Trends and Challenges in Process Development for new Viral Vaccines

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Topics

- Trend - Where we are and where we go?
- Trend - Change of regulatory requirements
- Challenge - Process variability
- Challenge – Scale up
- Challenge - Formulation
- Design of process development
Major Drivers in Technologies

- **Recombinant DNA technologies**
  - expression of proteins in procaryontic, eucaryontic cells

- **Gene transfer vectors**
  - Plasmid vectors
  - Live viral vectors
    (Adenoviruses; Poxviruses; AAV etc.)

Regulatory Guidance Documents on Biotechnology / Vaccines

Guidance Documents on Biotechnology Advanced therapy
Major Drivers in Immunology

- Understanding of regulation of innate and adaptive immunity
  - toll like receptors
  - role and interaction of cytokines with CTL, T helper / suppressor cells

- Deep sequencing for mRNA
  - identification of regulatory important mRNA transcripts for immunological reactions after infection or immunization

Vaccine Design
- Tailoring of immunological important epitope structures
- Design of immunological modulation of vaccine potency
New Indications

- **Therapeutic vaccines**
  - Chronic infectious diseases (HBV; HIV, HCV...)
  - Chronic disease based on autoimmune / degenerative pathogeneses
  - Oncotherapeutic vaccines

- **Traditional prophylactic vaccines**
  - Infectious diseases
  - Emerging diseases
  - Bioterrorism

New regulatory requirements
Consequences

- **Prophylactic vaccines**
  - High level of scientific and regulatory experience
  - Major concern - safety
  - Active mechanism well understood
  - High number of subjects in clinical trials
  - Highest demands on characterization

- **Therapeutic vaccines**
  - Adverse events more likely tolerable
  - Long term AE’s unknown
  - Active mechanism still under scrutiny
  - Small scale studies
  - = Less stringent regulatory demands? No – **different**!
Environment for Development of new Vaccines

- Conditions
  - Indication
  - Market analyses
  - Invention
  - Product design
  - Product development
  - Preclinical studies
  - Process development
  - Manufacturing of clinical trials materials
  - Studies for Toxicity
  - Clinical trials Phase 1, 2, 3

Complex demands and conditions in a changing world .... PtC, Guidelines…
Regulatory Challenges

- Changes in Specifications
- Regulatory changes
- Development, improvements, optimization, scale up

Example:
Change in Process Validation

Variations

How to manage?
Challenge - Biology

- Biotech processes are highly variable
- In contrast to chemical synthesis biological processes are far from being understood
- Process control for the API is rather rudimentary in Biotechnology
- Scientific methodology for process development needs to be improved

How to improve?
Process Variability – Key Issues

- Starting materials
- Selection and characterization of biological seed materials
- Variability of QC tests (infectivity assays, biological potency tests …)
- Performance + quality aspects of virus replication in cells
- Process and product related impurities
- Complexity on up scaling of processes
- Formulation of vaccines is a major problem
Qualification of None Biological Raw Materials

Key topics:

- Pharmaceutical quality
- Batch to batch variability
- Stability
- Influence on process performance
# Selection and Qualification of cell substrates

<table>
<thead>
<tr>
<th>Examples</th>
<th>Identity / Purity</th>
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<tr>
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<td>Continuous monitoring</td>
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<td>Variability and extraneous agents</td>
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<td>Limited passage range</td>
<td>✓</td>
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<tr>
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**Safety concerns**

Tumorigenicity often not well enough known.
Recombinant Vectors for Viral Vaccines

- Orthopoxviruses
  - Rec MVA
  - Rec Vaccinia

- Avipoxviruses
  - Rec Fowl pox

- Adenoviruses
  - Rec AdV5

- Rhabdoviruses
  - Rec VSV

- Etc.
Issues related to recombinant viral vectors

- History
  - Contact to animal derived materials
  - Status of used animal derived materials (FBS)

- Absence of “wild type viruses”
  - Non recombinant viruses
  - Partially deleted genes / viruses
  - Inhomogeneous virus backbone population

- Genetic stability
### Nature of QC Test Variability in the Development Process

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<th>Development</th>
<th>Verification</th>
<th>Validation</th>
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<tr>
<td>Test for sterility Ph. Eur. (2.6.1) USP &lt;71&gt;</td>
<td>non</td>
<td></td>
<td>Before Phase 1 In presence of the test article (~ validation)</td>
<td></td>
</tr>
<tr>
<td>Content of the API (TCID₅₀, pfu..)</td>
<td>high</td>
<td>CTM phase 1</td>
<td></td>
<td>(phase 2)</td>
</tr>
<tr>
<td>Potency tests</td>
<td>high</td>
<td>Often developed only before phase 3</td>
<td></td>
<td>CTM Phase 3</td>
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Test Qualification

Test Validation

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 Highly variable test are validated too late!
Performance Criteria for Virus Replication

Knowledge about virus replication is rather poor!

For some vaccine candidates the specific output per cell varies between 20 and 500 pfu

pH changes!
Process related impurities / effects

- Leachables, carry over after cleaning, microbiological residuals (endotoxin)

- Absorption on surfaces (change of disposable materials, tubing, filter materials)

Investigation of effects and well controlled changes
Product related Impurities

- Host cell protein, DNA; cytokines
- Variability of virus envelop structures
- Posttranslational processing (Glycosylation pattern)
- Deleted virus populations (e.g. empty capsids, mutants)

Physical / chemical interactions e.g. aggregation
Scale up

- Process changes due to
  - Duration of process steps
  - Different temperature profiles
  - Change of share forces (pump speed, tube diameter etc.)
  - Sample volume to / bulk size relationship decreases
    (critical - none representative sampling procedures)

Challenge for process development
Formulation

- Major topics:
  - Stabilization of vaccine formulations
  - Interaction of the API with additives (adjuvants, buffer, stabilizer)
  - Aggregation
  - Physical degradation
  - Chemical degradation
  - Enzymatic degradation
New Design for Process Development

ICH Guidance Q8 – Pharmaceutical Development

Development based on risk analysis + process analysis

Biostatistical process analysis based on formal experimental design (DoE);

Goal: Process understanding and process robustness

Use of Process Analytical Technology +

better process characterization tools

....Process development studies should provide the basis for process improvement, process validation, continuous process verification....