CMC Considerations for Oncolytic Viral Products

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Outline

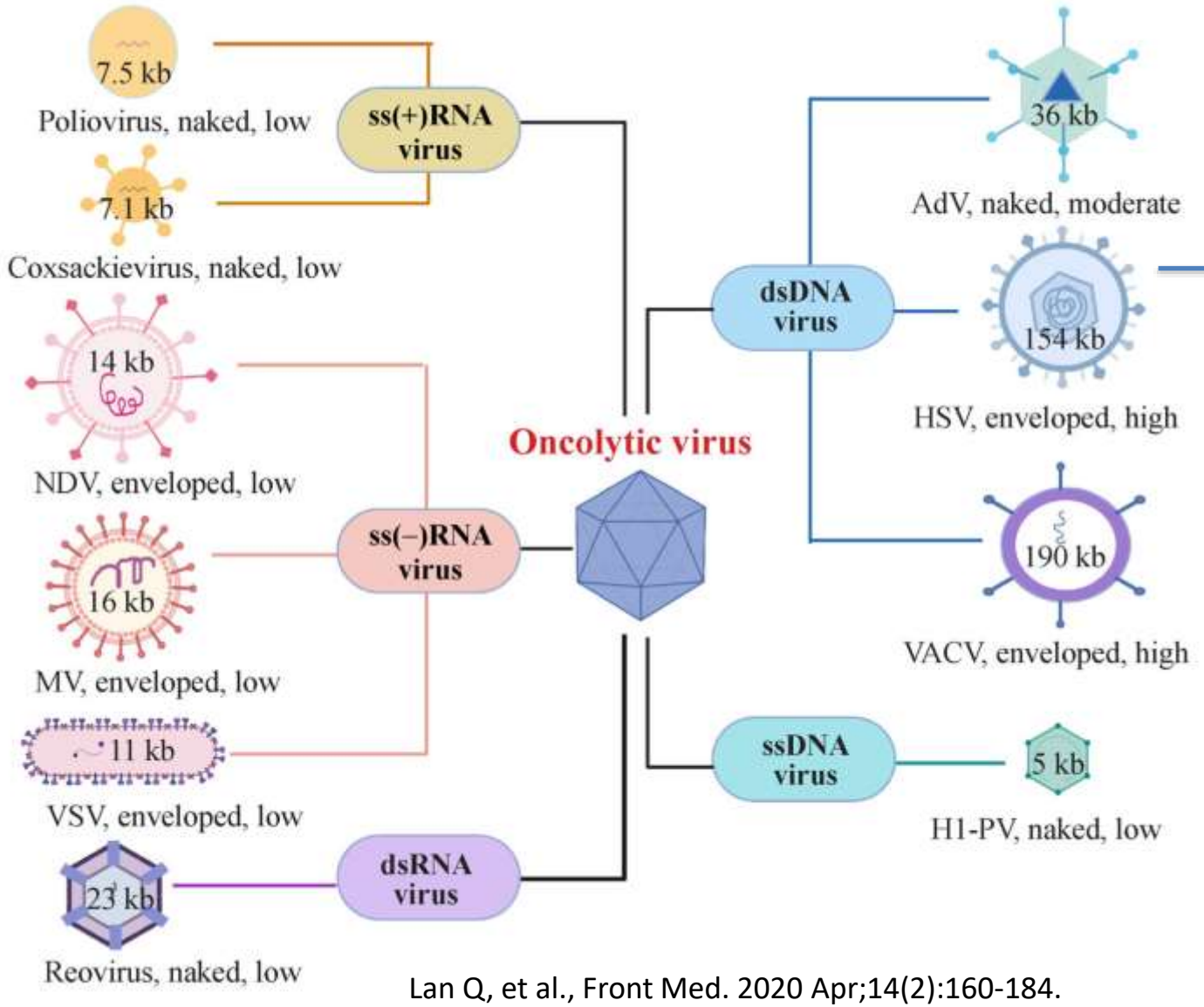
- Background
- Product manufacturing and testing
- Monitoring shedding of oncolytic virus during clinical trials
- Summary

