Clinical Issues to Consider in the Development of New Vaccines

Center for Biologics Evaluation and Research

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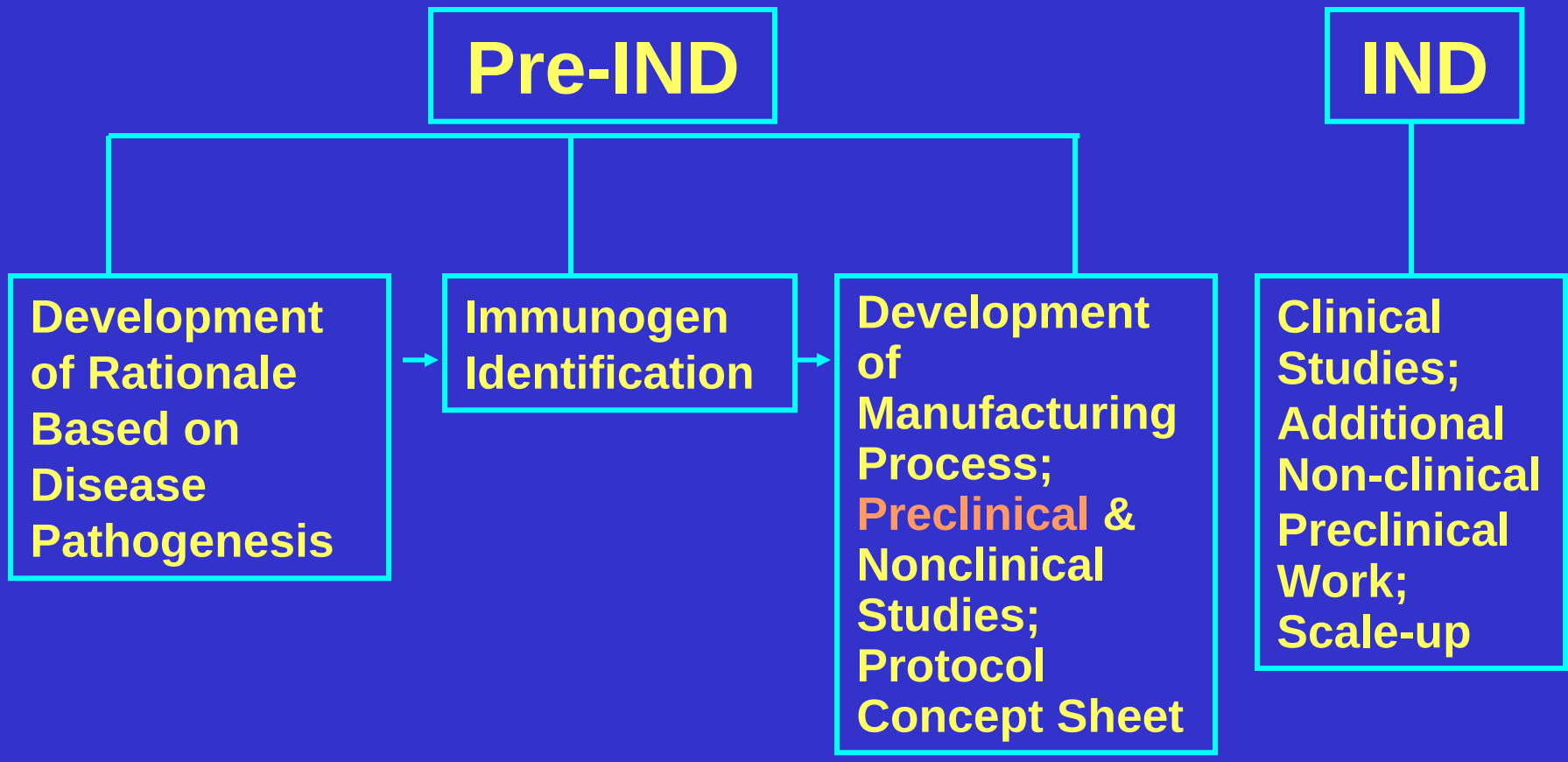
FDA

