U.S. FOOD & DRUG ADMINISTRATION

Update on COVID-19 Vaccines

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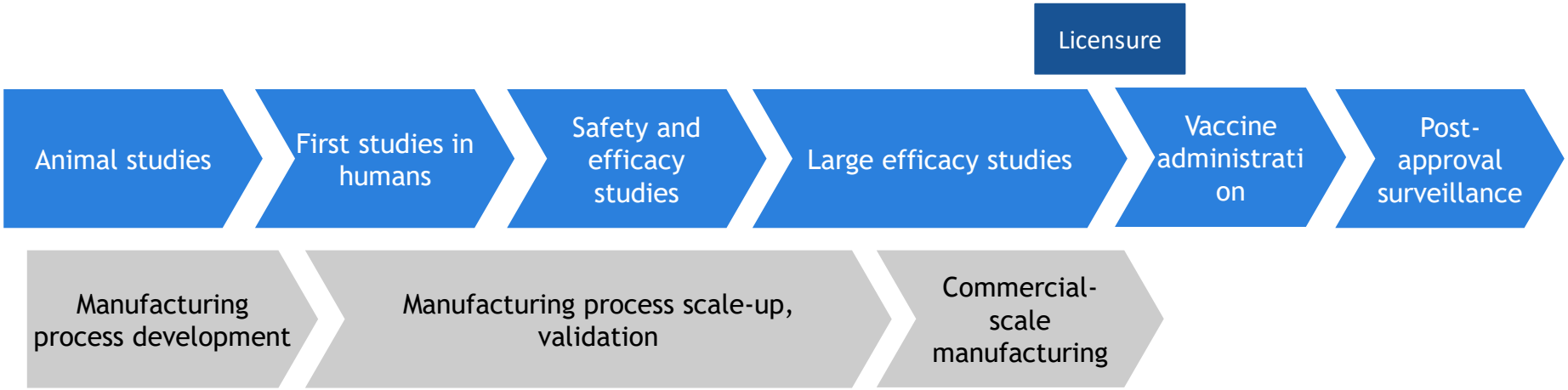
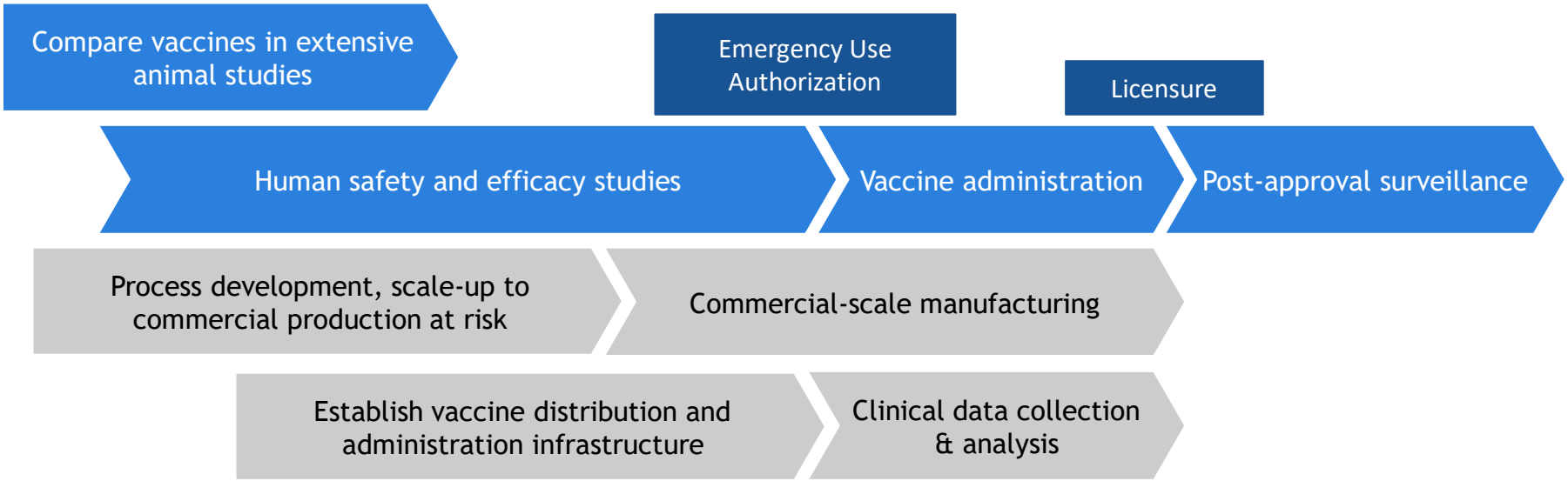
Today's Topics

