investigational new drug; IQR, interquartile range.

[a] Category includes all combination vaccines in which DTaP was a component.

[b] Includes 1 vaccine each for pneumococcus, adenovirus, human papillomavirus, cholera, shingles, hepatitis B, dengue virus, smallpox and monkeypox, and ebolavirus.

[c] Defined as IND (when clinical testing can begin) to FDA approval.

[d] Defined as BLA submission (when vaccine sponsors submit data for FDA approval) to FDA approval.

[e] Total clinical trials include pivotal and supportive studies supporting vaccine approval.

[f] If a pivotal efficacy study was also considered essential to establish lot-to-lot consistency, it was included in both categories.

Table 2. Features of the Aggregated Pivotal Efficacy Trials Supporting 21 Vaccines Approved by the FDA From 2010 to 2020

Feature	Median (IQR)
Total enrolled patients[a]	4961 (3537-7775)
Total patients in intervention group[a]	3552 (2398-4561)
≥1 Pivotal trial, No. (%)	
With randomization	21 (100.0)
With masking	17 (81.0)
With active/placebo comparator	20 (95.2)
With clinical primary end point[b]	8 (38.1)
Vaccine efficacy, %[c]	91.9 (79.6-98.0)

Abbreviations: FDA, US Food and Drug Administration; IQR, interquartile range.

[a] Values represent the total number of patients across all pivotal efficacy trials supporting FDA approval of given vaccine.

[b] Clinical primary end points represent the rate of laboratory-confirmed infection. The remaining 13 vaccine approvals were based on antibody immune response.

[c] Calculated among the 8 vaccines approved on the basis of a clinical primary end point. For vaccines with multiple pivotal efficacy trials using a clinical primary end point, the pooled vaccine efficacy was used. For Gardasil 9 (Merck), vaccine efficacy was only reported for human papillomavirus types 31, 33, 45, 52, and 58 because types 6, 11, 16, and 18 had an existing vaccine (Gardasil) that was used as a comparator in the pivotal efficacy trial.

up for serious adverse events for at least 6 months. Given the urgency of developing a COVID-19 vaccine, trials will need to be larger than those supporting prior vaccine approvals and include sufficient follow-up time for emergence of adverse effects.

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1. Associated Press-NORC Center for Public Affairs. Expectations for a COVID-19 vaccine. Accessed August 1, 2020. https://apnorc.org/projects/expectations-for-a-covid-19-vaccine/

2. Avorn J, Kesselheim A. Regulatory decision-making on COVID-19 vaccines during a public health emergency. *JAMA*. 2020. doi:10.1001/jama.2020.17101

3. US Food and Drug Administration. Biological approvals by year. Accessed August 20, 2020. https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year

4. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA*. 2014;311(4):368-377. doi:10.1001/jama.2013.282034