

SARS Vaccine Development: An FDA Perspective

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SARS Vaccine Development

“From the Bench to the Clinic”

- **Demonstrate that the product is safe and effective, and can be manufactured in a consistent manner.**
- **FDA is committed to facilitating the efficient, rapid development of a safe, and effective SARS vaccine.**

CBER Regulatory Policy

- **Based on sound scientific principles**
 - **Pre-clinical studies, product development, and clinical protocol design**
- **Case-by-case approach based on rational science and common sense**
- **Risk vs. benefit assessment**
 - **Identify and evaluate safety concerns (product, clinical, target population)**
- **Quality control of production process**
 - **Ensure a safe and consistent product**

Types of Vaccines

- Live attenuated virus
- Inactivated virus
- Subunit, recombinant protein
- Nucleic acid-based (e.g., DNA)

Both general safety concerns and vaccine type-specific issues must be considered.

Considerations for Vaccine Type

Live attenuated vaccine

- Level of attenuation
(adequate? method of determination?)
- Potential for reversion (markers?)
- Potential for transmission
(consequences?)

Considerations for Vaccine Type (con't)

Inactivated virus vaccine

- Effectiveness and kinetics of virus inactivation
- Preservation of critical, protective antigens/epitopes
- Concern with creation of potentially deleterious neo-antigens

Considerations for Vaccine Type (con't)

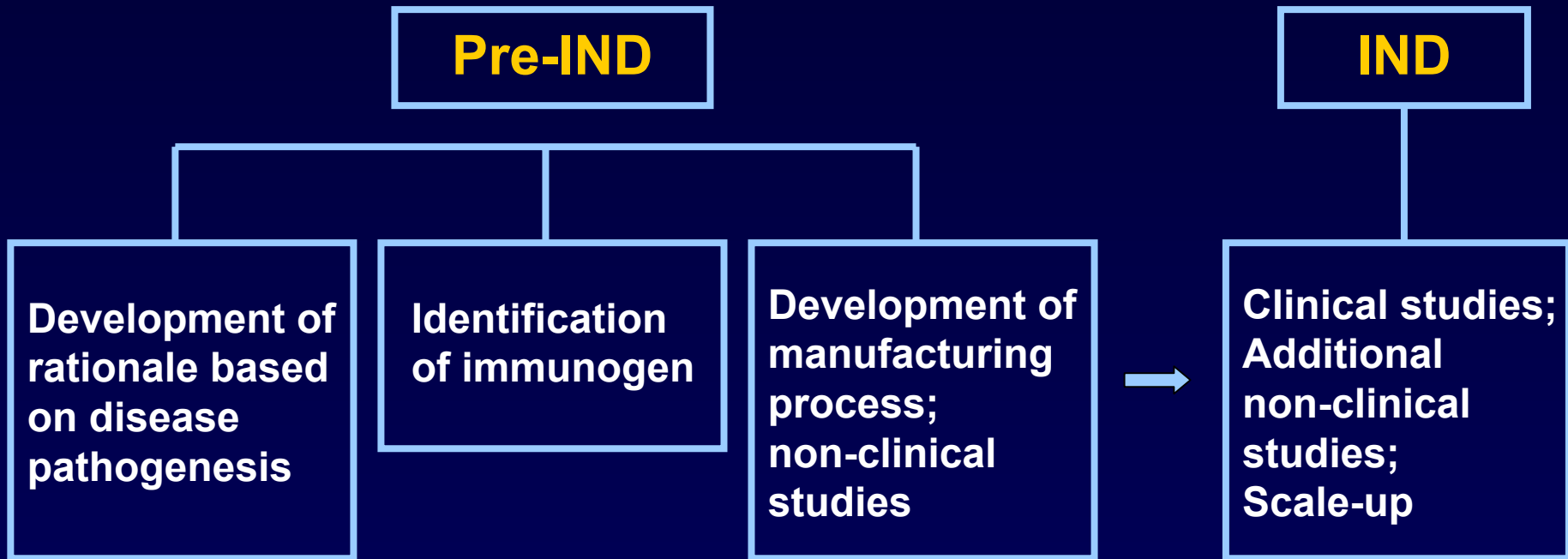
Subunit, recombinant vaccine

- Inclusion of critical protective antigens in a conformation that induces protective immunity

Nucleic acid-based vaccine

- Distribution
- Concern with integration (possible carcinogenicity or other deleterious effects)