U.S. Department of Health and Human Services
Food and Drug Administration

Purpose of Presentation

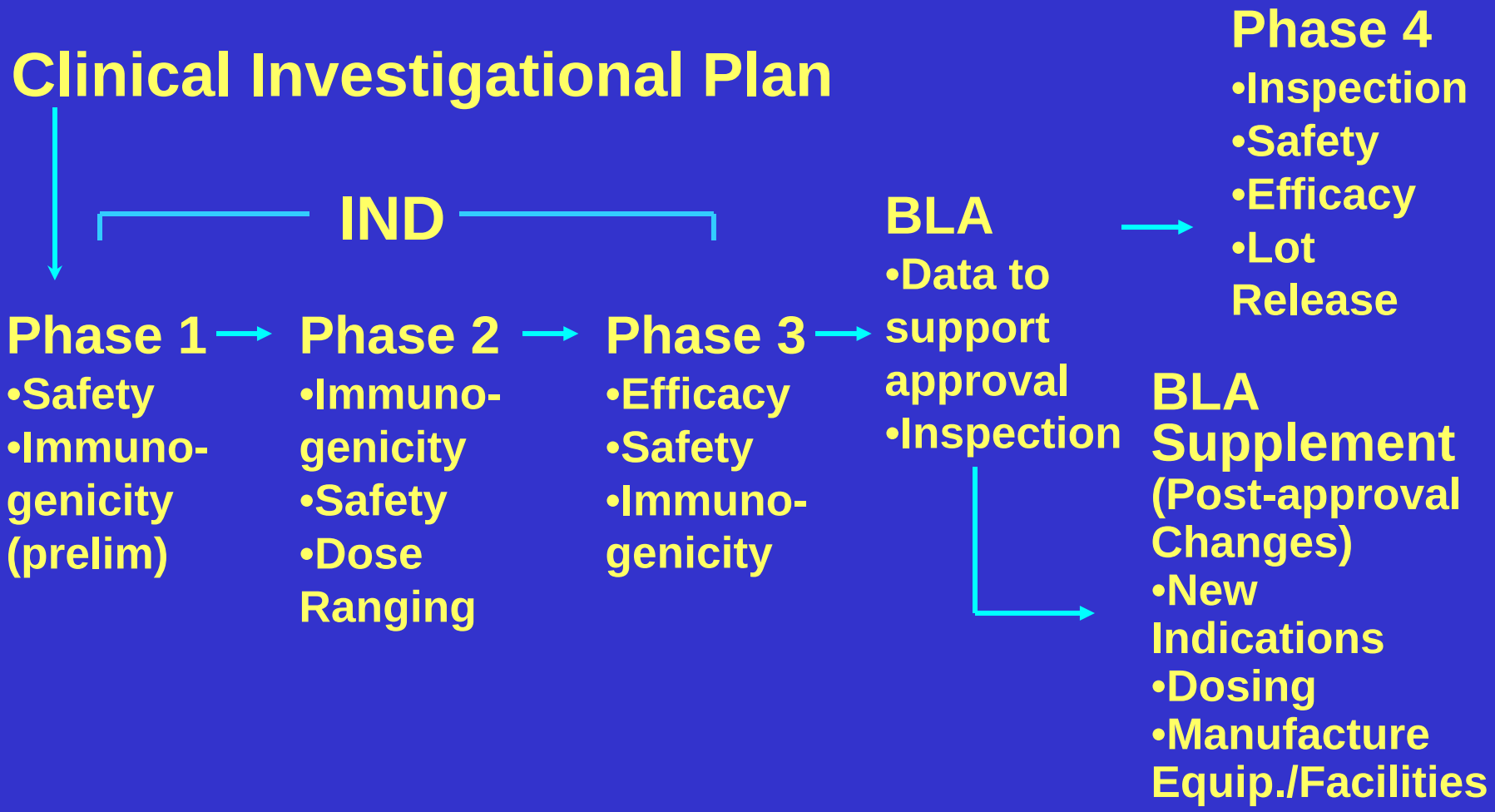
- Overview of preventive vaccine clinical development
- Focus on Phase 1 and 2 trials
- Identify special considerations for vaccine development
- Encourage sponsors to identify global development goals early
  - target populations
  - label indications
  - anticipated use