Oncolytic Virus (OV)

- Infects and lyses cancer cells but not normal cells
- MOAs: Direct tumor lysis and stimulation of immune responses

- Types
  - Naturally occurring
  - Genetically engineered
    - Expression of transgene to enhance the therapeutic effect
    - Modifications that reduce virulence and promote tumor-specific targeting

Examples of OVs

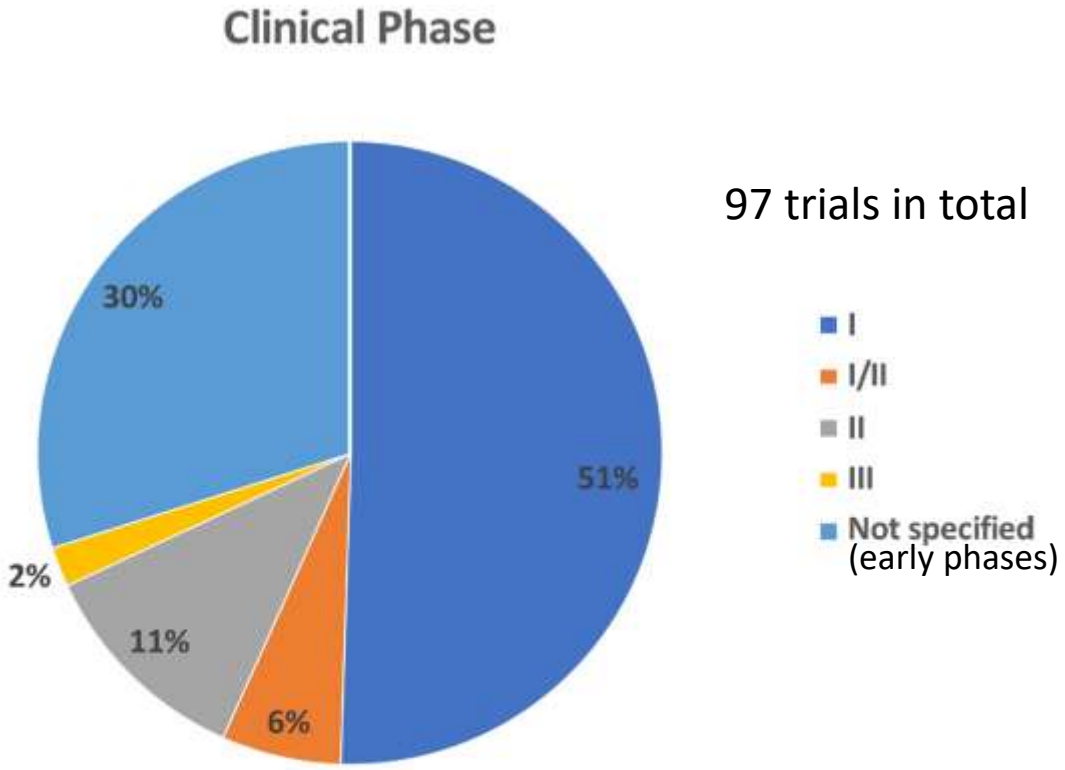


- T-VEC (Imlygic): FDA-approved for advanced melanoma

Lan Q, et al., Front Med. 2020 Apr;14(2):160-184.

Clinical Landscape of OVs

- Tumor types: Solid tumors and hematological tumors
- ROAs: Intratumoral, intravenous, intraperitoneal, intravesical, etc.
- Combination therapies: Chemotherapy, radiation, pro-drugs, immune checkpoint inhibitors, etc.

