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Image from clinicaladvisor.com

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Key Inforbits

- Vaccine Approval Process
- Developmental Stages of New Vaccines
- COVID-19 Vaccines

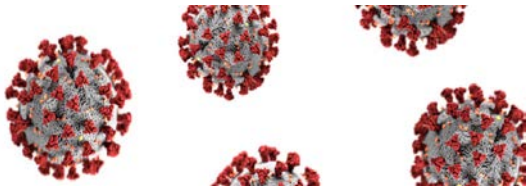


Image from Knoxville Institute of Dermatology

Vaccines – What's the Big Deal? What is a vaccine?

A vaccine is a biological substance that contains the same antigen as the virus. The antigen is either killed or weakened so that it doesn't make the patient sick. The vaccine stimulates the immune system to produce antibodies as if exposed to the virus. Once vaccinated, an individual will develop immunity to that virus without being directly exposed to the virus.[1] Vaccines essentially prevent the spread of contagious diseases. It typically can take 5-10 years to develop a vaccine.[2] During the current pandemic, developing a COVID-19 vaccine has been the priority.

With the goal of developing a COVID vaccine by the end of 2020 or early next year, it does pose the question of whether patients will be at a higher risk with a new vaccine. By rushing timelines and approvals, it may not expose dangers that are not anticipated that are related to the vaccine, such as issues of safety and efficacy. In 2016 when Dengavxia, a vaccine to prevent the dengue infection was produced, it increased hospitalizations for children who had received this vaccine. Later in 2017, a statement was released that Dengvaxia could pose a risk to people who had received this vaccination that had not had a prior dengue infection. With COVID-19 being such a new pandemic and surrounded by unknowns, there is no way to gauge the safety and effectiveness of the vaccine once it is produced and distributed in the general population in an expedited manner.[3]

So How Does it Happen? The Vaccine Approval Process[1]

- In the United States, the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research regulates vaccine usage.
- New vaccines must follow a strict approval process that includes:
    - An Investigational New Drug (IND) Application
    - Pre-licensure vaccine clinical trials
    - A Biologics License Application (BLA)
    - Inspection of the manufacturing facility
    - Presentation of findings to FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC)
    - Usability testing of product labeling

Table 1: Developmental Stages of New Vaccines

Step 1: **Exploratory Stage[4]**  Image from Clinical Trials Arena	• Involves basic laboratory research and often lasts 2-4 years • Scientists identify natural or synthetic antigens that might help prevent or treat disease • If laboratory tests show the vaccine has potential, then it will typically move to animal testing.

Step 2:
Pre-Clinical Phase[2,5]
 
Image from Sannova Analytical Inc.
	• Often lasts 1-2 years
	• Tissue-culture or cell-culture systems and animal testing to assess safety and its ability to provoke an immune response
	• Researchers may do challenge studies with animals, meaning they vaccinate the animals then try to infect them with the target pathogen.
	• Researchers may suggest a safe starting dose and a method of administering the vaccine for the next phase of research.
	• If the vaccine is safe in animals and studies suggest that it will be safe in people, clinical trials with volunteers are next.
	  ○ If safety data already exists for adjuvants used in COVID-19 vaccine candidates, developers are not required to retest that data.
	• Investigational New Drug (IND) Application
	  ○ A request for authorization from the FDA to administer the vaccine to humans.[6]

	■ The IND describes the vaccine, method of manufacture, and quality control tests for release. ○ Reviewed by the FDA for safety to assure that research subjects will not be subjected to unreasonable risk ○ The FDA has 30 days to approve the application. ■ If there is no response from the FDA, the researcher may begin the clinical trial. ○ Once the application is approved the vaccine will enter a Phase 1 clinical trial. ● Manufacturers of potential COVID-19 vaccines may contact the FDA to determine the necessary amount of pre-clinical evidence to progress to the clinical trial process on a case-by-case basis.
Step 3: **Clinical Development[4,5]**  Image from theconversation.com	**Phase 1 Clinical Trials** ● This is the first attempt to assess the safety of the vaccine and determine the type and extent of immune response that the vaccine provokes in a small group of adults, approximately 20-100. ○ If the vaccine is intended for children, it must be tested in adults first and gradually step down the age of the test subjects until the target is reached. ● The trial may be non-blinded (open-label; researchers and subjects know whether a vaccine or placebo is used) ● In a small minority of subjects, researchers may use the challenge model, attempting to infect subjects with the pathogen after the experimental group has been vaccinated. ○ Participants are carefully monitored, and conditions are carefully controlled. ● If no serious side effects are found and with evidence of efficacy, the trial can move on to Phase 2. ● For COVID-19 vaccine candidates, enhanced respiratory disease (ERD) caused by vaccine administration is a recommended safety endpoint. **Phase 2 Clinical Trials** ● Tests are randomized, well controlled, and include a placebo group.