- Accelerating vaccine development
- Three Emergency Use Authorization vaccines
- COVID-19 variants and vaccines
- Use of COVID-19 vaccines

Traditional Vaccine Development



Accelerated Vaccine Development



Vaccine Development – Accelerating the Process

- Clear guidance on expectations from products
- Facilitate early conversations with regulators
- Integrating different phases into one clinical trial
- Manufacture large quantities of product at risk
- Use optimal path to facilitate product availability

Two Guidance Documents

- Development and Licensure of Vaccines to Prevent COVID-19
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19
- Emergency Use Authorization for Vaccines to Prevent COVID-19
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19

Biologics License Application (BLA)

- Biologics are licensed under both section 351 of the Public Health Service Act and the Federal Food Drug and Cosmetic Act
- Product must be safe, pure, potent, effective
- The standard used is that there is substantial evidence of efficacy from adequate and well-controlled clinical trials

Emergency Use Authorization (EUA)

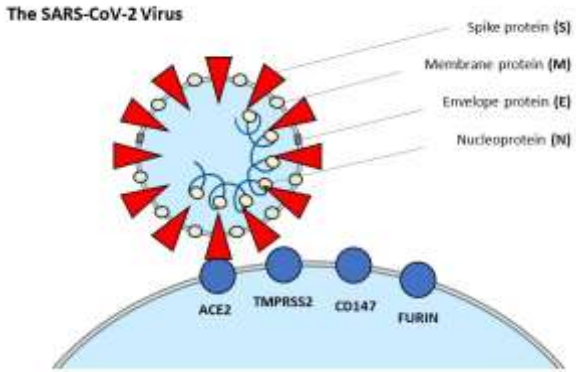
- Put in place after 9/11 to ensure that potentially lifesaving medical products could be available to people in medical need when there is not an approved and available alternative
- The standard used is that the product “may be effective” and its “known and potential benefits outweigh the known and potential risks”

EUA for a COVID-19 Vaccine

- Must demonstrate clear and compelling efficacy in a large well-designed phase 3 clinical trial
- Careful evaluation of quality, safety, efficacy
- Public advisory committee meeting
- Enhanced post-deployment surveillance

Advanced Candidates – March 2021

- mRNA
  - BNT162b2 (Pfizer-BioNTech) – EUA granted Dec 11, 2020
  - mRNA-1273 (Moderna) – EUA granted Dec 18, 2020
- Non-Replicating Viral Vector
  - Ad26.COV2.S (Janssen) – EUA granted Feb 27, 2021
  - ChAdOx1 (Astra Zeneca-Oxford)
- Protein Subunit
  - NVX-CoV2373 (Novavax)
  - MRT5500 (Sanofi-Translate Bio)



Vaccine Trial Demographics

Vaccine	Pfizer-BioNTech (2 doses 21 d apart)	Moderna (2 doses 28 d apart)	Janssen (1 dose)
Total patients	43,552	30,350	39,321
Receiving vaccine	21,768	15,180	19,630
Receiving placebo	21,784	15,170	19,691
Black/African Amer.	9.8%	9.7%	17.2%
Hispanic/Latino	26.2%	20.0%	45.1%
At least age 65	21.4%	25.3%	20.4%

