FDA Recommendations for Adenoviral Vector Characterization: Where We Are and Where We're Going

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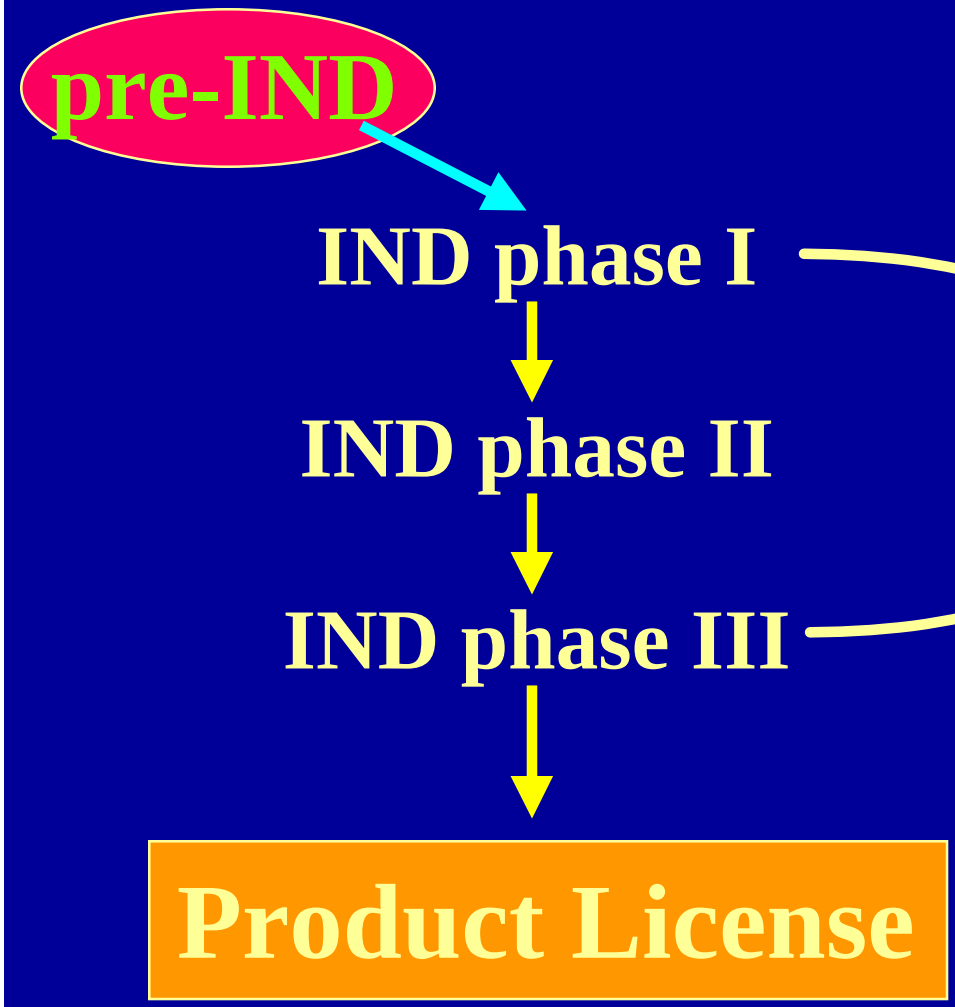
Importance of a Reference Standard

- Vector product review process and goals
- Product criteria for adenovirus-based vectors
  - discuss current criteria
    - origin and evolution of criteria
- Highlight areas where a standard will improve safety and reliability

Regulatory and Approval Process



MONITORING

annual reports
amendments

post-approval surveillance

adverse reaction monitoring

lot release data review

CBER Review

- **Product**
  - **manufacturing and quality control**
  - **product and process**
- **Preclinical**
  - **safety before**
  - **rationale**
  - **efficacy**
- **Clinical**
  - **safety**
  - **clinical monitoring**
  - **informed consent**

Vector Quality

- Goal: Safety, Purity, Potency
- Process and Product
  - cell substrates
    - Master Cell Banks
    - Working Cell Banks
  - viral bank
  - manufacturing ingredients
  - final product


FDA Advisory Committees
Reviewer Experience
Gene Therapy Community
Preclinical data
Clinical Trial
Product Review
RAC/OBA
CFR Requirements

Evolution of Criteria

- Case-by-case → Product class
  - CBER review
    - meetings of product class reviewers
  - RAC
  - Advisory Committees
  - Experience
- March 6 Gene Therapy Letter

Master Cell Bank: Safety

- Sterility
- Mycoplasma
- Adventitious Virus
  - in vitro and in vivo virus
  - bovine and porcine viruses (ancillary product dependent)
  - human viruses: EBV, HBV, HCV, CMV, HIV 1&2, HTLV 1 & 2, AAV, B19, (other cell substrate specific ?)
  - RCA

Working Cell Bank

- Safety
  - Sterility
  - Mycoplasma
- Characterization
  - Morphology
  - Isoenzyme
- Adventitious Virus
  - In vitro virus

Master Virus Bank: Characterization

- Identity
  - sequence insert and flanking regions
  - restriction map

    (Advisory Committee meeting Nov 16, 2000)
- Activity
  - transgene specific protein expression
  - other
- Titer
  - infectious titer
  - particle count

Master Virus Bank: Safety

- Sterility
- Mycoplasma
- Adventitious Virus
  - in vitro and in vivo virus
  - bovine and porcine viruses (ancillary product dependent)
  - human viruses: EBV, HBV, HCV, CMV, HIV 1&2, HTLV 1 & 2, AAV, B19,
  - RCA

Final Product: Safety

- Sterility
- Mycoplasma
- Endotoxin
- General Safety
- Adventitious Virus
  - In vitro virus
  - AAV
  - RCA: <1 RCA per 1 x 10ex9 PFU

Final Product: Characterization

- Identity
  - restriction map, structural characterization
- Activity
  - transgene specific
- Potency
  - required by phase II/III
- Titer
  - particle count/ infective particle Ratio <100:1
- Purity
  - cell substrate DNA, protein

Adenovirus Standard

- Improve precision of titers
  - particle and infectious
  - RCA
- Improved safety and efficacy
  - control of clinical doses
    - safety and dose/response
  - comparability between clinical trials
  - comparability between preclinical studies