	● Phase 2 tests the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunization, and method of delivery.
	● A larger group of several hundred individuals participate in Phase 2 testing and successful vaccines move on to Phase 3.
	Phase 3 Clinical Trials
	● Tests are randomized and double bind and involve the experimental vaccine being tested against placebo or another vaccine.
	● Phase 3 assess vaccine safety and efficacy and identify common side effects in a large group of people.
	  ○ The FDA has stated that it prefers the primary efficacy endpoint for COVID-19 vaccine candidates to be acute, virologically confirmed COVID-19 infections.
	● For COVID-19 vaccine candidates, the FDA has stated that follow-up for phase 3 trials should continue through 1-2 years post vaccination.
	  ○ Follow up for adverse events is preferred at 7 days, 21-28 days, and 6 months post vaccination.
	  ○ An Emergency Use Authorization (EUA) may be issued by the FDA following interim analysis during phase 3 trials. If issued, it would allow the vaccine to be made available to the public before the trial period is completed.

Step 4:
Regulatory Review and Approval[5,7]
 
Image from Clinical Lab Manager
	● If successful through Phase 3 clinical trials, the vaccine developer submits a Biologics License Application (BLA) to the FDA.
	  ○ An EUA may be given by the FDA to allow the use of COVID-19 vaccines before a BLA is received.
	● The FDA inspects the facility where the vaccine will be made and approves the labeling.
	  ○ Onsite inspections for COVID-19 vaccines may be waived if the facility has a history of compliance with the FDA.
	● The FDA has the right to conduct its own testing of the vaccine.
	● The FDA will continue to monitor the production of the vaccine after licensure to ensure continuing safety.

Step 5 and Step 6: Manufacturing and Quality Control[4]
 	
 
Image from John Hopkins University
	• Once a vaccine is licensed, FDA regularly inspects vaccine manufacturing.
	• Vaccines are manufactured in batches called lots.
	  ○ Manufacturers must test all lots to ensure they are safe, pure, and potent.
	  ○ Vaccine lots cannot be distributed until they are released by the FDA.
	• The Vaccine Adverse Event Reporting System (VAERS) is the system where adverse events related to vaccines are reported and analyzed.
	  ○ VAERS is sponsored by the FDA and CDC.
	  ○ Reports in VAERS can come from patients, healthcare providers, manufacturers and pharmacists. Reporting can be completed at https://vaers.hhs.gov/.
	  ○ Each vaccine has a list of adverse events that must be reported by healthcare providers and manufacturers if they occur with the vaccine.

Where is the COVID-19 vaccine in this process?!?[8]

