FDLI's Fundamentals of Vaccine Regulation Course: Scientific Ingenuity and Rigorous Review

Manufacturing, Scaling, Supply Chain, and Administration Issues

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Establishment and Listing

- Required under 21 CFR Part 207
- Establishment requirements apply to facilities, including foreign facilities, unless they are not exporting the product to the US
- Listing requirements apply to Products
- Listing obligations more complicated when there are multiple parties involved in manufacturing—there may be multiple listings for the same product

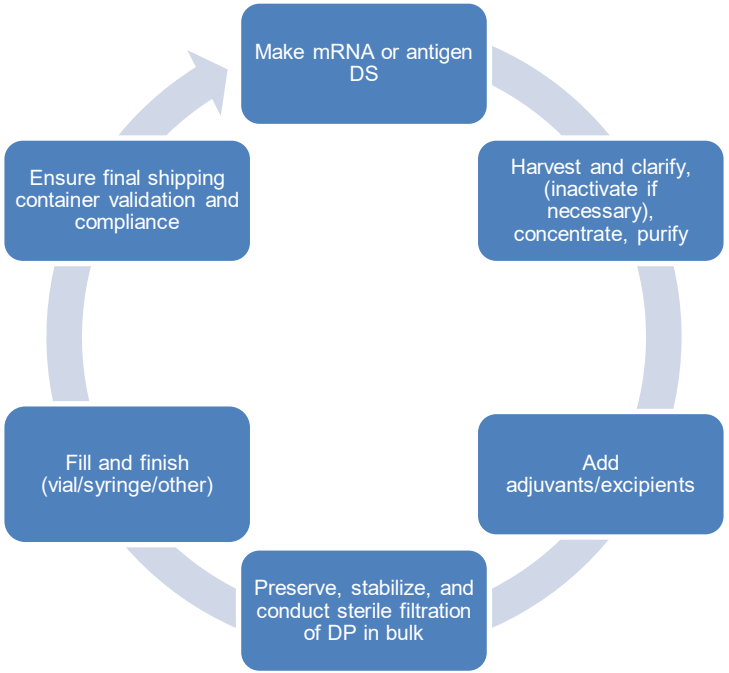
Manufacturing Standards

- Generally vaccines like all biologics must be show to be safe, pure (free from extraneous/pyrogenic materials), and potent (effectiveness)
- 21 CFR 600 provides general standards for biologics
- 21 CFR 210/211 cGMPs also apply to biologics

Manufacturing Standards for Covid Vaccines

- Covid Vaccine CMC review conducted by 2 separate FDA CMC teams
- Office of Vaccines Research and Review (OVRR)
- Office of Compliance and Biological Quality, Division of Manufacturing and Product Quality (OCBQ/DMPQ)

Manufacturing Steps for Covid Vaccines



Manufacturing Standards for Covid Vaccines

- Source materials must be adequately controlled
  - History of cell and virus banks must be documented and qualified
  - All animal derived materials used in cell culture and virus growth must be identified and qualified
  - All excipients must be adequately qualified
  - Container/closure must be validated

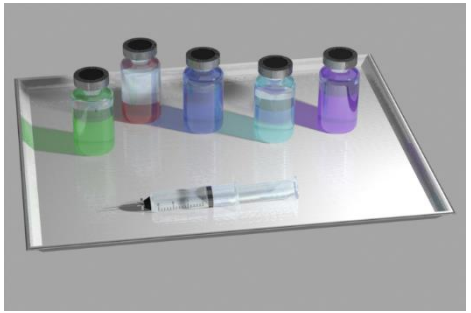
Manufacturing Standards for Covid Vaccines

- Substantial process data must be submitted
  - Critical process parameters and the specifications for them
  - Critical quality attributes
  - In-process intermediate and final product testing programs for drug substance and product, including process validation protocols

Manufacturing Standards for Covid Vaccines

- Substantial control release tests and specifications must be submitted, for purity, identity and potency
- Novel or non standard analytical procedures for release must be validated for precision, accuracy, sensitivity, specificity, and reproducibility
- Validation data for storage conditions is required
- Stability data (continuing obligation to provide under EUA) provided on rolling basis

Manufacturing Standards for Covid Vaccines



- Equipment data and validation
- Facility information
  - Design to avoid contamination and mix-ups
  - Major utility system validation (water, air, HVAC)
  - Facility and equipment cleaning processes

Manufacturing Standards for Covid Vaccines

- Quality Control Unit information
  - QC unit is responsible for review and release of components, DS, containers and closures. Labeling, in-process materials and final DP
  - QC unit approves validation protocols and reports, conducts deviation investigations and develops and implements CAPAs

Corporate Partnerships—US Supply

Pfizer/BioNTech	Moderna	NovaVax
Andover, MA	Lonza Portsmoth, NH	FujiFilmDiosyn, RTP/NC
Kalamazoo, MI	Catalent, IN	Endo/Par, MN
St. Louis, MO	Moderna new facility, Norwood, MA	AGC Biologics, WA
		NovaVax new facility, MD