Vaccine Development



IND = Investigational New Drug application

Stages of Review and Regulation



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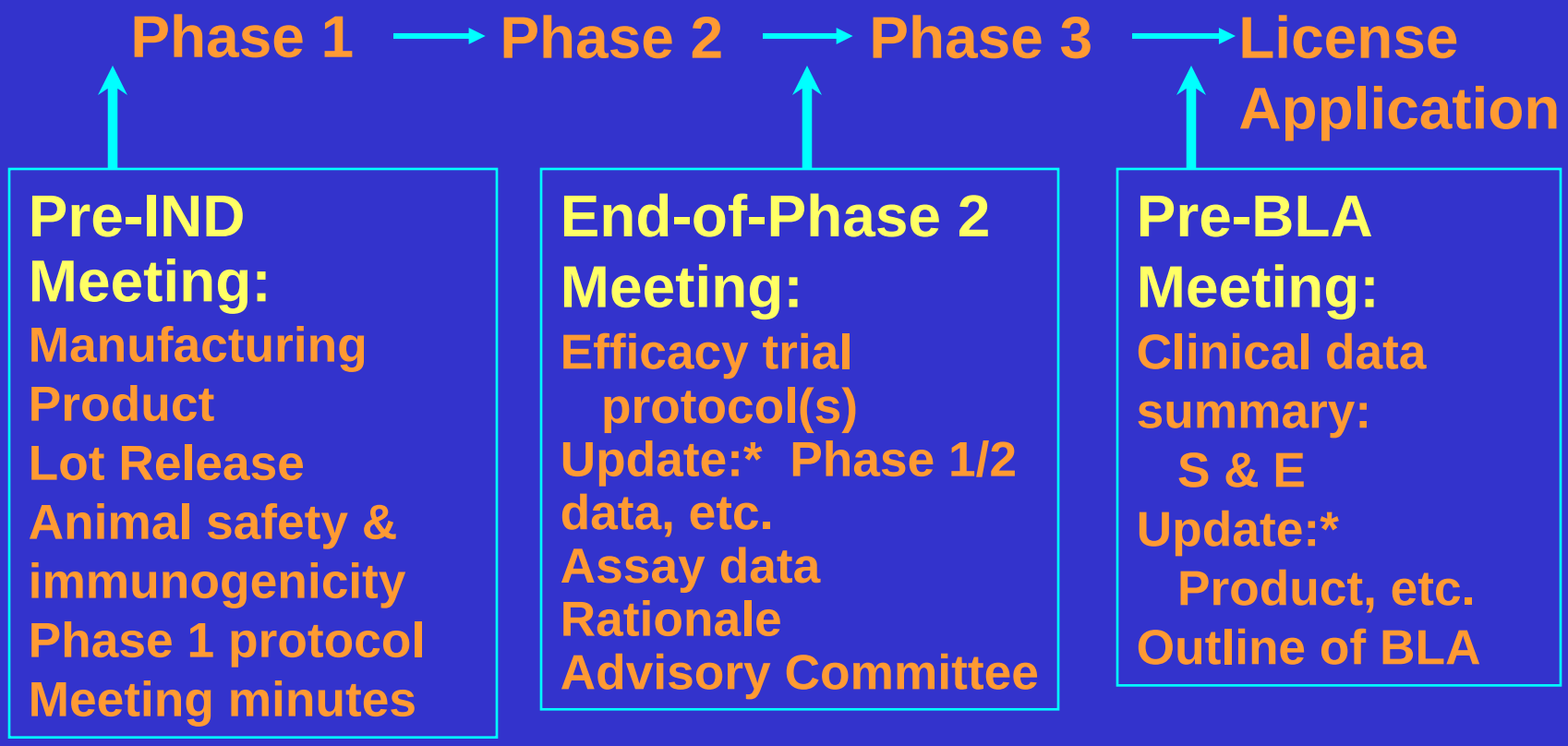
Recommended Meetings with FDA

(21 CFR 312.47)