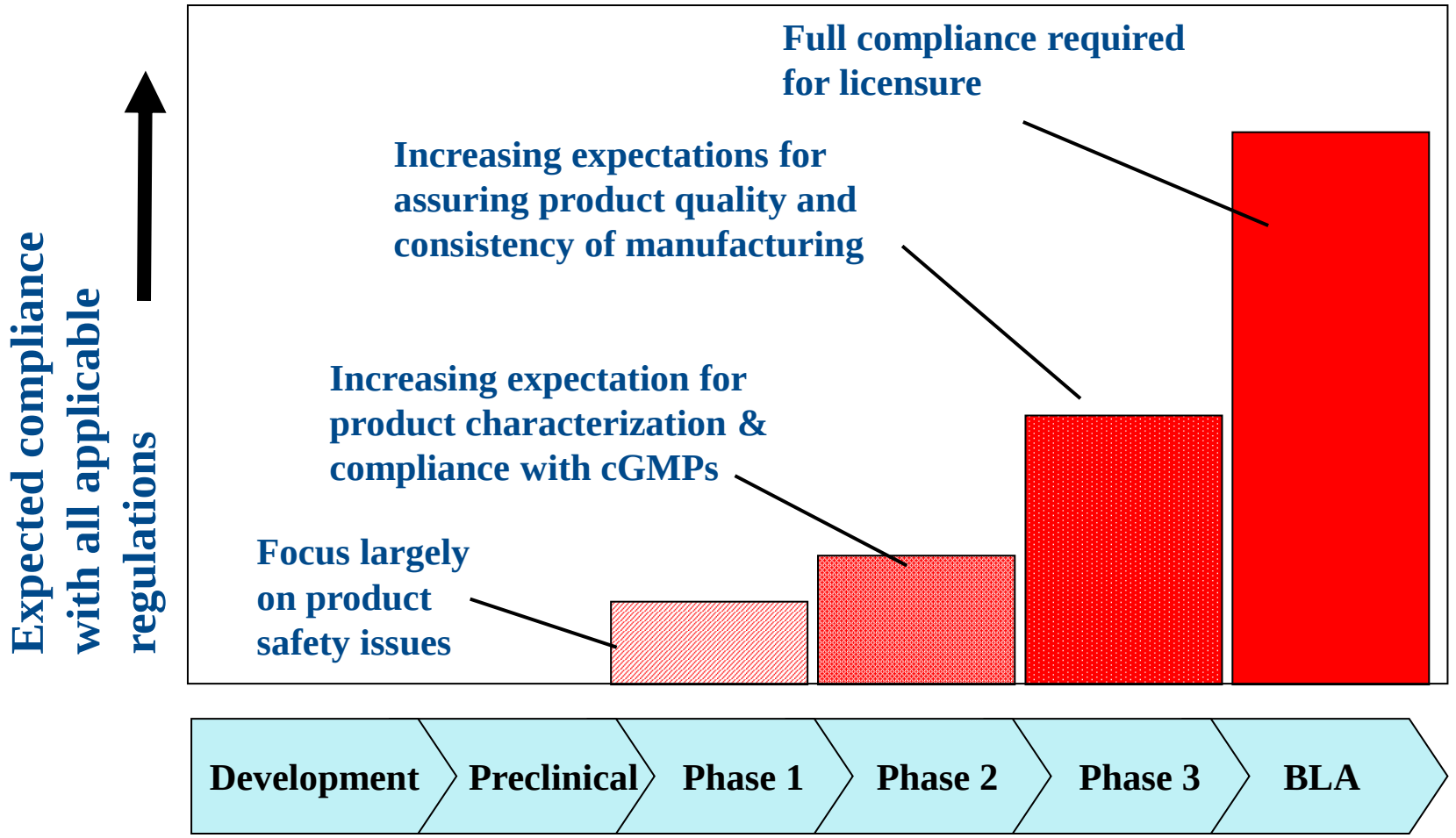


97 trials in total

Figure 1 Pie chart showing the distribution of oncolytic viruses by clinical stage. The majority of studies were phase I (n=49; 51%) or not specified (n-=29; 30%). There were 6 (6%) phase I/II trials, 11 (11%) phase 2 and only two phase 3 clinical trials.

Macedo N, et al. J Immunother Cancer. 2020 Oct;8(2):e001486.