Vaccine Development

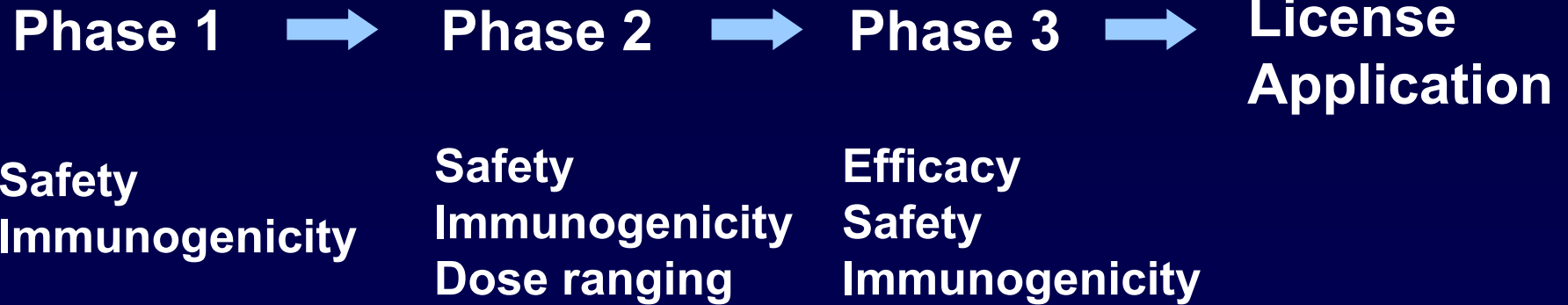


IND = Investigational New Drug application

Vaccine Development: Non-clinical Studies

- **Safety and toxicity**
 - **Study design predicated on intended clinical use**
 - **Conducted under GLP conditions**
- **Level of attenuation, shedding**
- **Reversion to wild-type phenotype**
- **Challenge/protection (relevant animal model)**
 - **Provides insight for selecting human dose, schedule of doses, route of administration, effect of adjuvant**
 - **Immunogenicity, type of immune response**
 - **Identify potential specific adverse events (e.g., antibody-dependent enhancement of disease upon challenge of vaccinated animals with wild-type virus)**

Stages of Vaccine Development



Clinical Development: Considerations

- **Conduct a clinical efficacy trial, if feasible; will provide the most comprehensive information on vaccine efficacy, and potential for immunopathogenesis caused by vaccination.**
- **Validated assays are needed to measure immune responses, and also to diagnose disease as part of a case definition.**
- **If an efficacy trial is not feasible, efficacy data from animal studies may be considered if relevant, well characterized animal models are available.**
- **Use of “animal rule” in this case would require concurrence from FDA advisory committee, in advance.**

Animal Efficacy Rule

New Drug and Biological Drug Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies are not Ethical or Feasible

- **Applicable only when product approval based on standard criteria cannot be applied**
- **Intended for treatment or prevention of life-threatening or serious conditions**
- **Still need human clinical trials to evaluate safety and PK/immunogenicity data**
- **Limitation: Safety evaluation of the product is not addressed by this rule (need to accumulate additional human safety data post-licensure)**