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*Shouldn't be a surprise

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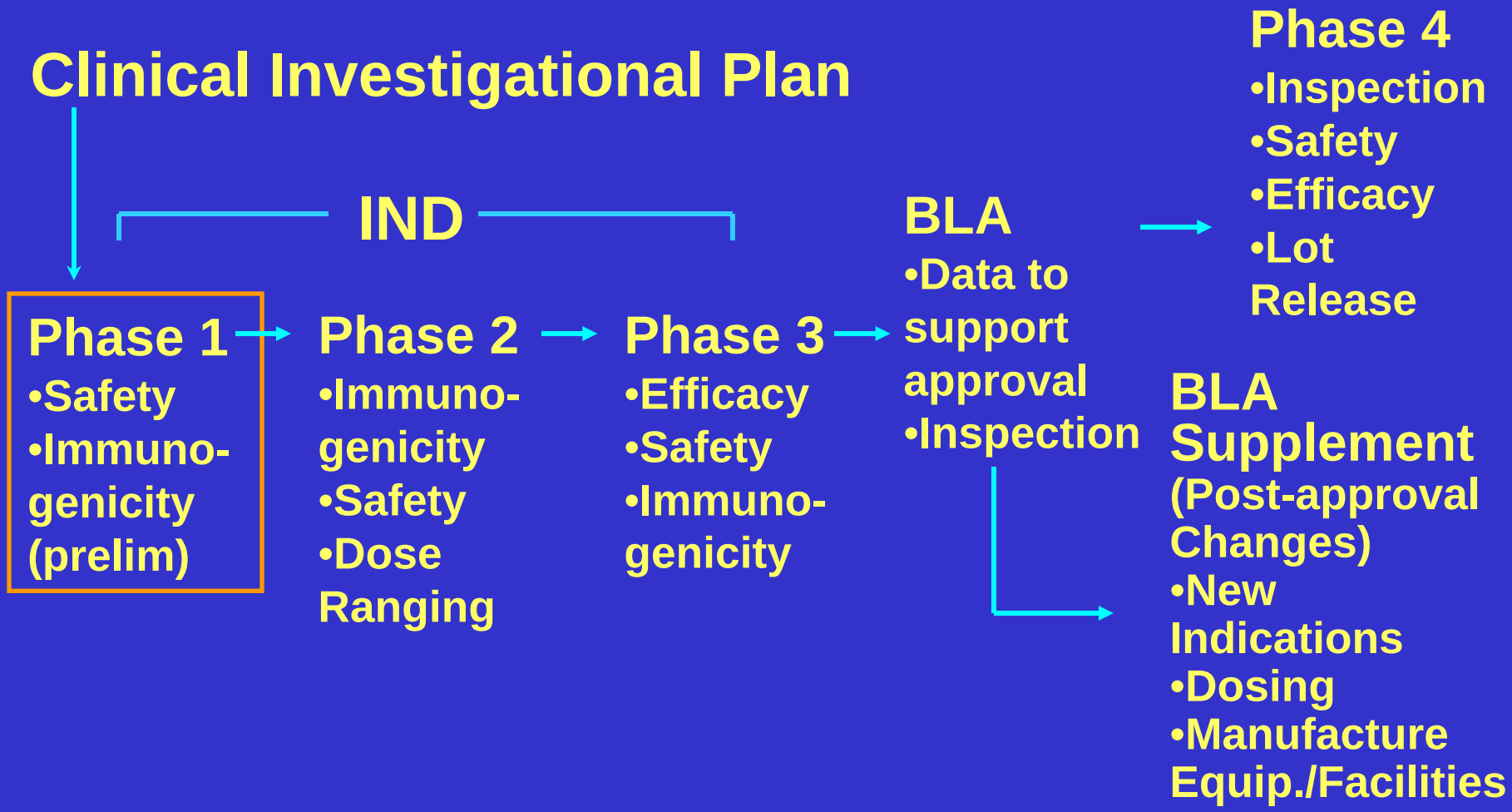

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Phase 1 Study
General Considerations

- Objectives and endpoints
  - Primary: Safety and tolerability
  - Secondary: Preliminary immunogenicity
- Closely monitored (safety)
- Adults, at least for first phase 1 study
- Sample Size
  - Small study: e.g., 20 to 80
- Special instructions for vaccinees, if needed

Phase 1 Study Features and Components

- Consider vaccine-specific features when planning trial (e.g., live vaccine)
- Develop Inclusion and Exclusion Criteria
  - Healthy adult volunteers
  - Age range: 18-40 years recommended (esp. for first phase 1 study)
  - Special considerations
    - age, serostatus, concomitant medications allowed, etc.
    - where applicable, vaccinee contacts
      - E.g., vaccinia

Safety Monitoring

- **Goals:**
  - **Protect subjects by monitoring local, systemic, and potential end-organ toxicity**
  - **Identify major toxicity**
- **Clinic visits**
  - **Symptom review, diary cards**
  - **Clinical exam**
- **Laboratory studies**
  - **CBC: hematologic**
  - **Chemistries: e.g., hepatic, renal (U/A), endocrine**
  - **Others? Per pre-clinical toxicology study, previous experience with similar vaccines, etc.**

Safety Monitoring (cont'd.)