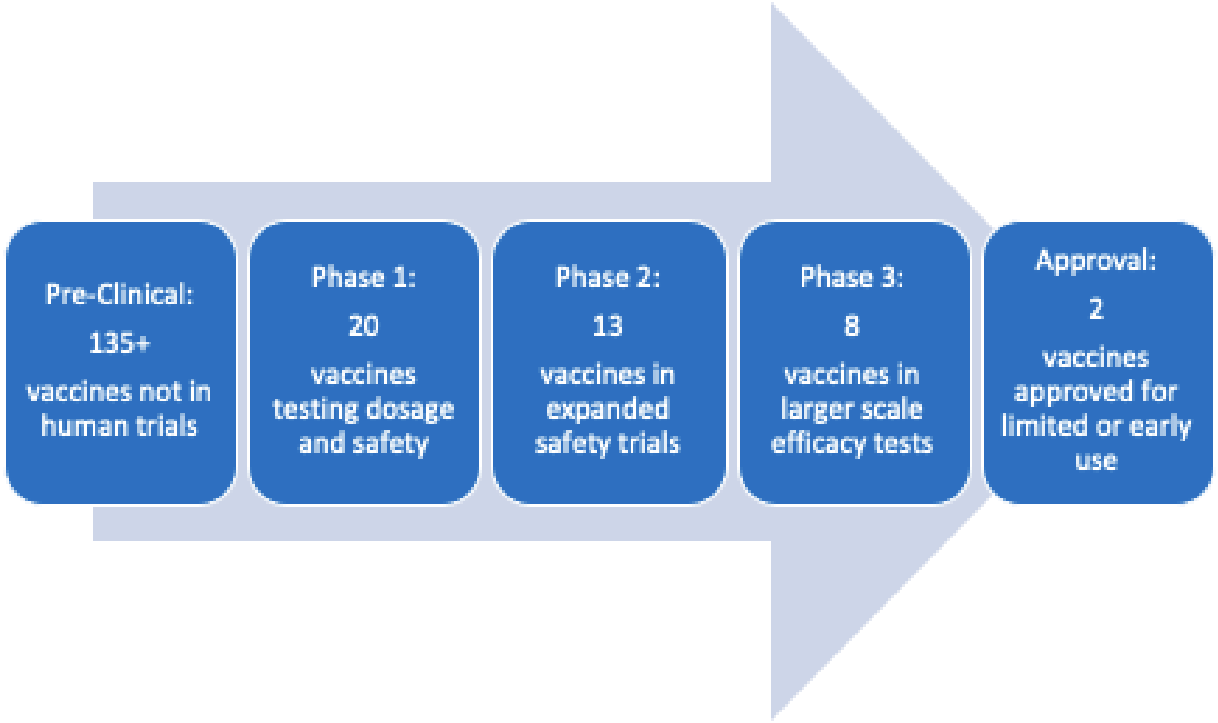


Table 2: Phase 3 and Approved for Use COVID-19 Vaccines[8]

Phase	Company	Description
Phase 3	Moderna	In March, Moderna put the COVID-19 vaccine into human trials and launched a Phase 3 trial on July 27. The final trial will enroll 30,000 healthy people at roughly 89 sites in the United States.
Phase 3	BioNTech, Pfizer, Fosun	In May, the German company, BioNTech, collaborated with Pfizer and Fosun Pharma, a Chinese drug maker, and launched a Phase 1 / 2 trial. Some participants that received the vaccine experienced moderate side effects such as sore arms and sleep disturbances. On July 27, these companies announced the launch of a Phase 2 / 3 trial with 30,000 volunteers in the U.S, Argentina, Brazil, and Germany.
Phase 3	AstraZeneca	AstraZeneca, a British-Swedish company, and the University of Oxford developed a vaccine that is based on a chimpanzee adenovirus, ChAdOx1. The Phase 1 / 2 demonstrated the vaccine did not cause any severe side effects and was safe. This vaccine is now in Phase 2 / 3 trials in India and England and Phase 3 trials in the U.S., Brazil, and South Africa.
Phase 3	Sinovac Biotech	Sinovec, a pharmaceutical company in China, has produced CoronaVac, an inactivated vaccine. Phase 1 / 2 trials concluded in June with 743 people reporting no serious adverse events. Phase 3 trials began in July in Brazil and Indonesia.
Phase 3	Wuhan Institute of Biological Products	The Wuhan Institute of Biological Products developed an inactivated vaccine. The Phase 1 / 2 trial demonstrated that some trial participants experienced fevers and other side effects. In July, they launched Phase 3 trials in the United Arab Emirates. The chairman said in August that the vaccine could possibly be ready for public use by the end of 2020.
Phase 3	Sinopharm	Sinopharm is also testing a second inactivated vaccine that was produced in Beijing Institute of Biological Products; 5,000 trial participants are receiving the Wuhan Institute version and 5,000 trial participants are receiving the Beijing Institute version.
Phase 3	Murdoch Children's Research Institute	The Bacillus Calmette-Guerin vaccine, an older tuberculosis vaccine, also offers protection against COVID-19. It is currently undergoing phase 3 trials in Australia through the Murdoch Children's Research Institute.