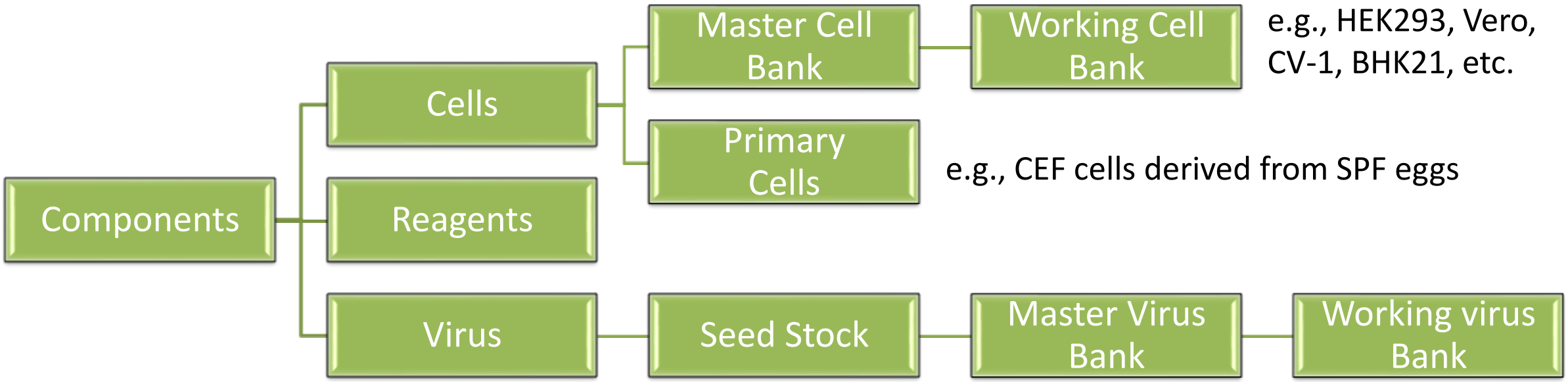
Product Characterization Increases with Phase of Clinical Investigation



Ensuring Product Safety and Quality

- Qualification of components
- A well-defined process and process controls
- Appropriate product testing

Components


Components
Cells
Reagents
Virus
Master Cell Bank
Working Cell Bank
Primary Cells
Seed Stock
Master Virus Bank
Working virus Bank
e.g., HEK293, Vero, CV-1, BHK21, etc.
e.g., CEF cells derived from SPF eggs

Master and Working Cell Banks

- Origin, derivation history, culture conditions

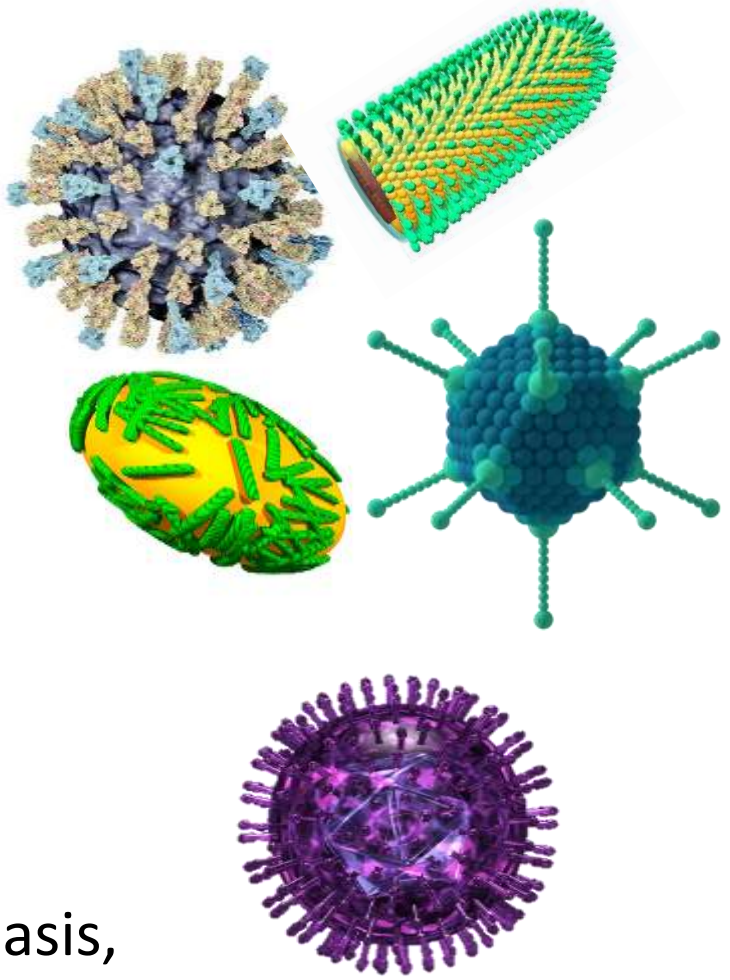
- Qualification Testing
  - Identity *
  - Sterility (bacteriostasis/fungistasis) *
  - Mycoplasma*
  - Adventitious viral agent testing (AVA): *in vitro** and *in vivo*
  - Detection of viral particles by Transmission Electron Microscopy (TEM) analysis
  - Retroviruses (reverse transcriptase activity)
  - Bovine and porcine, and other species-specific viruses
  - Viability *
  - Stability
  - Tumorigenicity (required prior to Phase 3 clinical trials)

