ICH Q5A (R2) Expansion of scope to include viral vectors

Application of Prior Knowledge for Adenovirus-Vectored Vaccines

Gilles Chénard and Femke Berkhoff
December 6, 2022 | Janssen Vaccines & Prevention B.V.

Melinda, *Tree of Life*
Melinda's artwork reflects her journey living with HIV.

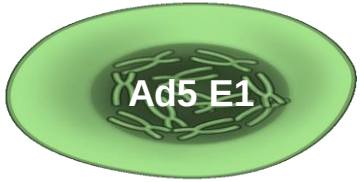
Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Content

1. Overview of Janssen's Adenovirus Manufacturing platform
2. Safety-related in-process and release testing
3. ICH Q5A (R2) update
    - Prior knowledge and viral clearance
    - Prior knowledge and testing for Replication Competent Viruses
4. Summary of challenges and opportunities

Overview of Janssen's Adenovirus Manufacturing Platform and Products

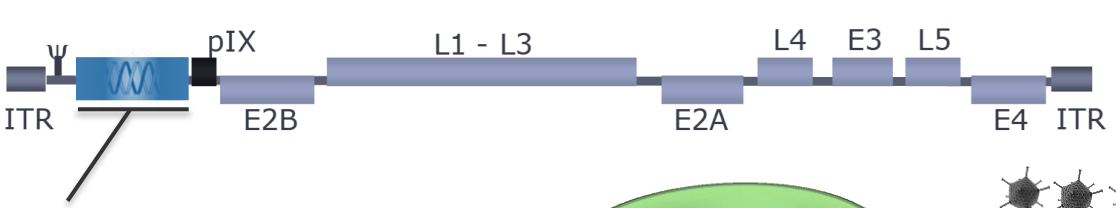
- **PER.C6® Cell Line**

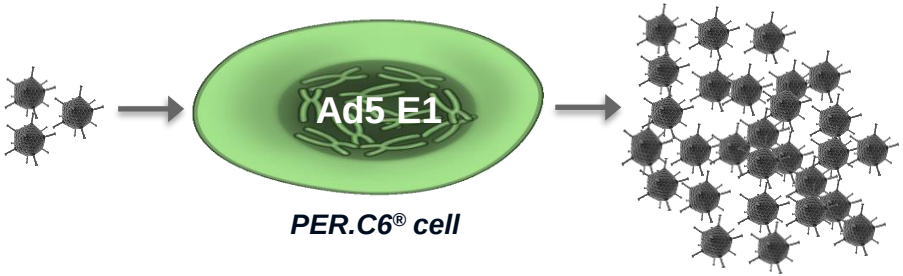


- **AdVac® Viral Vector**

- **Janssen Ad26-vectored vaccines against:**
  - Ebola: Ad26.ZEBOV (approved in 2020)
  - Covid-19: Ad26.COV2.S (approved in 2021)
  - RSV: Ad26.RSV.preF (in development)
  - Influenza: Ad26.FLU.003 (in development)
  - Other vaccines in early development