- Safety and activity (e.g., immunogenicity):
  - Items to be assessed/time schedule
    (Well organized summary in a table)
  - Active post-vaccination monitoring
  - Monitoring tools
    - Submit to IND with protocol, regardless of Phase
      - Prototype Case Report Forms (CRFs)
      - Diary cards
      - Scripted interviews
    - Other, e.g., photographs

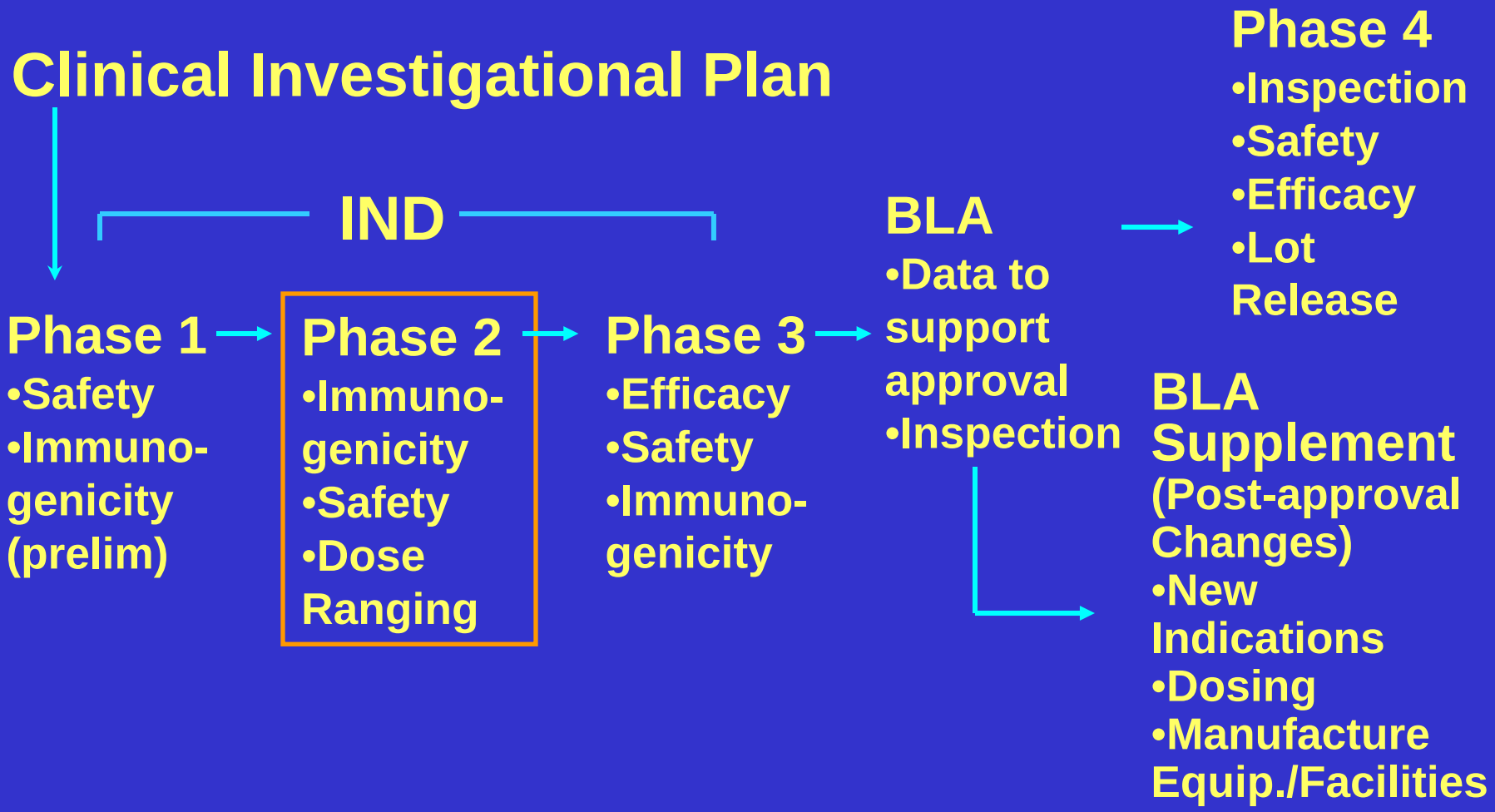
Safety Monitoring (cont'd.)