* Working Cell Bank testing

Master and Working Virus Banks

- Origin, derivation history, culture conditions

- Testing and characterization
  - Sterility (bacteriostasis/fungistasis)
  - Mycoplasma
  - Adventitous viral agent testing: in vivo and in vitro
  - Species-specific pathogens
  - Identity (e.g. by sequencing)
  - Activity
    - Titer/infectivity
    - Differential infection/cytotoxicity
  - Stability
  - Additional testing may be required on a case-by-case basis, e.g., drug sensitivity, transgene expression, etc.

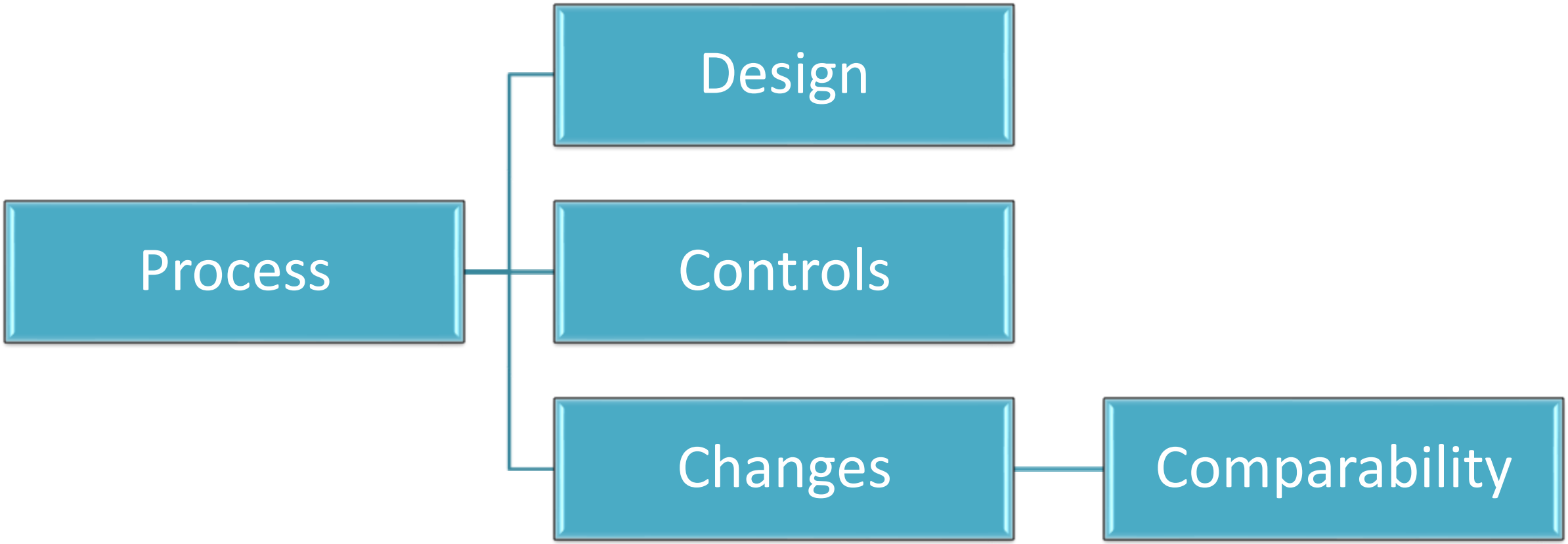


Reagents

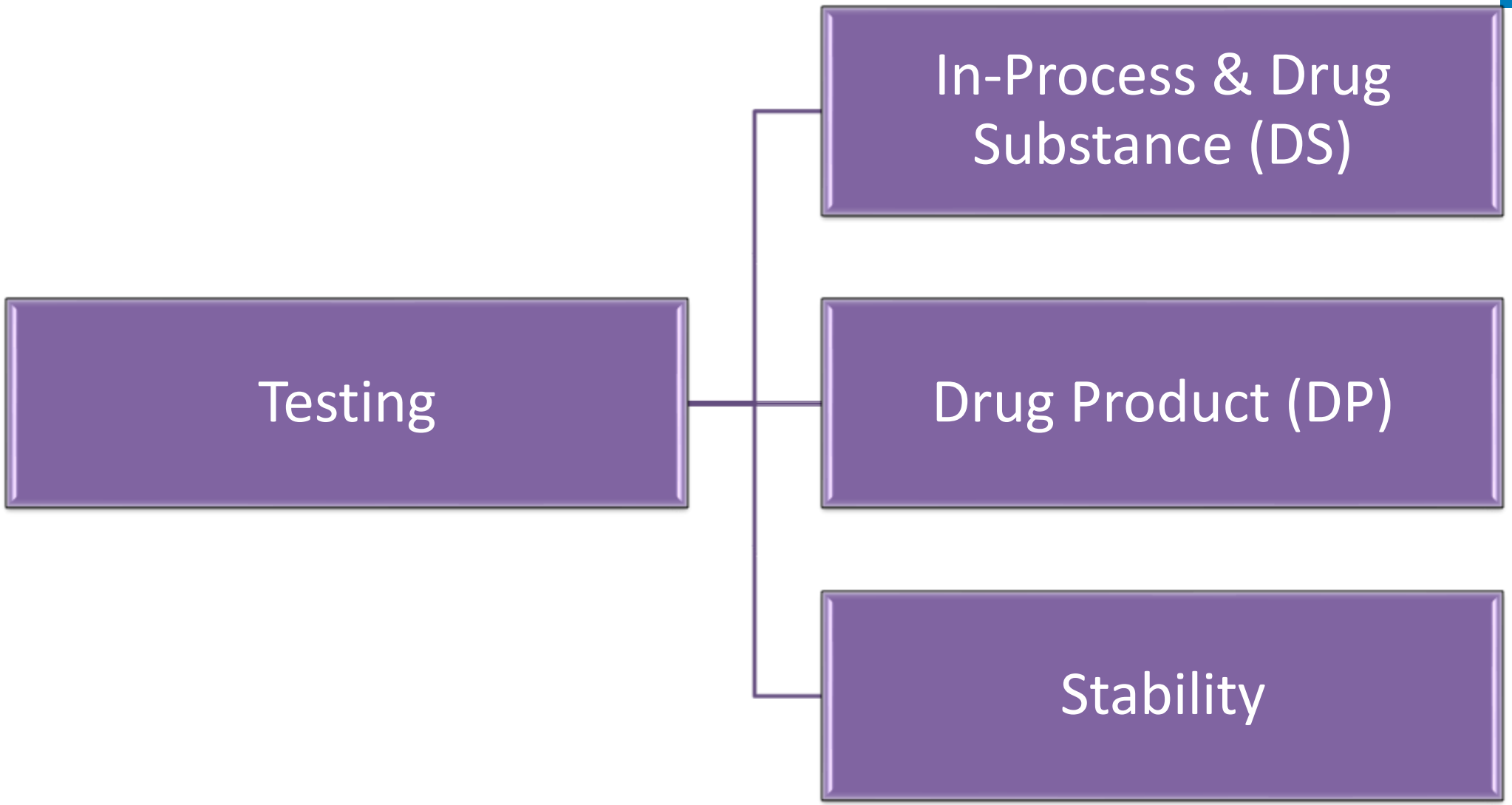
- Media
- Serum
- Media supplements (e.g., transferrin, insulin, trypsin, etc.)
- Ancillary materials (e.g. buffer, chemicals, WFI, etc.)
- Reagents used in downstream purification (e.g., nucleases, column materials)

