Regulatory Considerations for Plant-Based Biologics Manufactured in Contained Facilities

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Objectives

Relevant Regulations:

Assuring the Safety and Effectiveness of Plant-based Biologics

Manufacturing Considerations:

Safety, Purity and Potency

Product Development

Summary

Regulations/Guidance Relevant to Plant-Based Biologics

- Consider the potential environmental impact of all aspects of the manufacturing process:

  Draft Guidance for Industry on Bioengineered Plants for Use in Humans and Animals, September 2002

- Refer to the regulations regarding Biologics (in 21 CFR):

  21 CFR Parts 312 - IND Regulations

  21 CFR Parts 210, 211 - **Current** Good Manufacturing Practices

  21 CFR Parts 600, 601, & 610 - Biological Products: General, Licensing and Standards

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Regulatory Definitions

Safety: **“**Relative freedom from harmful effect… when prudently administered, taking into account the character of the product in relation to the condition of the recipient at the time**.”** *(21 CFR 600.3(p))*

Purity: **“**Relative freedom from extraneous matter in the finished product**,…”** *(21 CFR 600.3(r))*

Potency: **“**Specific ability of the product … to *effect* a given result**.”** *(21 CFR 600.3(s))*

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CMC Considerations for Plant-Based Biologics

- Consistency of manufacturing
- Purity (adventitious agent and residual host cell contaminant testing)

- Post-translational modification
  - Different glycosylation pattern than mammalian system
  - Effect on immunogenicity?

- Formulation and potency evaluation
  - Need for specific potency reagents/methods to standardize and assess stability

Consistency of Manufacture: Considerations

- Banking of the plant lines for genetic stability and product consistency
- Storage and germination of Master Seed Stock and Working Seed Stock need to be controlled
  - Germination rate as stability indicator
  - Reduce possibility of cross pollination
- Health status at harvest

Adventitious Agent Testing

- Minimize the introduction of contaminating adventitious agents
  - Ensure purity of biological raw materials
- Evaluate where in the manufacturing process there is potential for introduction of adventitious agents
- Ensure a controlled manufacturing process and remove adventitious agents, if necessary

Evaluation of Vaccine for Adventitious Agents

Homogenization

Antigen Purification

Virus clearance studies, if feasible

Adventitous agent testing on bulk

Bulk

Phase 1 clinical trial material

Viral Clearance Studies

Viral clearance strategy for the plant-based products is the same as that for products manufactured in other cell substrates.

- Viral clearance
  - Removal of contaminating viruses
  - Perform spiking studies to estimate the clearance afforded by each step
  - Use different (orthogonal) methods to remove viruses; multiple uses of similar steps (*e.g.*, filtering with the same type of filter twice) does not lead to increased viral clearance

- An effective virus removal step should give reproducible reduction of virus load shown by at least two independent studies.

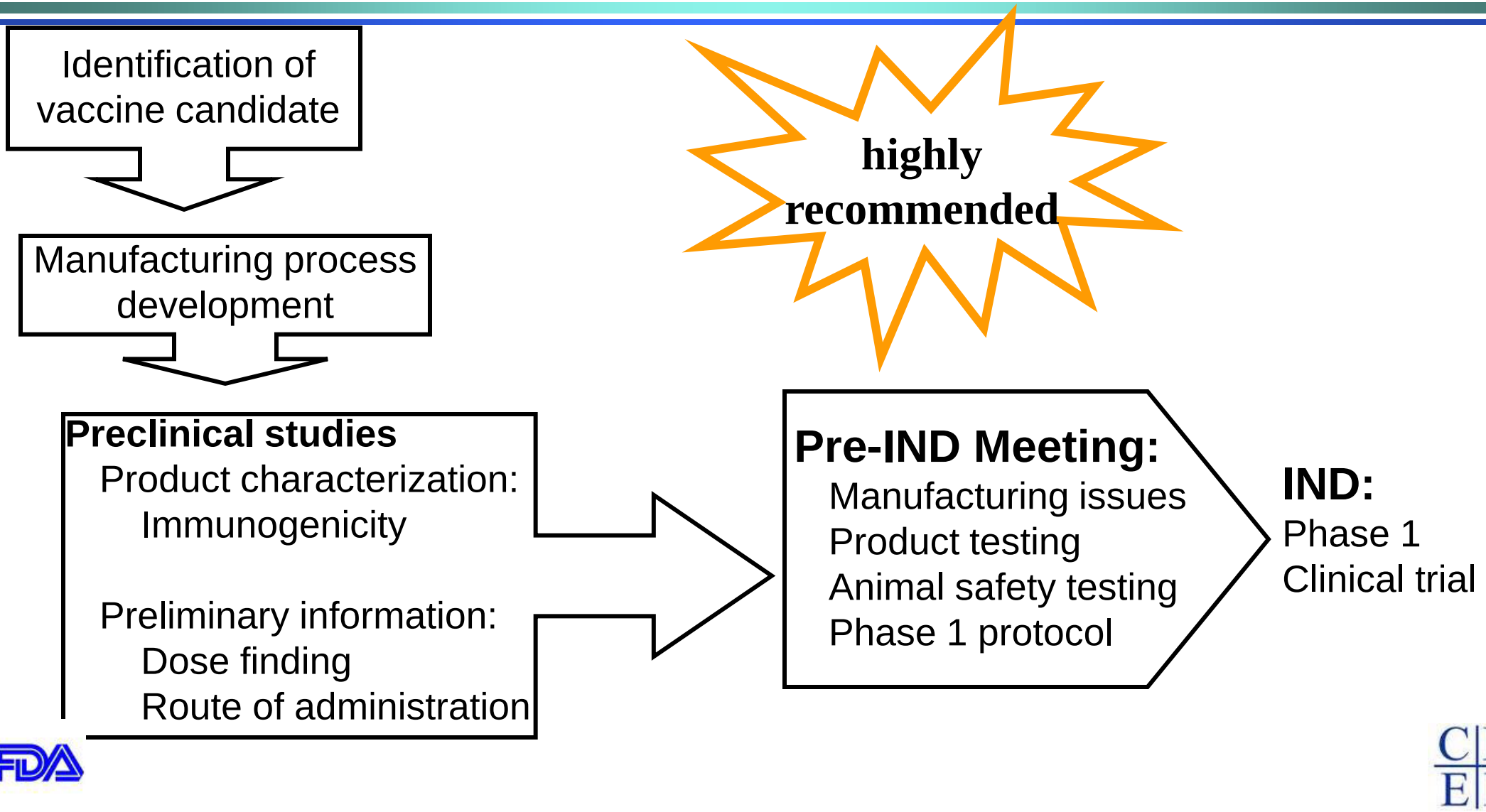
- For VLP products, viral clearance may be difficult

Adventitious Agent Testing

When viral clearance studies are not feasible, adventitious agent testing of the bulk needs to be undertaken in same way as performed for products manufactured in other cell substrates.

- Non-Specific Methods – known/unknown agents
  - *in vivo* (animals)
  - *in vitro* (cell culture)
  - physical/biochemical/molecular
- Species-specific – known agents
  - Assays for known viruses
- Cultivatable and non-cultivatable mycoplasmas (and spiroplasmas, if appropriate)

Product Development



Summary

- The regulatory pathway for the development of plant-based vaccines manufactured in contained facilities is the same as for other preventive vaccines.
- Considerations needed for safety, purity and potency of the plant-based biologics are similar to those manufactured in other cell substrates.

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm

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