- Toxicity Grading Scales
  - Define grades for specifically monitored parameters (clinical and laboratory AEs)
  - Based on healthy volunteers
- Stopping rules
  - Provide specific criteria
  - Address grade 3 (severe) or grade 4 (serious) adverse events
  - If criteria met, stop vaccination and investigate
    - Safety review
    - If appropriate, resume study +/- changes to protocol / I.C.

Phase 1 Study Features and Components (cont'd.)

- Dose escalation
  - Even in first Phase 1 study
  - Provide details of dose escalation scheme
    - Clear criteria for dose escalation
    - Safety review of lowest dose cohort

Stages of Review and Regulation



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Phase 2 Study
General Considerations

- Goals:
  - Immunogenicity
    - Dose-ranging data
    - Identify preferred dose, schedule, formulation, route of administration for advancement to Phase 3
  - Safety
    - More precise estimates of common adverse events
      - Local reactogenicity
      - Systemic effects

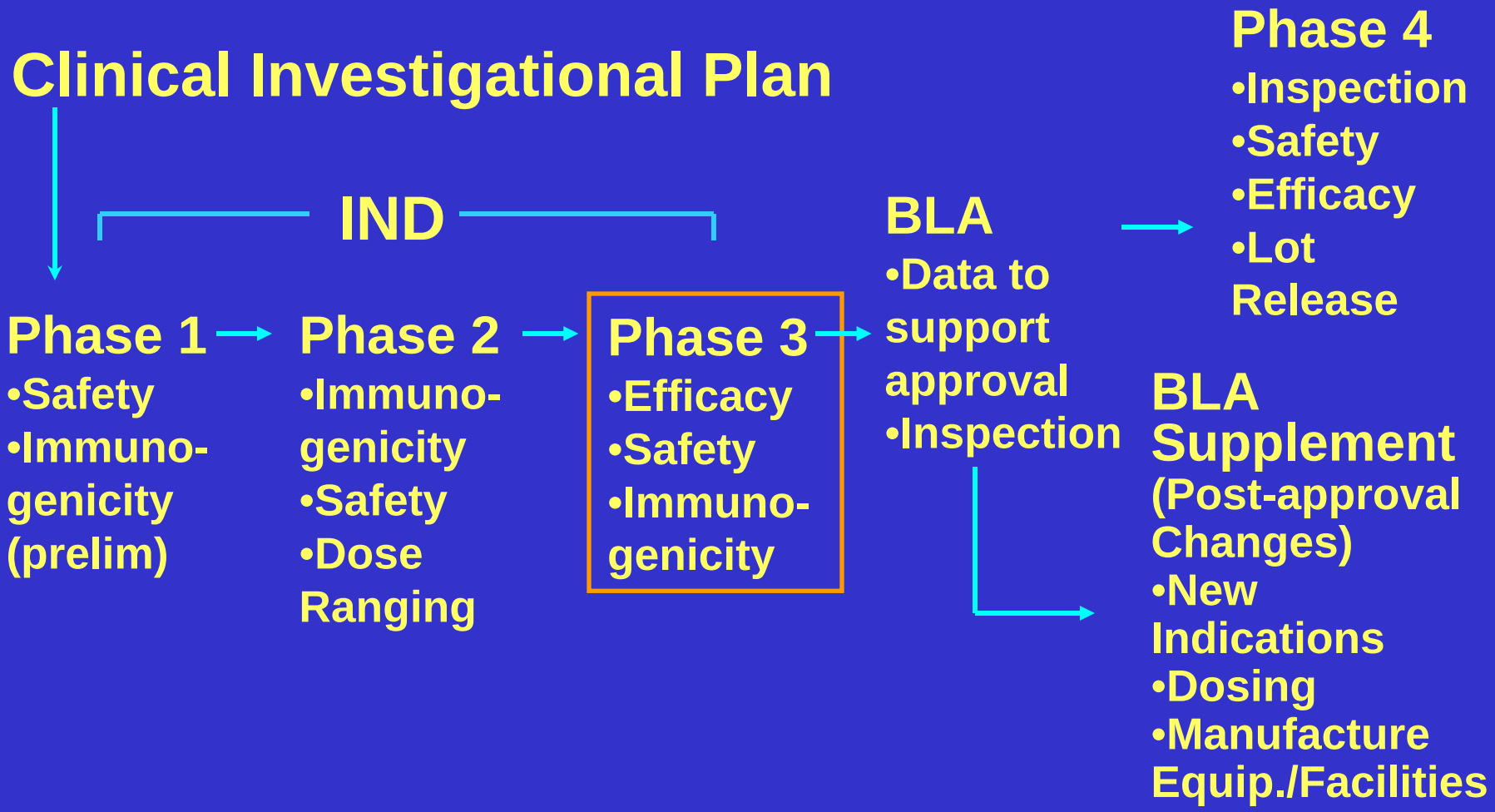
Phase 2 Clinical Trials

- Up to several hundred subjects in a trial
- Broader study population
- Often randomized & controlled
- Vaccine-elicited immune responses
  - Qualitative
  - Quantitative
  - Duration
- Safety
- Pilot evaluation of efficacy endpoints (where feasible)

Phase 2 Clinical Trials

- Planning for Phase 3
- Logistics and Protocol:
  - Compliance with protocol
  - Accrual of subjects
  - Target populations for licensure
  - Monitoring tools
  - Sample handling

Stages of Review and Regulation



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Phase 3 Development
General Considerations

- Develop adequate safety, immunogenicity, and efficacy data to support
  - Proposed use(s) and indication(s)
  - Target population(s)

Phase 3 Study
General Considerations

- **Objectives and Endpoints:**

  - **Pivotal efficacy - options**
    1) **Clinical endpoint, if feasible**
    2) **Immune response endpoint**
    3) **“Animal Rule”, if appropriate**

  - **Pivotal pre-licensure safety database**
    - **Sample Size: Thousands for safety in humans, regardless of path to licensure**

Phase 3 Vaccine Efficacy Trial Protocol

- Study population/background epidemiology
- Control group
- Randomization scheme/Study masking
- Items assessed/time schedule:
  - Clinical & lab parameters: safety, immunogenicity, microbiology and efficacy
- Prospective 1^0 & 2^0 efficacy endpoints