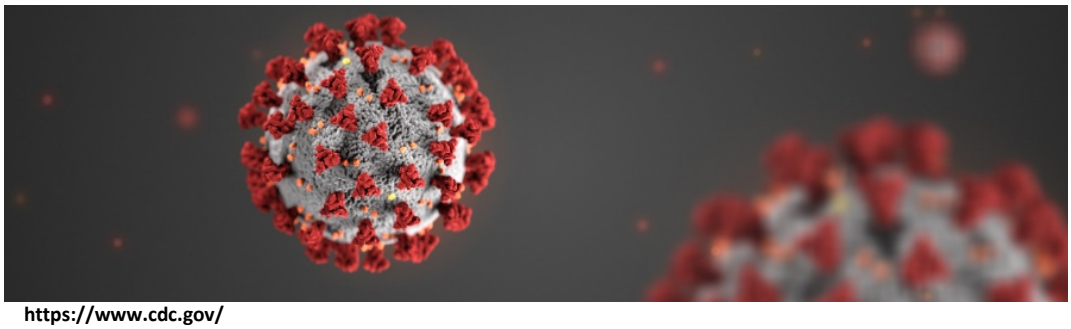
Phase 3/ Approved for Limited Use*	CanSinoBIO	One COVID-19 vaccine is a Phase 3 and approved for limited use. CanSino Biologics produced a vaccine based on an adenovirus called Ad5. The Chinese military approved this vaccine as a "specially needed drug" on June 25 and approved it for a year.
Phase 1/ Approved for Early Use	Gamaleya Research Institute	This COVID-19 vaccine is a Phase 1 and approved for early use. The Gamaleya Research Institute, a part of Russia's Ministry of Health, began a Phase 1 trial in June. The name of the vaccine is Gam-Covid-Vac Lyo and contains two adenoviruses, Ad5 and Ad26.

*Currently one of the 8 vaccines in phase 3 trials and one of the two vaccines approved for limited use.

Conclusion

The process of developing a vaccine and getting it to the market is long and provides many steps to help ensure that the final product is safe and effective. The process begins in an exploratory phase designed to find an antigen that can produce an immune response to the desired disease. It then goes to pre-clinical trials where it is tested in animal models to see if it has potential for use in humans. Then the vaccine begins human clinical trials. It goes through small phase 1 trials to ensure that there are no serious adverse events, phase 2 trials to test for adverse events and efficacy in a larger patient population, and then robust randomized, blinded, and placebo-controlled phase 3 trials that tests for safety and efficacy. After all three phases of clinical trials are completed, if safety and efficacy goals are met, a vaccine can be licensed by the FDA. The FDA will continue to inspect the facilities where the vaccine is prepared and monitor for adverse events caused by the vaccine. All of the steps in the process for developing a vaccine go toward ensuring that a safe and effective product is available for patients.

This development process usually takes several years, however the current COVID-19 pandemic necessitates that it be done more quickly. The FDA will work with vaccine developers on a case-by-case basis to determine what data is required for their vaccine candidate to allow for clinical trials. Once in clinical trials, the FDA may use Early Use Authorizations to allow a vaccine to reach the public sooner. There are currently many companies and institutions that are at various steps in the process of producing a vaccine for COVID-19 with some projecting a viable product by the end of 2020 or the beginning of 2021.



https://www.cdc.gov/

References:

1. Vaccine Testing and Approval Process. US Department of Health and Human Services. Atlanta, GA, Centers for Disease Control and Prevention; 2014 May 1 [cited 2020 Aug 18]. Available from: https://www.cdc.gov/vaccines/basics/test-approve.html
2. Vaccine Development, Testing, and Regulation. History of Vaccines. The College of Physicians of Philadelphia; 2018 Jan 17 [cited 2020 Aug 18]. Available from: https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation
3. Haseltine WA. The risks of rushing a COVID-19 vaccine. Scientific American [Internet]. 2020 Jun 22 [cited 2020 Aug 19]. Available from: https://www.scientificamerican.com/article/the-risks-of-rushing-a-covid-19-vaccine/
4. Ensuring the Safety of Vaccines in the United States. US Department of Health and Human Services. Atlanta, GA, Centers for Disease Control and Prevention; 2018 June 27 [cited 2020 Aug 18]. Available from: https://www.cdc.gov/vaccines/hcp/conversations/ensuring-safe-vaccines.html
5. Development and Licensure of Vaccines to Prevent COVID-19: Guidance for the Industry. U.S Food and Drug Administration. FDA; 2020 Jun [cited 2020 Aug 24]. Available from: https://www.fda.gov/media/139638/download
6.Development & Approval Process. Center for Biologics Evaluation and Research. U.S. Food and Drug Administration. FDA; 2020 Jun 25 [cited 2020 Aug 18]. Available from: https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber
7. Vaccine Product Approval Process. Center for Biologics Evaluation and Research. U.S. Food and Drug Administration. FDA; 2018 Jan 30 [cited 2020 Aug 18]. Available from: https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process
8. Corum J, Grady D, Wee S-lee, Zimmer C. Coronavirus Vaccine Tracker [Internet]. The New York Times; 2020 Aug 19 [cited 2020 Aug 19]. Available from: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html?auth=link-dismiss-google1tap

The Last "Dose"...

"One lucky shot deserves another."

-Shaquille O'Neal [Retired professional basketball player, 1972 to]

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