Scaling Up Considerations

- Complexities involved in scaling up to commercial lots for Covid vaccines
  - New technology platforms and components required additional validation from clinical supply to commercial scale production lots over shortened timeline
  - Qualified personnel must be available
  - Changes between Phase 3 product/process and commercial scale required multiple bridging/comparability studies
  - Large number of contract manufacturers and sites involved in component and finished product manufacture and filling required technology transfer and validation of processes at multiple sites
  - Many contractors working for multiple vaccine manufacturers requiring different process needs and data requirements

More Scaling Up Considerations

- Need for qualification of DS and DP batches for **each** facility manufacturing product
- Need for FDA agreement on supportive data to change processes—how many batches necessary to show comparability?
- Can longer term stability data be collected during vaccine roll out? Will this be available to all manufacturers?
- How much advance notice to FDA before lot release, e.g., BioNTech provides COAs 48 hours before lot distribution--how does that affect your process and downstream supply chain?

Supply Chain Considerations

- Will supplies be available on real time basis, e.g., filters, growth media, excipients, vials, syringes?
- If there is a disruption in supply, will US invoke DPA and how does that affect your contract obligations and commitments?
- How will ex-US contract manufacturers affect your manufacturing time line?
- What to do about environmental disruptions, e.g., fire at Serum Institute HQ in India, flood at Wockhardt fill/finish facility in Northern Wales?
- How will industry collaborations affect supply chain here and abroad?
- What data/inspections will FDA require for upgraded or new facilities to manufacture vaccine components or product?
- Will new Biden EO on Ensuring the Future Is Made in All of America by All of America's Workers and centralized waiver system for buying non US suppliers affect vaccine production?

Inspections

- Biologics/Vaccine subject to same pre-approval inspection protocols as drugs; *see* FDA SOPP 8410
- During Covid, inspections deferred
- Covid vaccine facilities present challenges for FDA in view of number of facilities involved
- BioNTech decision notes FDA reviewed inspection histories for all involved sites
- Moderna decision notes that FDA conducted at least one site inspection

Post Approval Changes

- Generally post approval changes can be accomplished through supplements under 21 CFR §312.71; see also FDA SOPP 8401.4/SOPP 8401.2
- Question whether FDA will use some other process for supplements to EUAs
- Question whether new supplement or BLA will be required for second generation or substantially different vaccine delivery system, especially if presented in a combination product, e.g., nasal spray

Use of Defense Production Act

- The DPA is intended to compel allocation of necessary supplies and services to the government, even where not previously sold to the government
- DPA is exercised through rated orders for goods
- If you receive a rated order, you must provide the government with the supplies or services in that order before you fill preexisting commercial contractual commitments, even if it means contract breach to existing customers
- BUT the DPA implementing regulations provide that a person shall not be held liable for damages or penalties for any act or failure to act resulting directly or indirectly from compliance with any provision of the DPA

Use of Defense Production Act

- Rated orders do not establish price of goods—the buyer must agree to regularly established terms of sale or payment
- Department of Commerce delegates authority to various agencies to issue rated orders and HHS has such authority
  - HHS issued rated orders in 2020 for respirators and N95 masks and other PPE
  - HHS has not yet issued rated order for Covid vaccines or treatments other than hydroxychloroquine

Distribution and Storage of Vaccine

- HHS is currently making vaccine deliveries to states for allocation based on the number of eligible adults in the state and allowing in-state distribution based on states' specific identified priorities and plans
- Weekly allocation of Pfizer here and Moderna here vaccines available by state.

Biden Plan

- Encourage states to loosen priority categories
- Reach out to hard hit communities; educate locally
- Construct and install vaccine centers and initiate mobile vaccine options
- Reimburse states to use National Guard and other resources to administer vaccines Use local pharmacies to administer vaccines
- Release all vaccine when available (but stay with 2 dose schedule)
- Provide budgets to hire more healthcare workers and loosen state laws on who can administer vaccines (e.g., EMTs, dentists) (note recent amendment to HHS Covid Declaration)
- Use DPA when necessary to ensure continuous availability of vaccines and related supplies

Encouraging Vaccine Administration

- Federal Government and national and local non-profits partnering to educate on need for vaccines
- Biden Plan has specific provision for reaching hard to find communities, i.e., those without internet access, immigrants, homeless
- Private sector identifying ways to assist in reaching isolated communities—transportation, iphone access, public libraries, etc.
- Private sector designing tools that apply in more transient communities—e.g., digital wallet with vaccine records
- Employer mandated vaccine programs with accommodation policies likely will be upheld under existing similar programs for flu shots, although further federal guidance is necessary
- All vaccine sites are required to comply with HIPAA requirements addressing privacy issues