Efficacy Trial Endpoints

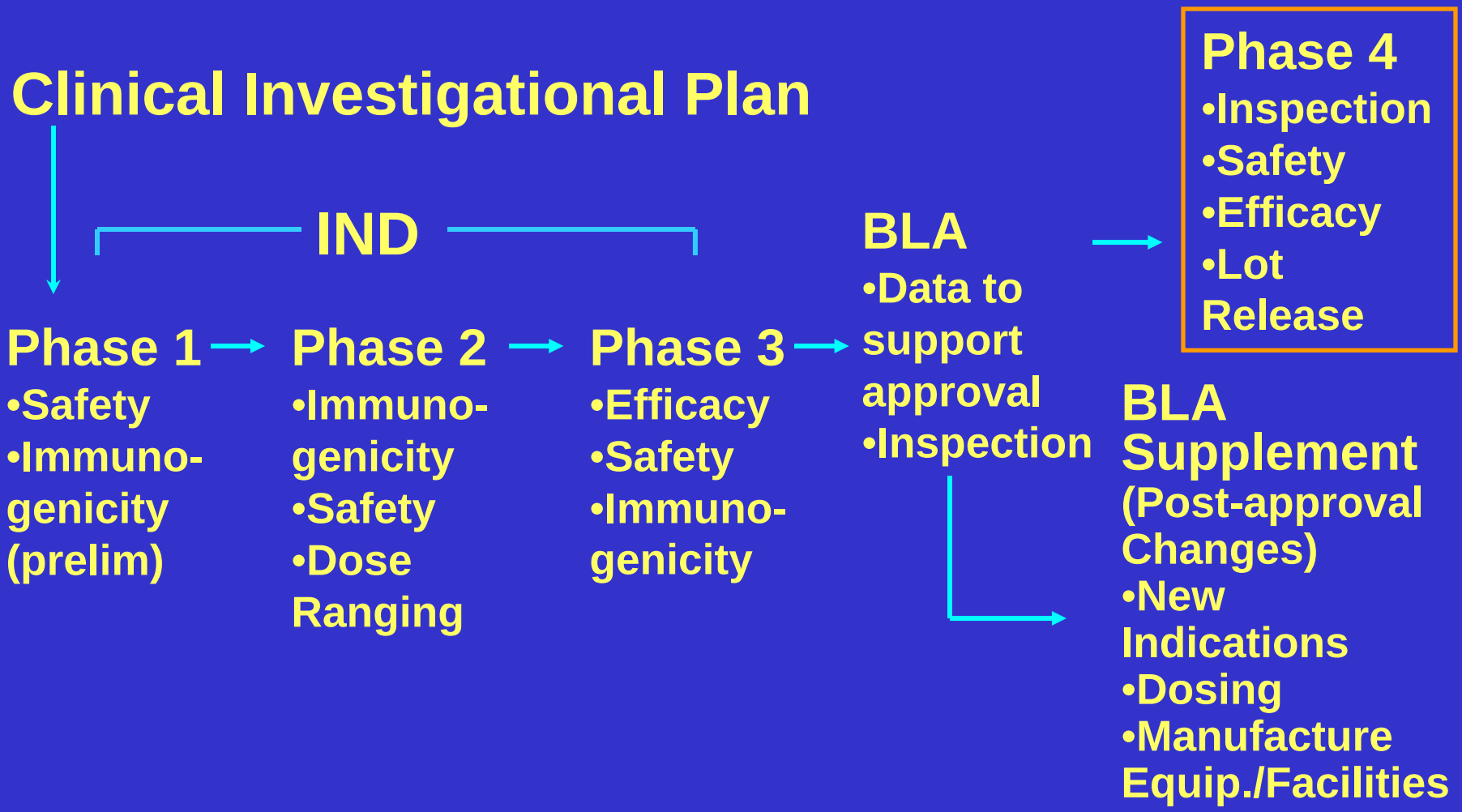
- Clinical relevance of case definition, esp. for primary endpoint
- Specificity of case definition emphasized*
- Validation of assays before efficacy study
  - Performance Parameters

*Lachenbruch PA: Sensitivity, Specificity, & Vaccine Efficacy. Controlled Clin Trials 19:569-574, 1998.
*Orenstein WA et al. Assessing Vaccine Efficacy in the Field: Further Observations. Epidemiol Rev 10: 212-241, 1988.

Phase 3 Protocols

- Use of animal rule
  - Criteria for dose used in Phase 3 must consider results of animal efficacy studies
    - Compare immune responses in animals and humans
- Develop Phase 3 safety data at appropriate dose
  - Randomized, controlled safety data most interpretable
  - Appropriate control group

Stages of Review and Regulation



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Post-marketing Studies

- Limitations of pre-licensure studies
  - Rare adverse events
  - Delayed onset / long term effects
  - Sub-population
  - Efficacy
- Specific post-marketing commitments at the time of approval
  - Review of recent vaccine approval letters may be instructive

Published Guidance
FDA, ICH

FDA Guidance Documents for Industry

- **http://www.fda.gov/cber/guidelines.htm**
- **http://www.fda.gov/cder/guidance/**

International Conference on Harmonisation

- **E6: http://www.ich.org/ich5e.html#GCP**

Conclusions:

- **Early and frequent regulatory communication**
  - **Pre-IND Meeting: feedback on phase 1 trial design**
  - **Early articulation of development goals**
    - **Target population(s)**
    - **Indication(s)**

Conclusions:

- **“Animal rule” if applicable**
- **Develop data on relevant dose in Phase 2 to be investigated in Phase 3**
- **Adequate safety data**