The AdVac® / PER.C6® vaccine platform



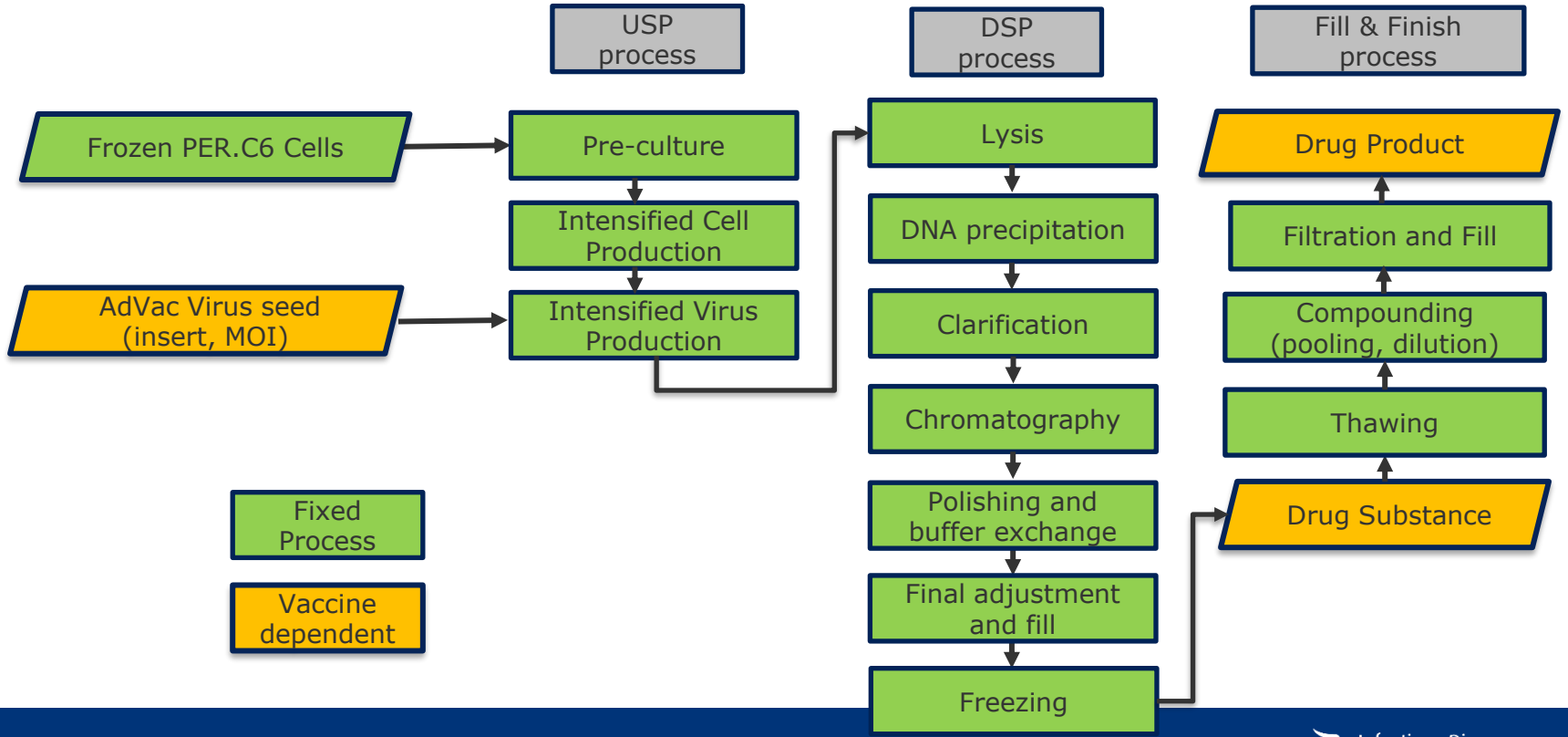


Cells
- Cell line expressing Ad5 E1
- Grow in suspension using serum-free media

Vector
- Human Adenovirus serotype 26 (Ad26)
- non-enveloped virus
- ΔE1 (making room for insert)

No sequence homology between cells-vector

AdVac® Manufacturing Process flow



In-process control testing

- Viral safety control tests performed during manufacturing:
  - Tests on control cells (prior to virus production)
  - Tests for extraneous agents in cell cultures (CPE, Haemadsorbing viruses)

- Testing performed is part of the overall Safety Control Strategy which is based on Risk Assessments in line with regulatory guidelines, incl. Table A-5 of ICH Q5A (R2) Annex 7

Drug substance release testing

Attribute	Test	Acceptance criteria
Identity	Virus identity Viral protein fingerprinting	Identity confirmed Identity confirmed
Purity and impurities	Host cell impurities	Within established limits
Potency	Transgene Expression Infectious units	Expression confirmed Within established limits
Quantity	Virus particles	Within established limits
Safety	Bioburden Bacterial Endotoxins Replication Competent Adenovirus (RCA)	Within established limits Within established limits ≤ 1 RCA / 3 x 10^{10} virus particles
General	Appearance pH Polysorbate 80 concentration	Within established limits Within established limits Within established limits

ICH Q5A (R2) update (1)

Viral-vectored vaccines now in scope: ➔ viral clearance validation now applicable!

New products may face more stringent requirements than approved products made with the same manufacturing platform!

6.6 Application of Prior Knowledge for Evaluation of Viral Clearance

"*The decision on the acceptability of virus clearance data without product-specific experiments is made on a case-by-case basis while considering the whole viral safety concept for a medicinal product, …*"

Observations:

- The possibility to avoid product-specific studies maintains current development times and acknowledges the effectiveness of the overall viral safety control strategy of existing platform products.
- No minimum requirements defined for prior knowledge acceptability.