Selection of the highest quality reagents available, establishing vendor/reagent qualification, documentation of the source and derivation is important

Process



Testing


Testing
In-Process & Drug Substance (DS)
Drug Product (DP)
Stability

In-Process Testing

- Examples:
  - Cell density
  - Cell viability
  - Bioburden
  - Process/product related impurities
  - Viral titers
  - Mycoplasma and *in vitro* AVA testing on Unclarified Bulk Harvest

In vitro AVA Testing

- Challenging due to amplification of the viral product causing cytopathic effects (CPE) in testing cells

- Alternative testing approaches:
  - Use antibodies to neutralize the virus prior to testing (dilution as little as possible)
  - Test on uninfected production control cells (parallel culture)
  - Use advanced and sensitive method, e.g., NGS, as a supplementary approach to the standard AVA testing

Product Testing

- Sterility (CFR 610.12)
- Identity (CFR 610.14)
  - Nucleic acid: e.g., PCR, Sequencing
  - Protein: e.g., Western Blot, ELISA
- Purity (CFR 610.13)
  - Endotoxin
  - Residual contaminants (DNA, protein, culture reagents, column materials, etc.)
  - Particle to Infectivity (PI) ratio
  - Sequence variants
- Potency (CFR 610.10)
  - Direct or indirect measure of biological activity
    - Titer (TCID50, pfu, or viral particle)
    - Transgene expression/function
    - Tumor-specific cell killing
  - Quantitative
- Appearance
- Reference standards

Product Stability

- Long-term storage
  - Appearance
  - Potency (titer)
  - Sterility
  - Quality (degradation products)
- Accelerated & Stress conditions
- Short-term storage: product formulation at clinic and administration (device compatibility)
  - Potency (titer)
- Shipping
  - Potency (titer)
  - Sterility
  - Quality (degradation products)

Shedding

- “Shedding” – release of oncolytic products from the subject through excreta (feces), secreta (urine, saliva, nasopharyngeal fluids, etc.), or the skin (pustules, sores, wounds)
- Shedding is distinct from biodistribution.
- Assess the potential for environmental release and transmission

Shedding

- Product-specific factors should influence the study design
  - Characteristics of the virus (replication competence, persistence/latency, immunogenicity, tropism, etc.)
  - Route of administration, dose, regimen
- Preclinical shedding data may inform the design of human shedding studies
- Collect shedding data in Phase 1 and continue through Phase 2 and Phase 3

Considerations for Shedding Study Design

- Types of samples collected
- Frequency and duration of sample collection
  - Frequent sampling immediately following administration
  - Continue sampling until 3 consecutive data points ≤ LOD
  - Sampling to capture 2nd peak of shedding may be necessary
- Methods of detection
  - Detection of product-specific nucleic acids
  - Analysis of positive samples for infectivity/growth

Summary

- Product safety is a key consideration in early phase studies due to the replication competence of the OV.

- Because OVs are complex biologics manufactured using materials of biological origin and terminal sterilization is not possible, product safety should be established through aseptic processing, material qualification, well-defined manufacturing process, and adequate testing.

- The collection of shedding data in preclinical and clinical studies with well-designed study plan for sample collection and the use of qualified methods is an important aspect of clinical development of OV products.

Guidance

- Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (January 2020)
- Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (February 2010)
- Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (January 2011)
- Guidance for Industry: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (August 2015)
- Guidance for Industry: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products (March 2015)
- ICH Considerations on Oncolytic Viruses (September 2009) and General Principles to Address Virus and Vector Shedding (June 2009)

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