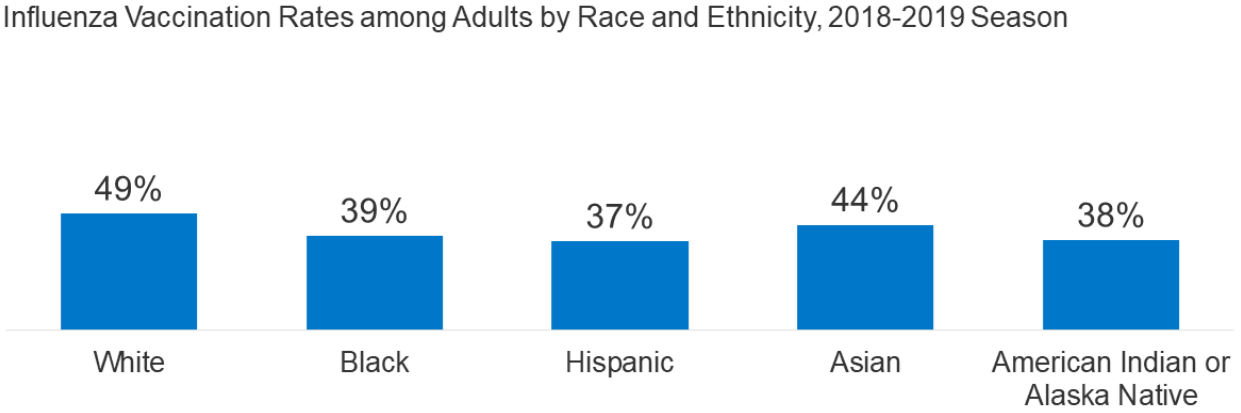
Ensuring Equity in Vaccine Distribution

- Current federal allocation based on number of adults in each state
- National Academies of Medicine recommended prioritizing vaccine allocation to areas identified as vulnerable through the CDC's Social Vulnerability Index (SVI)
- Kaiser Family Foundation has identified a number of issues associated with vaccine acceptance by people of color

Ensuring Equity in Vaccine Distribution

Figure 1

Influenza Vaccination Rates among Adults by Race and Ethnicity, 2018-2019 Season



NOTE: Adults are age 18 and older. Persons of Hispanic origin may be of any race but are categorized as Hispanic; other groups are non-Hispanic.
SOURCE: Centers for Disease Control and Prevention, Flu Vaccination Coverage, United States 2018-2019 Season, https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm

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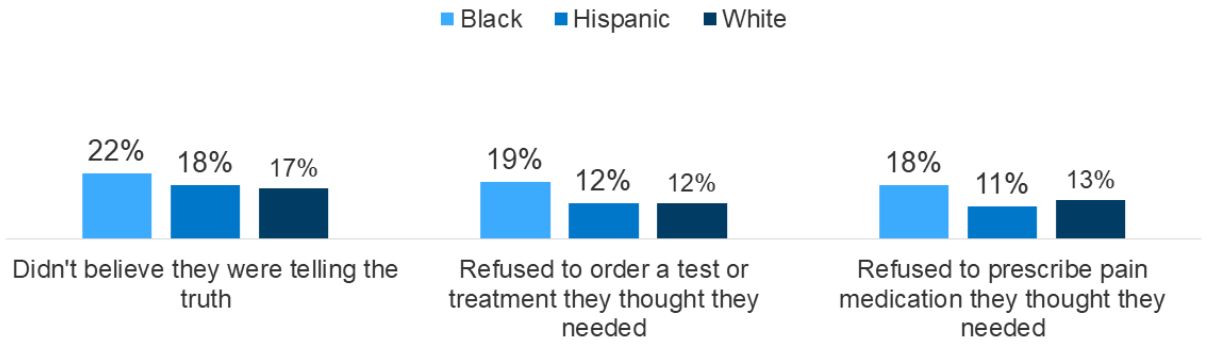
Ensuring Equity in Vaccine Distribution

Figure 3

Share of Adults Reporting Certain Negative Health Care Experiences by Race/Ethnicity

Share of the Adults who Reported that a Doctor/Health Care Provider did the Following in the Last Three Years:



SOURCE: KFF/The Undefeated Survey on Race and Health (conducted Aug. 20-Sept. 14, 2020). See topline for full question wording.

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Ensuring Equity in Vaccine Distribution

- State allocation plans
  - 25 of 47 (53%) states have one mention of racial equity in allocation plans
  - 12 of 47, or 26% state plans mention using providers to reach diverse populations
  - 23 of 47, or 49% of state plans mention specific communications plans to reach diverse populations

- From Kaiser Family Foundation, **Addressing Racial Equity in Vaccine Distribution available at https://www.kff.org/racial-equity-and-health-policy/issue-brief/addressing-racial-equity-vaccine-distribution.**

Ensuring Equity in Vaccine Distribution

- KFF recommends providing vaccine at easy to access drives up or walk up sites, variety of providers (Charlotte speedway, sports stadiums, local community centers, food banks, etc.)
- Various hours to accommodate shift work or multiple job earners
- No cost access for uninsured
- Trusted messengers delivering culturally and linguistically appropriate vaccine education and information

QUESTIONS??

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