Product Development: Considerations

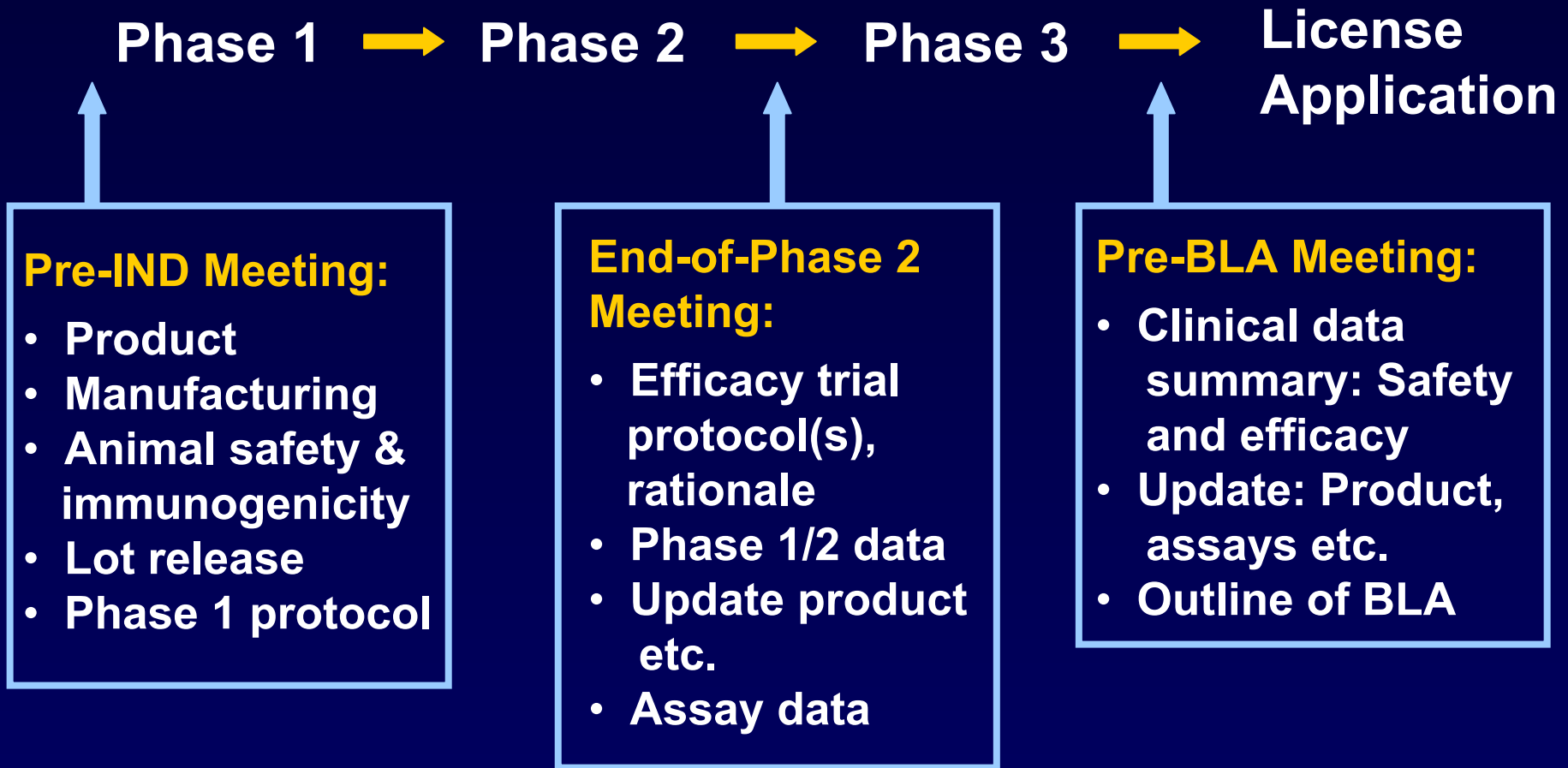
- **Source and quality of starting materials (especially animal-derived or human-derived materials)**
- **Characterization of cell substrate: identity, origin and passage history, adventitious agents (viruses, bacteria, fungus, mycoplasma, TSE agents), endogenous retroviruses, tumorigenicity (if appropriate)**
- **Characterization of viral seeds (Master, Working): identity, production history, adventitious agents**
- **Validation for inactivation or removal of adventitious viruses**
- **In-process testing (specifications)**
- **Release testing of bulk and final products (specifications)**
- **Stability studies (establish vaccine shelf life)**

Vaccine Development: Suggestions

- Know the history of the product and the process (e.g., origin of all raw materials used for production and all steps taken to manufacture the vaccine).
 - “Manufacture” of the vaccine implies all manipulations conducted from the original isolation of the virus, creation of virus seeds, through production of the final product.
- Document materials and process thoroughly.
- Retain samples throughout the process.
- Consult CBER guidance documents.
- Utilize the opportunity to interact with CBER
- Incorporate CBER’s recommendations into product/clinical development plans.

Meetings with FDA

(21 CFR 312.47)



SARS Vaccine Development

- Investigators must consider the general guidelines provided for evaluating the safety and efficacy of a vaccine.
- FDA can facilitate the process by providing guidance on manufacturing and other product-related concerns, animal studies, and clinical trial design

Goal: Accumulate adequate safety, immunogenicity and efficacy data to support licensure of the vaccine.

US Code of Federal Regulations

- **21 CFR 50 – Protection of Human Subjects**
- **21 CFR 56 – Institutional Review Boards**
- **21 CFR 58 – Good Laboratory Practices**
- **21 CFR 210, 211 – Good Manufacturing Practices**
- **21 CFR 312 – Investigational New Drug Applications (INDs)**
- **21 CFR 314.126 – Adequate and Well-Controlled Studies**
- **21 CFR 610 – General Biological Products Standards**

Guidance Documents

- **CBER Guidances/Guidelines/Points-to-Consider Documents**

www.fda.gov/cber/guidelines.htm

- **International Conference on Harmonization (ICH) Guidances**

www.fda.gov/cber/ich/ichguid.htm

- **Code of Federal Regulations (CFR)**

www.gpoaccess.gov/cfr/index.html

- **Federal Register (FR) Notices**

www.accessdata.fda.gov/scripts/oc/ohrms/index.cfm