Vaccine Efficacy in Phase 3

Primary efficacy was determined against moderate and severe/critical COVID-19

Vaccine	Pfizer-BioNTech	Moderna	Janssen
Primary efficacy (vaccinated/placebo)	95% (8/162)	94.1% (11/185)	d14 66.9% (116/348) d28 66.1% (66/193)
Young population	age 16-54 95.6% (5/114)	age 18-64 95.6% (7/156)	age 18-64 d14 63.7% (95/260) d28 66.1% (52/152)
Older population	age 55+ 93.7% (3/48)	age 65+ 86.4% (5/114)	age 65+ d14 76.3% (21/88) d28 66.2% (14/41)
Severe COVID-19	1/9	0*/30	d14 14/60; d28 5/34

*One severe case reported 2 months after vaccination

Vaccine Safety in Phase 3

		Second dose					
		Pfizer-BioNTech		Moderna		Janssen	
Reaction (2nd injection)	Placebo*	<55	55+	<65	65+	<60	60+
Injection site pain	14%	78%	66%	90%	83%	57%	33%
Fatigue	22%	59%	50%	68%	58%	44%	30%
Headache	21%	52%	39%	63%	46%	44%	30%
Muscle pain	10%	38%	29%	61%	47%	39%	24%
Chills	4%	35%	23%	48%	31%	N/A	N/A
Joint pain	8%	21%	19%	45%	35%	N/A	N/A
Fever	0.4%	16%	11%	17%	10%	13%	3%

*Average value across all studies, all doses, all ages

Safety Monitoring by CDC and FDA

- Passive monitoring through the Vaccine Adverse Event Reporting System (VAERS) and the v-safe text monitoring system for COVID-19 vaccine safety
- Active monitoring through Vaccine Safety Datalink, the Clinical Immunization Safety Assessment, and large databases such as the CMS Medicare Database and Sentinel/BEST covering ≥100 million lives
  - Combination of claims data and EHR data
  - Monitoring about 15 safety outcomes of interest

Vaccine Severe Allergic Reactions

- Anaphylaxis with the Pfizer-BioNTech and Moderna vaccines
  - Heightened surveillance in place in collaboration with CDC
- These vaccines should not be administered to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine
- Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration

COVID-19 Variants

- UK variant (B.1.1.7)
- South Africa variant (B.1.351)
- Brazil variant (P.1)
- California variant of interest (B.1.427/B.1.429)
- Others…

Adapting COVID-19 Vaccines

- Repeat dose toxicity studies or development and reproductive toxicology studies may not be necessary
- Animal studies are encouraged
  - Prototype and modified COVID-19 vaccine directed against SARS-CoV-2 variant(s)
  - Subsequently challenged with wild-type viruses representing clinically relevant circulating variants, including the variant(s) of interest, are encouraged

Adapting COVID-19 Vaccines

- Effectiveness of a modified COVID-19 vaccine can be evaluated based on the efficacy of the manufacturer's authorized prototype COVID-19
- A determination of effectiveness should be supported by conducting clinical immunogenicity studies
- Sponsors should conduct a booster study in which the modified COVID-19 vaccine is administered to persons who previously received the prototype COVID-19 vaccine

Vaccine Dose and Schedule

- With deployment of vaccines in other countries and challenges in vaccine deployment in this country, questions of alternative dosage and administration schedules have been raised
  - Delay in administration of second doses
  - Single doses of two dose vaccines
  - Half doses of certain vaccines
  - Mix and match of vaccines

- If you don't have time to do it right, what makes you think you'll have the time to do it over – Seth Godin

COVID-19 Vaccine Development

- Vaccine development timelines shortened without compromising vaccine safety and efficacy standards
- Vaccine authorization or approval will follow a process that is as open to the public as possible
- The focus on the evaluation of safety and effectiveness through a transparent process is likely to improve confidence in any approved or authorized vaccine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