Challenge:

Ensuring consistent case-by-case assessment across all regions.

ICH Q5A (R2) update (2)

Changes relevant for adenovirus-vectored vaccines:

ANNEX 7: GENETICALLY-ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS

Tests for Endogenous, Helper and Replication Competent Viruses, as applicable

Test	MCB, WCB, Cells at the LIVCA	Virus Seed [k]	Unprocessed Bulk (Harvest)	Drug Substance
[g] replication competent viruses	+	+	(+)	(+)

" [g] *Replication Competent Virus (RCV) may develop at any step during manufacturing (e.g., at initial transfection or transduction steps and through production). Current recommendations include testing for RCV at multiple stages of manufacture to detect for recombination or for the vector virus to revert to parental or wild type phenotype. The manufacturing stages and test methods are when applicable and product dependent. For example, RCV testing is performed on cells and supernatant derived from the stably-transfected vector producer or packaging MCB and LIVCA and during the qualification of the virus seed or cell bank. Tests for RCV apply during production, with testing performed on vector producing cells and supernatant from each unprocessed bulk harvest or at each drug substance/final lot, when applicable. For example, replication-competent virus testing is typically performed at unprocessed bulk harvest to ensure detectability or drug substance step for Adeno-Associated Virus (AAV) based products indicated as (+) in the table.*"

ICH Q5A (R2) update (3)

Company position on testing AdVac batches for RCV:

Advances in genetic engineering allow design of adenovirus vectors with greatly reduced risk of homologous recombination / RCV in comparison with first generation vectors.

The RCV risk for Janssen AdVac vectors manufactured using PER.C6 cells is considered negligible based the following prior knowledge:

- No sequence homology between the AdVac vector and the E1 cassette of the PER.C6 ➔ Homologous recombination is not possible.
- Genetic stability studies several passages beyond DP level showed no mutations affecting replication incompetency ➔ Vector is genetically stable.
- Historical testing data: To date more than 200 RCV tests (different AdVac vectors) ➔ no RCV has been detected.
- **Conclusion**:

<u>The RCV test for routine release of AdVac batches can be limited.</u>

ICH Q5A (R2) update (4)

Proposed changes shown in red are relevant for well-characterized viral-vectored vaccines:

Test	MCB, WCB, Cells at the LIVCA	Virus Seed [k]	Unprocessed Bulk (Harvest)	Drug Substance
[g]replication competent viruses	+[l]	+	(+)[l]	(+)[l]

" [g] Replication Competent Virus (RCV), depending on vector design, may develop at any step during manufacturing (e.g., at initial transfection or transduction steps and through production). Current recommendations include testing for RCV at multiple stages of manufacture to detect for recombination or for the vector virus to revert to parental or wild type phenotype. RCV testing may not be required on each unprocessed bulk harvest or at each drug substance/final lot based on a risk assessment. The manufacturing stages and test methods are when applicable and product dependent. For example, RCV testing is performed on cells and supernatant derived from the stably-transfected vector producer or packaging MCB and LIVCA and during the qualification of the virus seed or cell bank. Tests for RCV apply during production, with testing performed on vector producing cells and supernatant from each unprocessed bulk harvest or at each drug substance/final lot, when applicable. For example, replication-competent virus testing is typically performed at unprocessed bulk harvest to ensure detectability or drug substance step for Adeno-Associated Virus (AAV) based products indicated as (+) in the table."

" [l] testing based on a risk assessment"

Summary

- Adenovirus-vectored vaccines can be considered well established vaccines as they have no record of viral contamination or replication competent adenovirus.
- By allowing the use of prior knowledge to claim viral clearance, the expansion of the scope of ICH 5A (R2) to include viral vector products explicitly acknowledges that established manufacturing platforms are inherently safe.
- Prior knowledge may replace product-specific studies for viral clearance claims if the overall viral safety control strategy is deemed acceptable.
  - What are the minimum requirements for acceptability of prior knowledge?
  - Will the results of the case-by-case assessments be aligned across regions?
- Testing for RCV during routine manufacturing is not necessary when negligible risk has been demonstrated.

Thank you

Gilles Chénard MSc
Viral and Microbial Safety
Analytical Development
Janssen Vaccines & Prevention B.V.
Leiden, The Netherlands

gchenard@its.jnj.com
December 6, 2022

Melinda, *Tree of Life*
Melinda's artwork reflects
her journey living with HIV.

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson