cytiva

Adenovirus Vector Vaccine Production for Pandemic use

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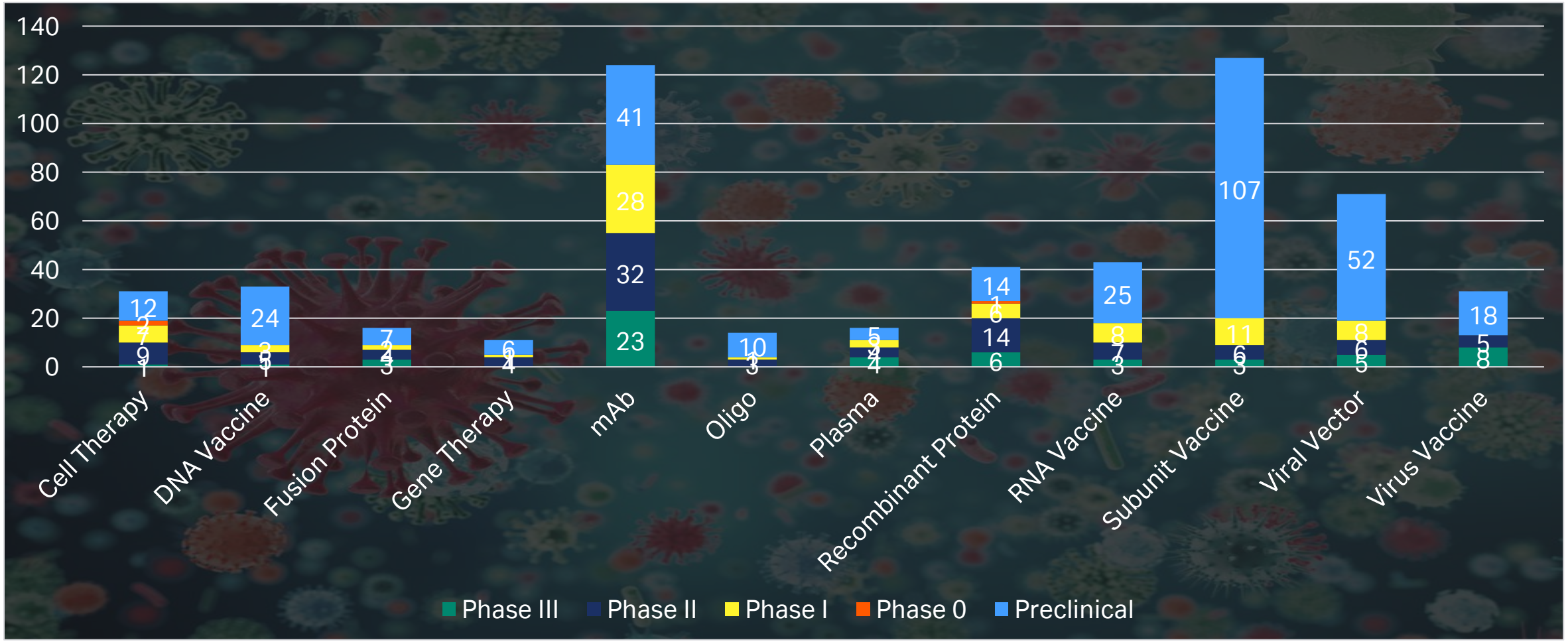
Content

- Introduction – Adenoviral vector vaccines
- Virus titer assay development
- Upstream cell culture and virus propagation
- Downstream purification
- Characterization
- Biomanufacturing options
- Conclusions

Introduction – Adenoviral vector vaccines

COVID-19 Clinical Activity

Molecule Types by Phase



Source: https://pharma.globaldata.com/sector/overview/802954

8Dec2020

Vaccine technologies – COVID-19 examples

Type	Mechanism	Examples	Expression system	Facility Biosafety level
m-RNA	• Lipid nanoparticle encapsulated m-RNA	BioNTech/Pfizer, Moderna, Curevac	Bacterial + Synthetic	1
Viral vector	• Adenoviral vector	AstraZeneca, Janssen (J&J), CanSino, Gamaleya	Mammalian	2
Inactivated virus	• Wildtype virus	Sinovac, Valneva	Mammalian	3
Recombinant protein +/- adjuvants	• S protein • VLP etc	Novavax, Sanofi Pasteur/GSK	Mammalian/Insect	1

Adenoviral vector vaccines

- Opportunities
  - Platform technology
  - Broad immune response
  - Scalable production process
  - Product relatively stable (compared to m-RNA)

- Challenges
  - Pre-existing immunity against some serotypes
  - Repeated vaccination can be less effective due to immunity against vectors

Sizes of common viruses

Antibody

~ 5 nm

Preventive vaccines

JE (40–60 nm)

Yellow Fever (40–60 nm)

HAV (30 nm)

VLP (40–60 nm)

Polio (30 nm)

Hep B (42 nm)

Rota (80 nm)

Flu (90–120 nm)

Corona (125 nm)

Mumps (200 nm)

Measles (100 × 300 nm)

Rabies (75 × 180 nm)

Recombinant virus vectors for cell and gene therapy

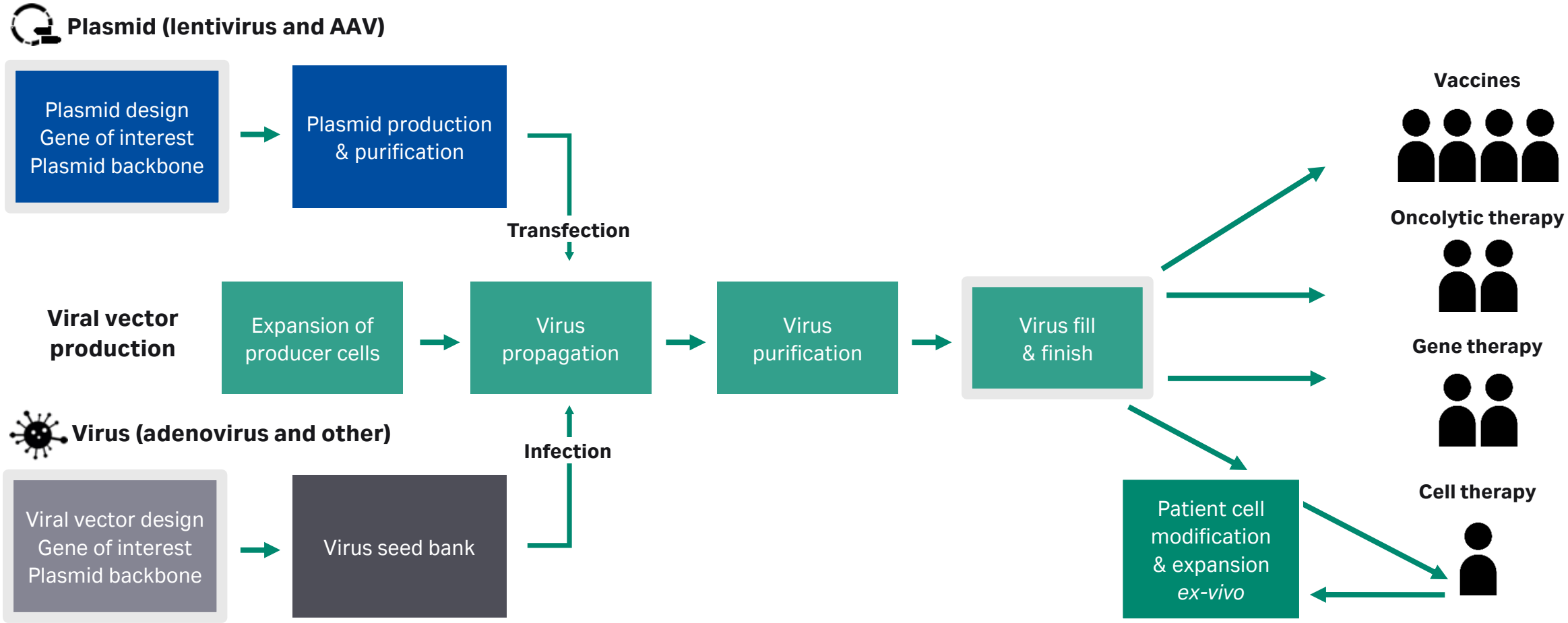
AAV (25 nm)

Lenti (80–120)

Adeno (70–90 nm)

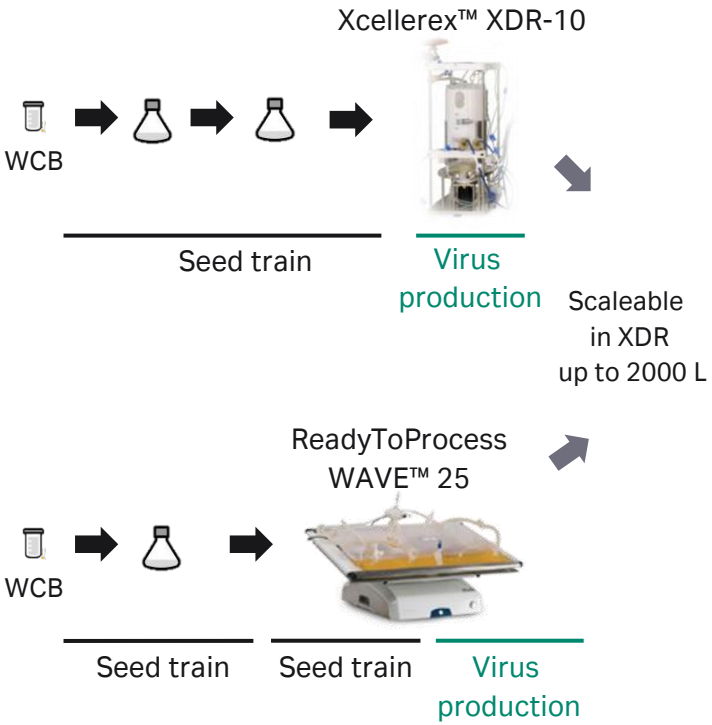
Pox (200 × 300 nm)

Viral vector production and clinical use



Adenovirus process

Upstream



Downstream

- **Cell lysis DNA fragmentation**
- **Clarification**
- **Conc. and buffer exchange**
- **Capture**
- **Polishing**
- **Conc. and buffer exchange**
- **Sterile filtration**

Analysis

Virus infectivity
% infected cells: flow cytometry

Virus infectious titer
$TCID_{50}$
Automated fluoresence microscopy
IN Cell

Total virus titer
qPCR
Biacore™ system
HPLC

Host cell
DNA: qPCR
Protein: ELISA

Characterization
SDS-PAGE, Western blotting, TEM, Nanosight™, HPLC

WCB = working cell bank
$TCID_{50}$ = 50% tissue culture infective dose

Virus titer assay development

Analytics: Critical for success and time consuming

Analytical methods

Virus titer

qPCR, HPLC, ELISA, NTA

Biacore™ assay/SPR

$TCID_{50}$, IN Cell assay/Microscopy

Impurities

Total DNA — *PicoGreen™ assay,* host cell DNA — *qPCR*

Total protein — *BCA assay,* host cell protein — *ELISA*

Process related (Benzonase™, detergent) — *ELISA, HPLC, LC-MS*

Characterization

Size, shape and purity — Electron microscopy

Viral proteins and impurities — SDS-PAGE, Western blot

Size, titer and aggregation — NTA

NTA = Nano tracking analysis
SPR= Surface plasmon resonance

Challenges

- Free viral protein and viral DNA may affect assays
- Detergents or buffer components may affect assays
- Accuracy may depend on sample impurity level
- Assay variation

Adenovirus infectious virus titer determination

$TCID_{50}$

Time for assay 8–11 days

Cytopathic effect

Manual determination — time consuming

Operator dependent — high variability

Require more replicates due to variability

Automated fluorescence microscopy (IN Cell Analyzer)

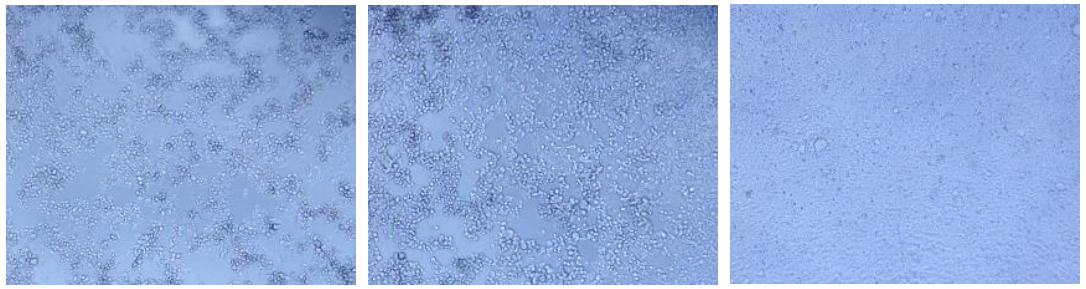
Time for assay 3 days

Viral antigen staining/GFP expression

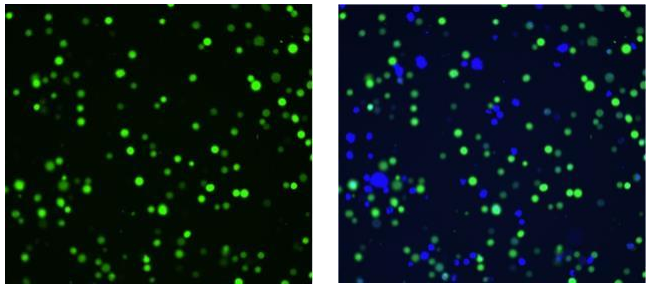
Automated counting — fast

Operator independent — low variability

Require reagents and equipment



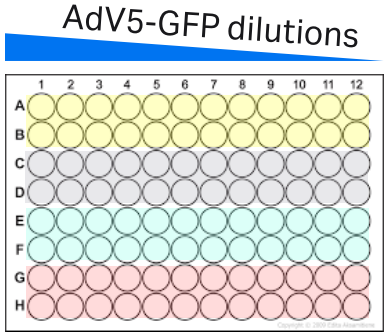
$1:10^5$ **$1:10^9$** **$1:10^{12}$**



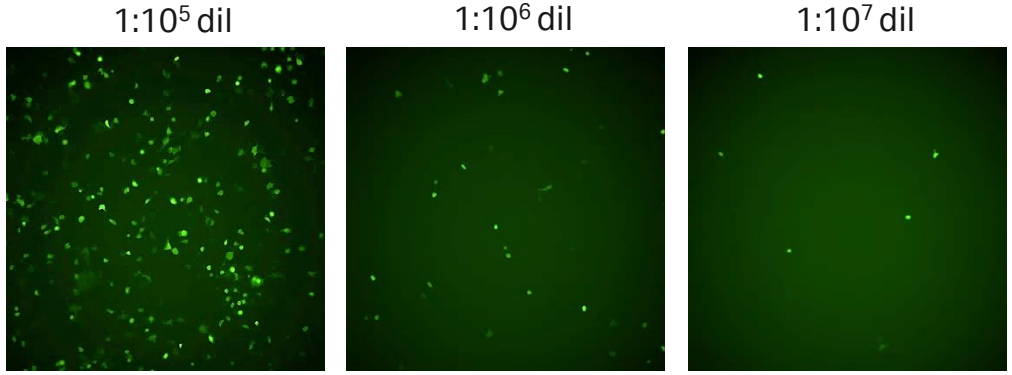
GFP **GFP/Nucleus**

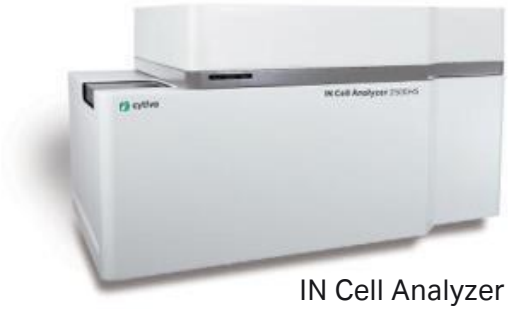
$TCID_{50}$ = tissue culture infectious dose
GFP = green fluorescent protein

Adenovirus infectious virus titer with IN Cell Analyzer



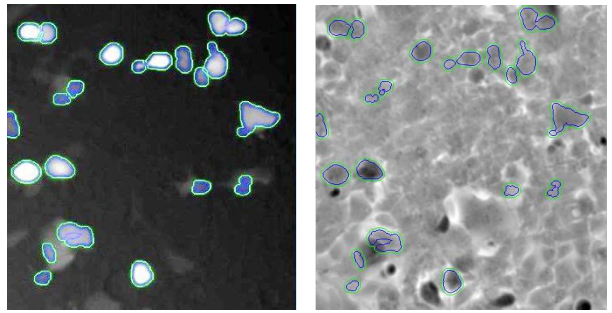
42 hrs





IN Cell Analyzer

Automated counting of GFP foci



GFP Brightfield

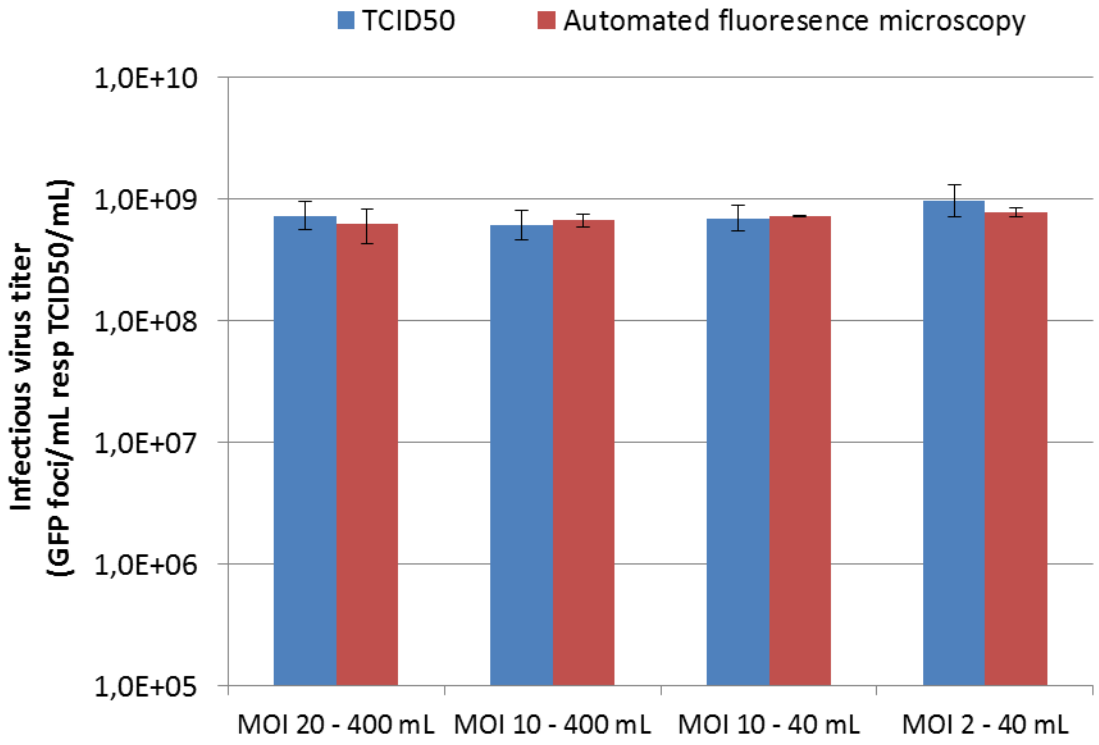
Infectious virus titer (iVP/mL)

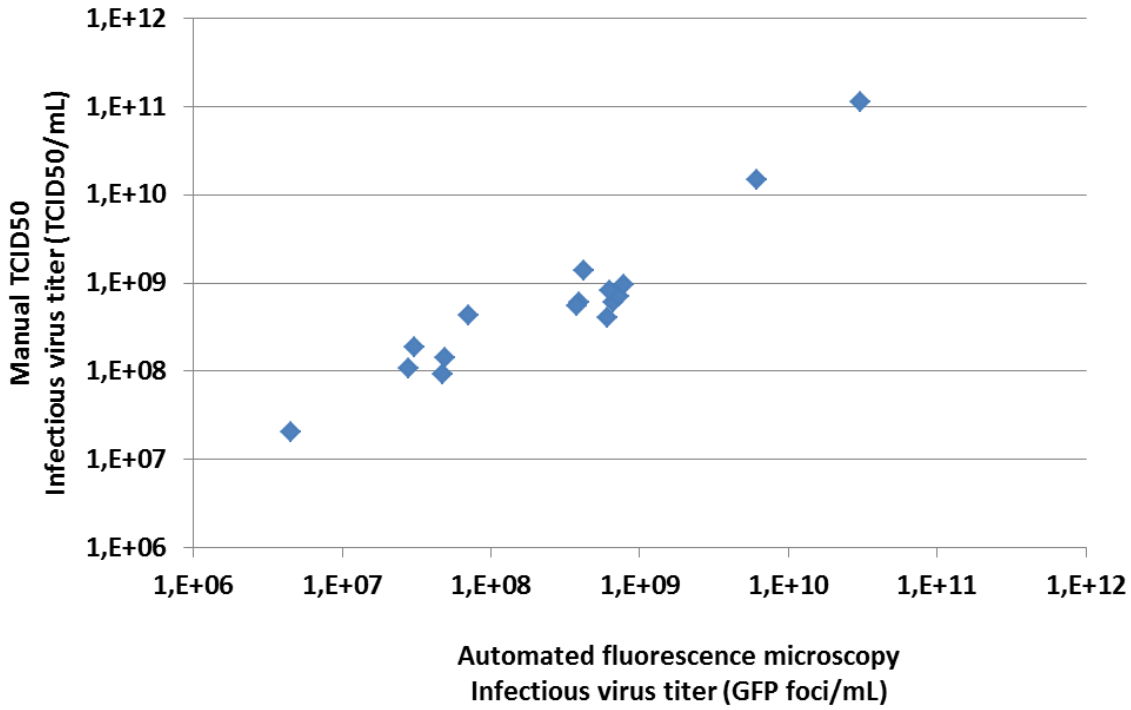
Automated fluorescence microscopy:

- Similar setup as $TCID_{50}$
- Cells in 96-well plate
- Serial dilution of virus
- Require fewer replicates

AdV5 = adenovirus serotype 5
GFP = green fluorescent protein
TCID = tissue culture infectious dose
iVP = infectious virus particles

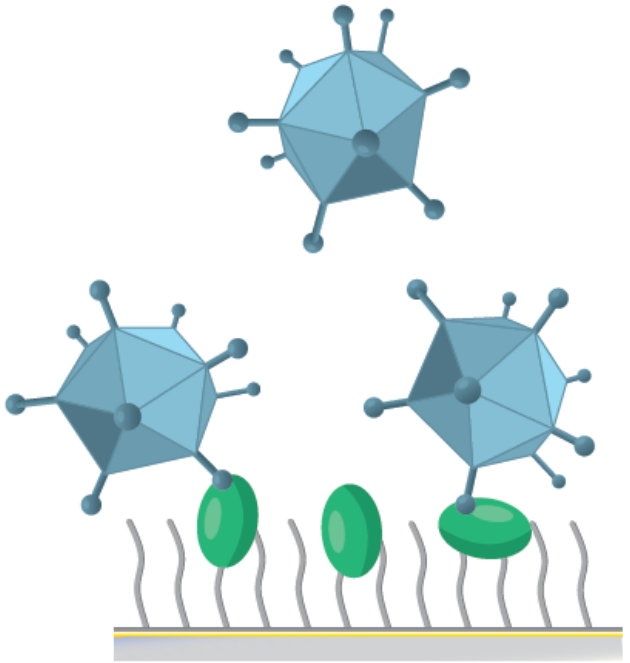
Good correlation between $TCID_{50}$ and automated fluoresence microscopy





$TCID_{50}$ = tissue culture infectious dose
GFP = green fluorescent protein
MOI = multiplicity of infection

Adenovirus titer with Biacore T200 assays

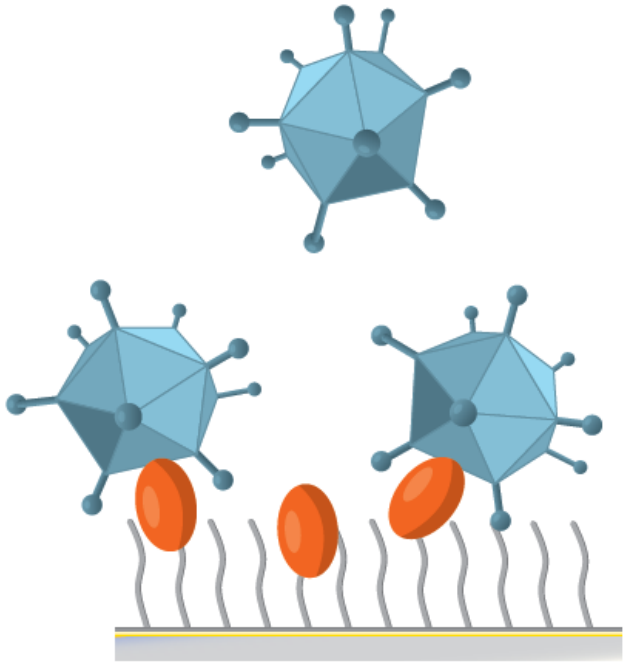


Adenovirus

CAR, adeonovirus receptor

CM5 Sensor chip

Coxsackie adenovirus receptor (CAR)



Adenovirus

FX

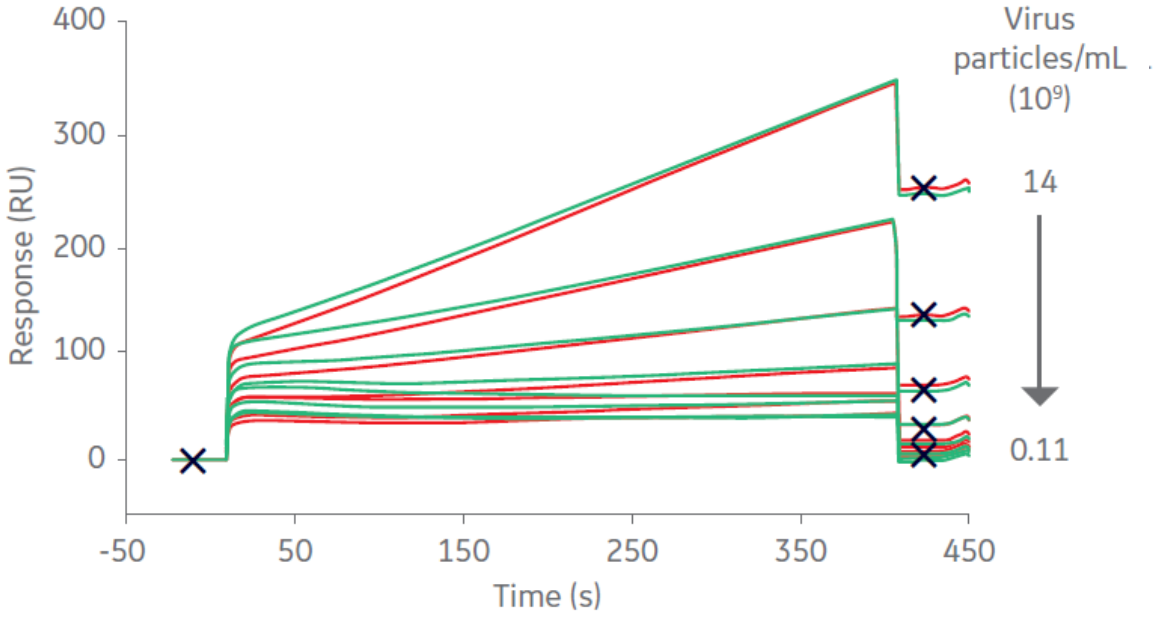
CM5 Sensor chip

Factor X (FX)

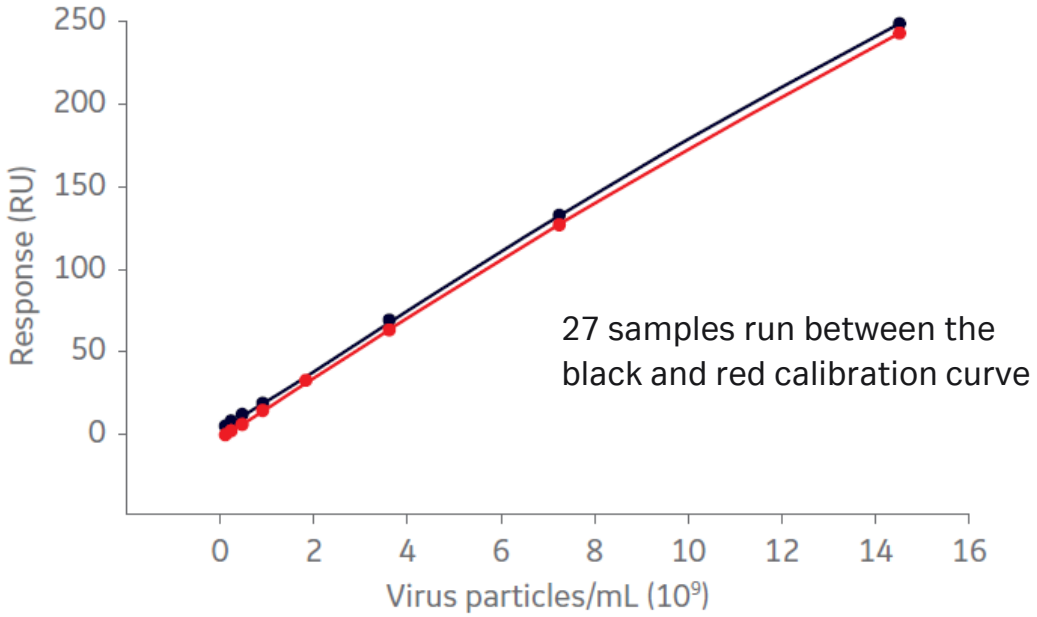
Biacore T200 assay for sensitive and reproducible virus titer determination

Coxsackie adenovirus receptor (CAR) assay

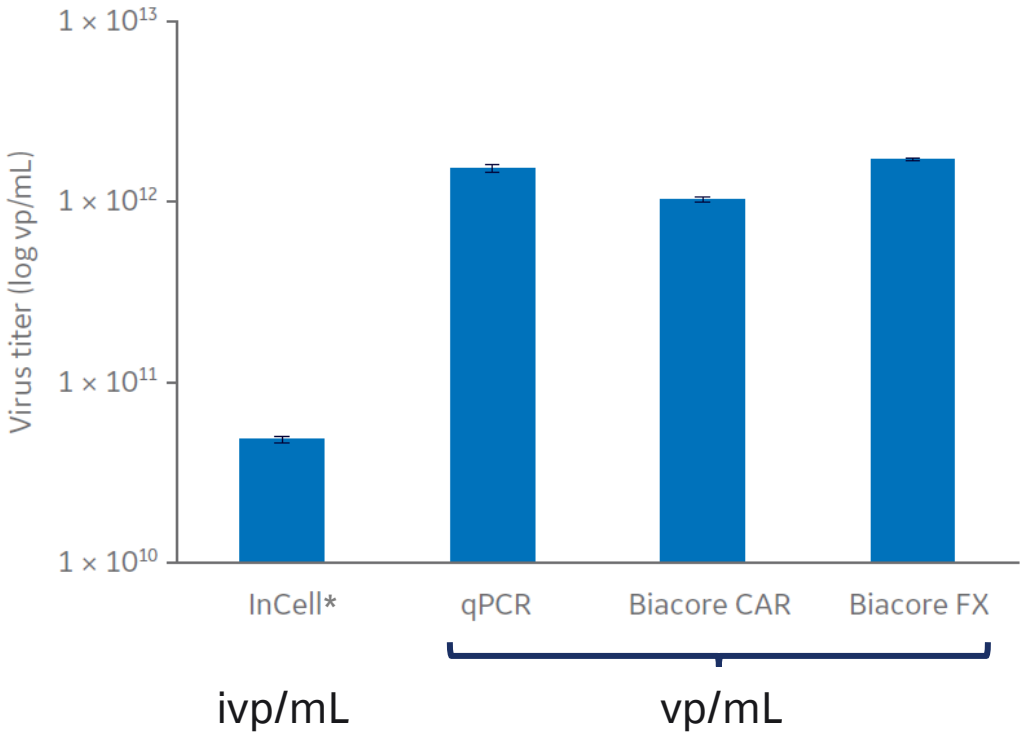
Response curves



Calibration curve



Biacore T200 Adenovirus titer results are comparable to qPCR



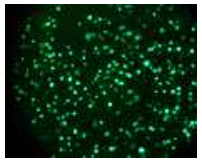
- Convenient assay
- Reproducible, CV < 5%
- Sensitive, sample dilutions (100 to 200-fold) reduce effect of buffer components
- Immobilized surface stable for at least one week

* Infections virus titer (ivp/mL) is expected to be lower than total virus titer (vp/mL).
Regulatory requirements for the ratio of total to infections virus particles is < 30 (FDA).

Upstream cell culture and virus propagation

Small scale productivity optimization strategy

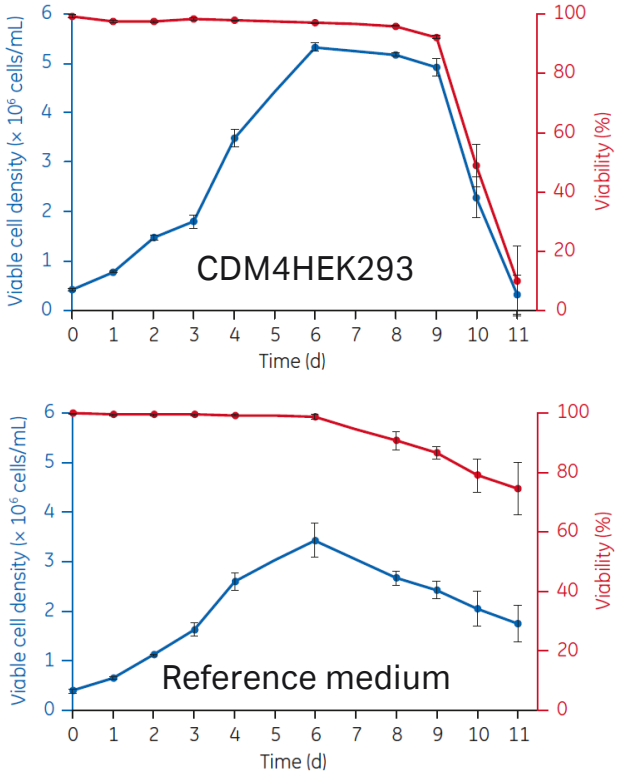
Recombinant adenovirus serotype 5 — GFP used as model virus propagated in HEK293 suspension cells
Screening of cell culture media
Optimization of MOI, TOI and TOH

Cell culture	Virus infection	Virus propagation	Virus productivity analysis
0 hr	~ 72 hr	~ 120 hr	
 Shake flasks (30–100 mL)	 GFP expression as % infected cells	Cell lysis/ virus release	**Infectious virus titer ivp/mL**
Cell culture medium evaluation **Cell density optimization 0.5–2 × 10^6 cells/mL at TOI**	**Optimization of MOI 0.01–10** **Medium exchange evaluation**	**Optimization TOH 36–72 h**	

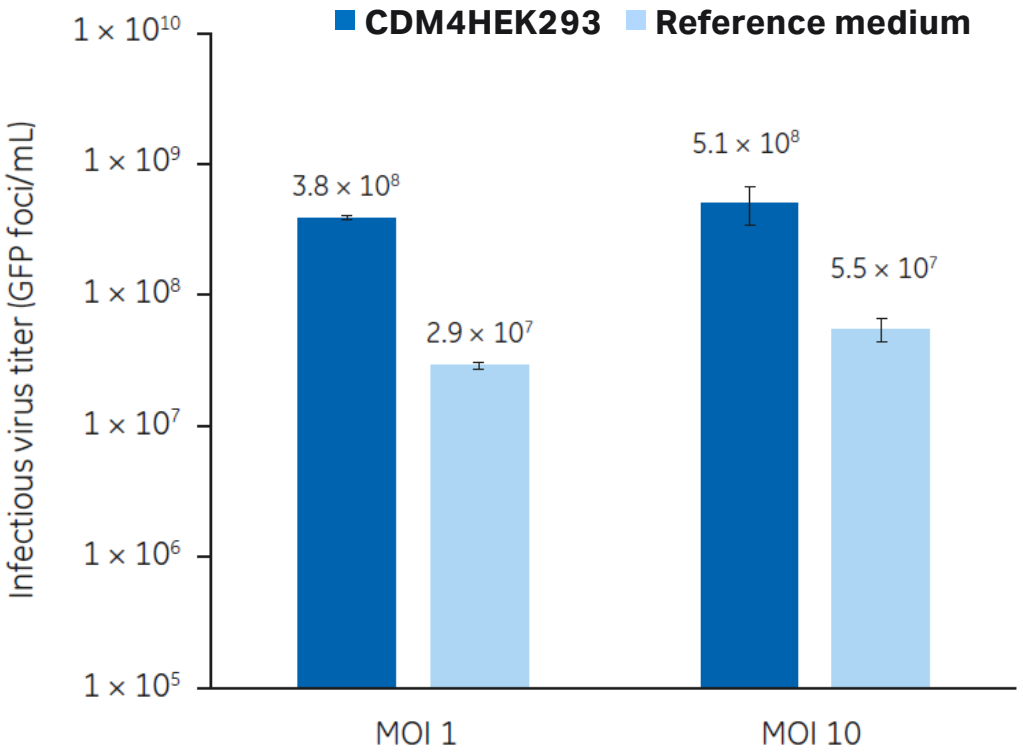
GFP = Green Fluorescent Protein
MOI = multiplicity of infection
TOI = time of infection
TOH = time of harvest
ivp = Infectious virus particle

HyClone CDM4 HEK293 cell culture medium was selected

Improved HEK293 cell growth



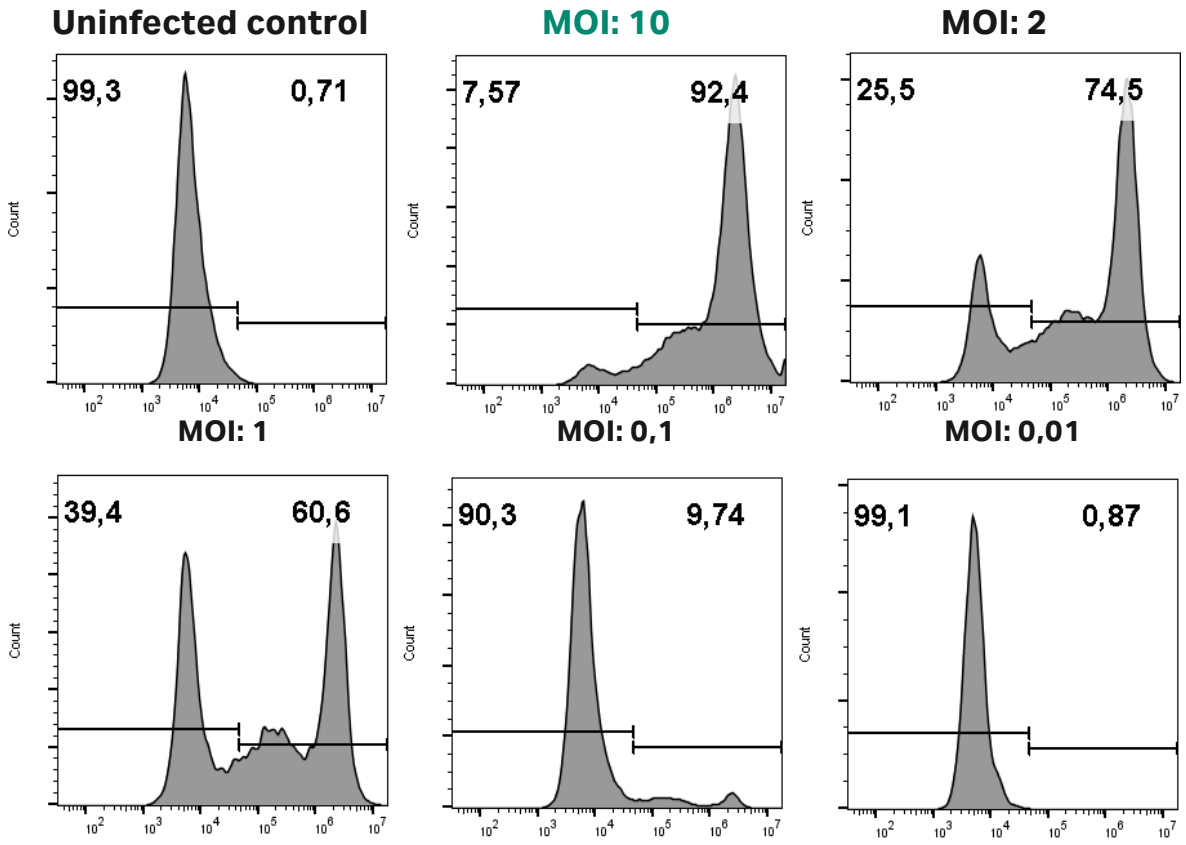
Higher infectious virus titer



GFP = Green Fluorescent Protein
MOI = multiplicity of infection

Adenovirus infectivity at varying multiplicity of infection

Multiplicity of infection (MOI) of 10 gives highest number of infected cells.

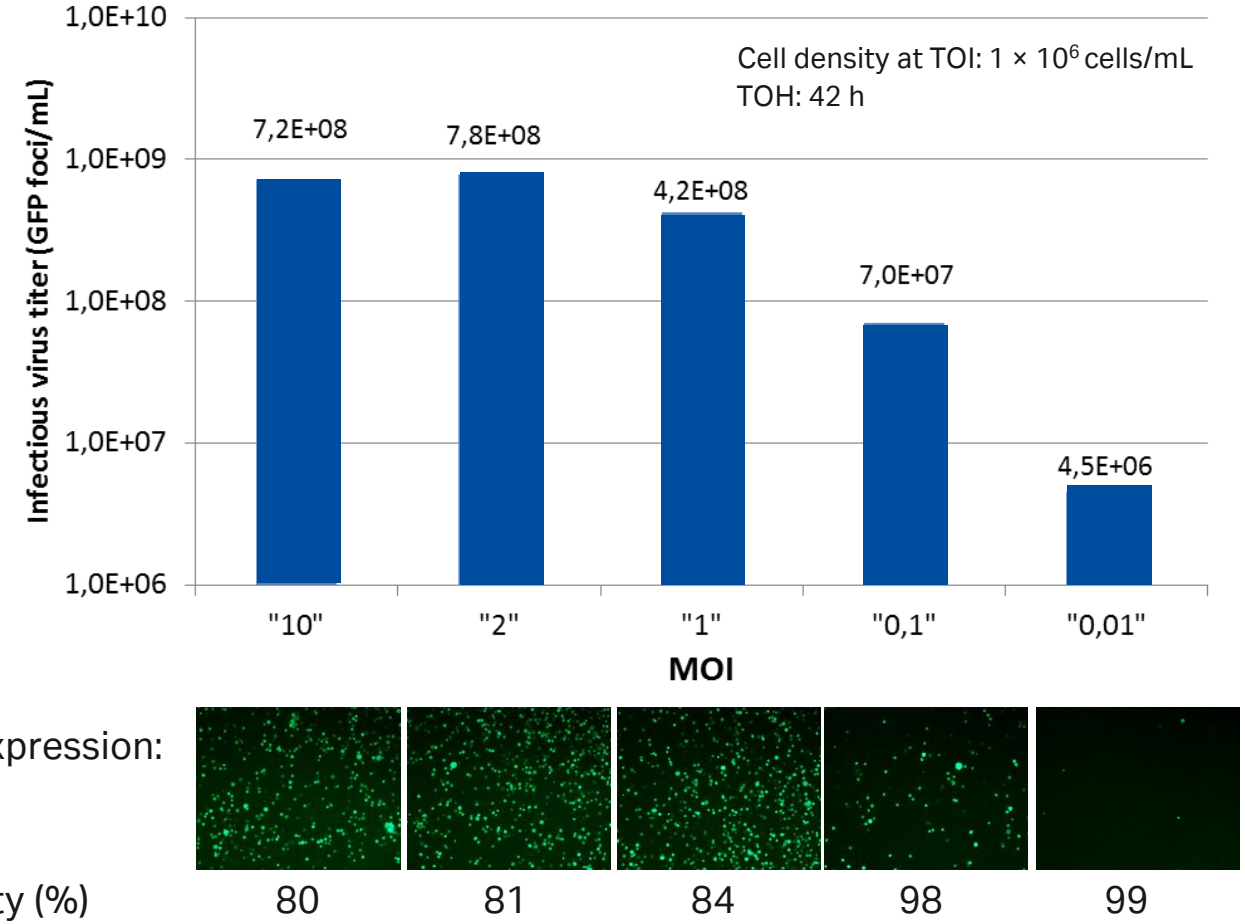


Percentage infected cells 24 h post infection (assayed by flow cytometry)

Infectious virus titer assayed in harvest material

Adenovirus titer assayed with automated fluorescence microscopy (IN Cell Analyzer)

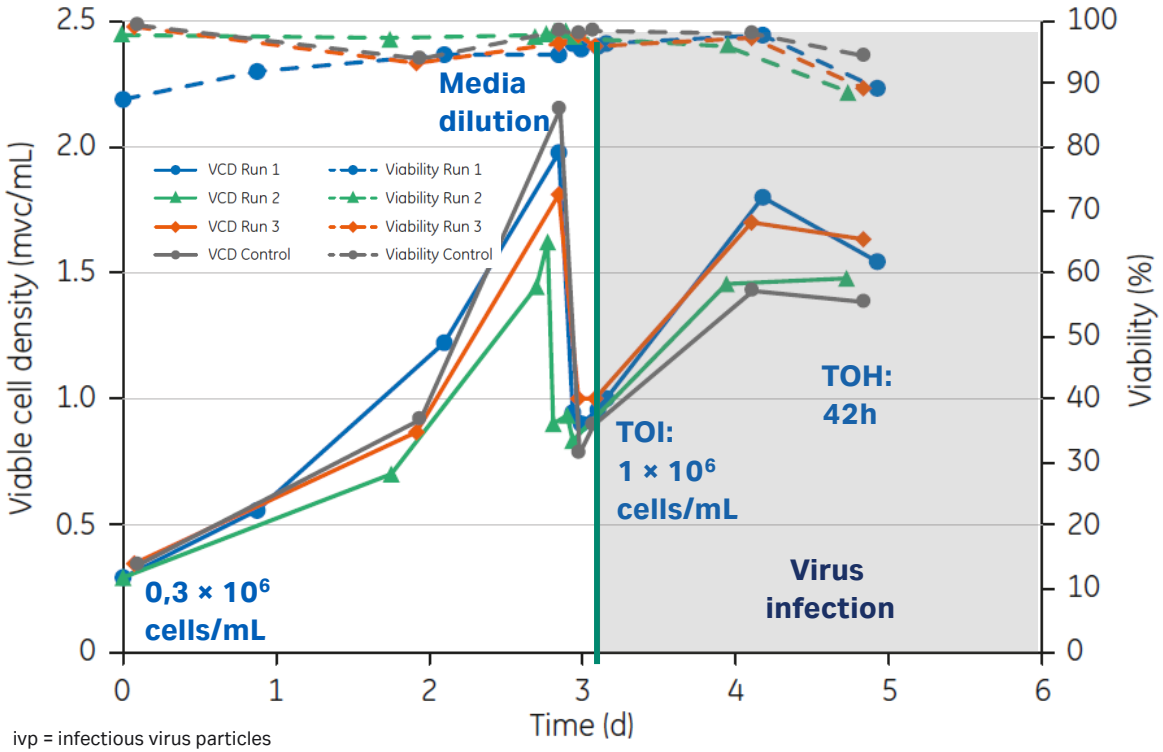
Highest productivity at multiplicity of infection (MOI) 2–10



TOI = time of infection
TOH = time of harvest
GFP = green fluorescent protein

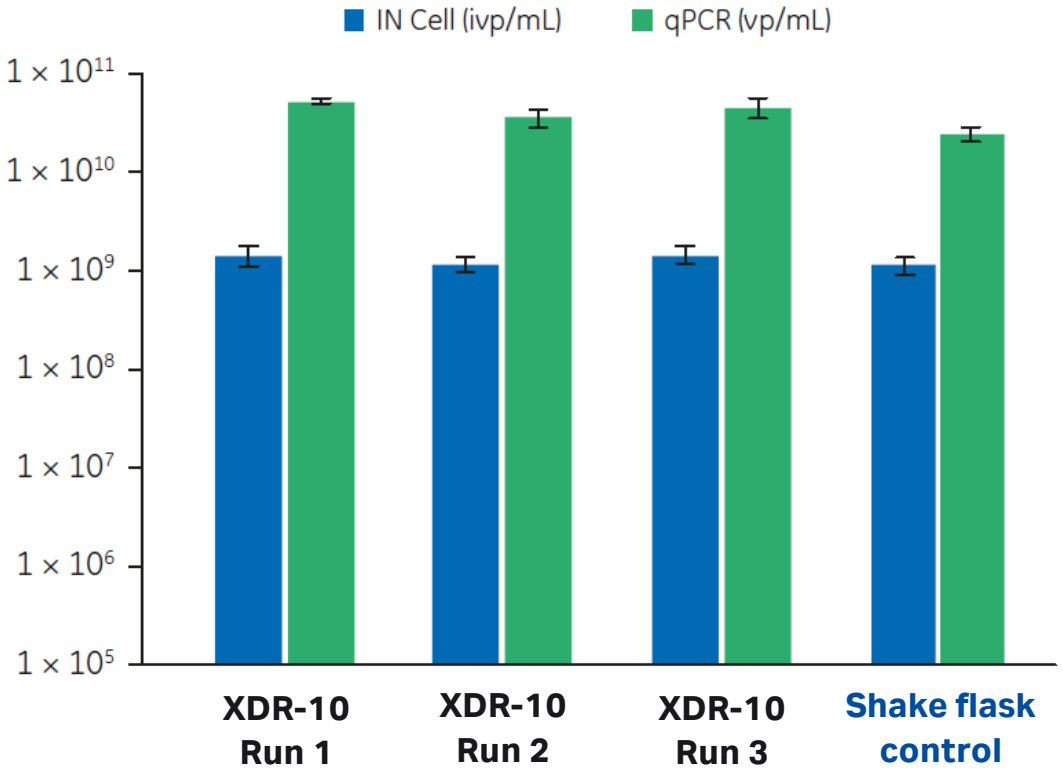
Reproducible adenovirus production in Xcellerex XDR-10 bioreactor

Cell growth and viability



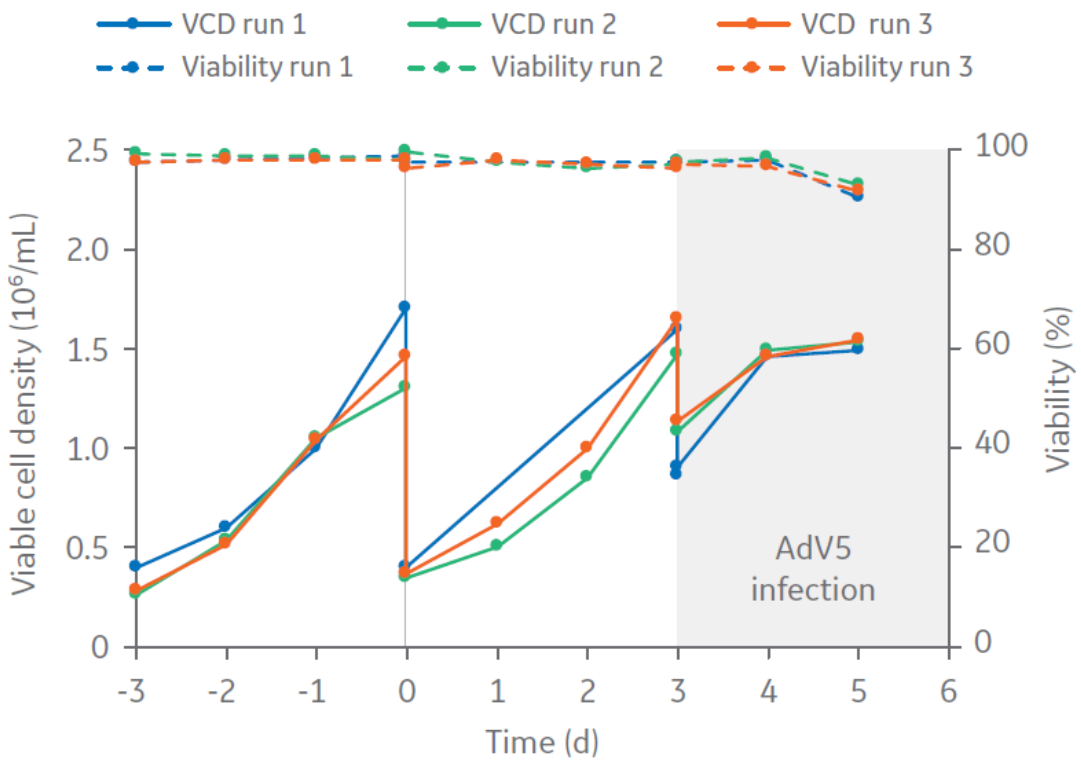
ivp = infectious virus particles
TOI = time of infection
TOH = time of harvest

Adenovirus productivity in XDR-10

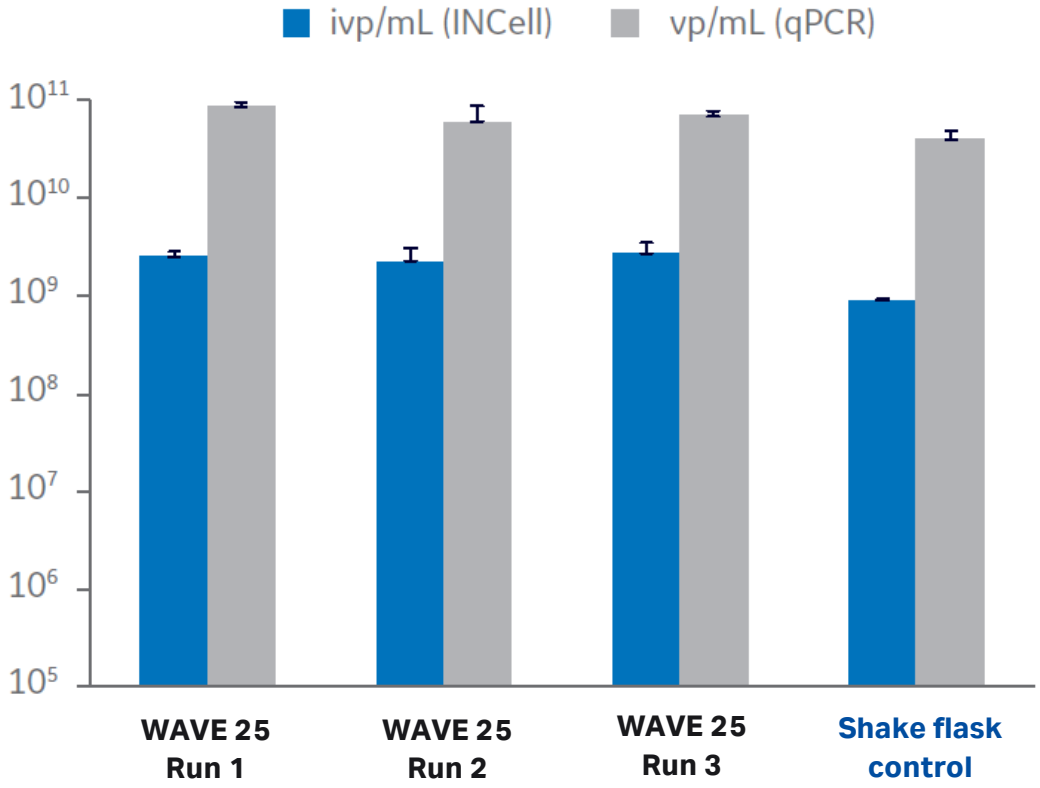


Reproducible adenovirus production in ReadyToProcess WAVE 25 bioreactor

Cell growth and viability



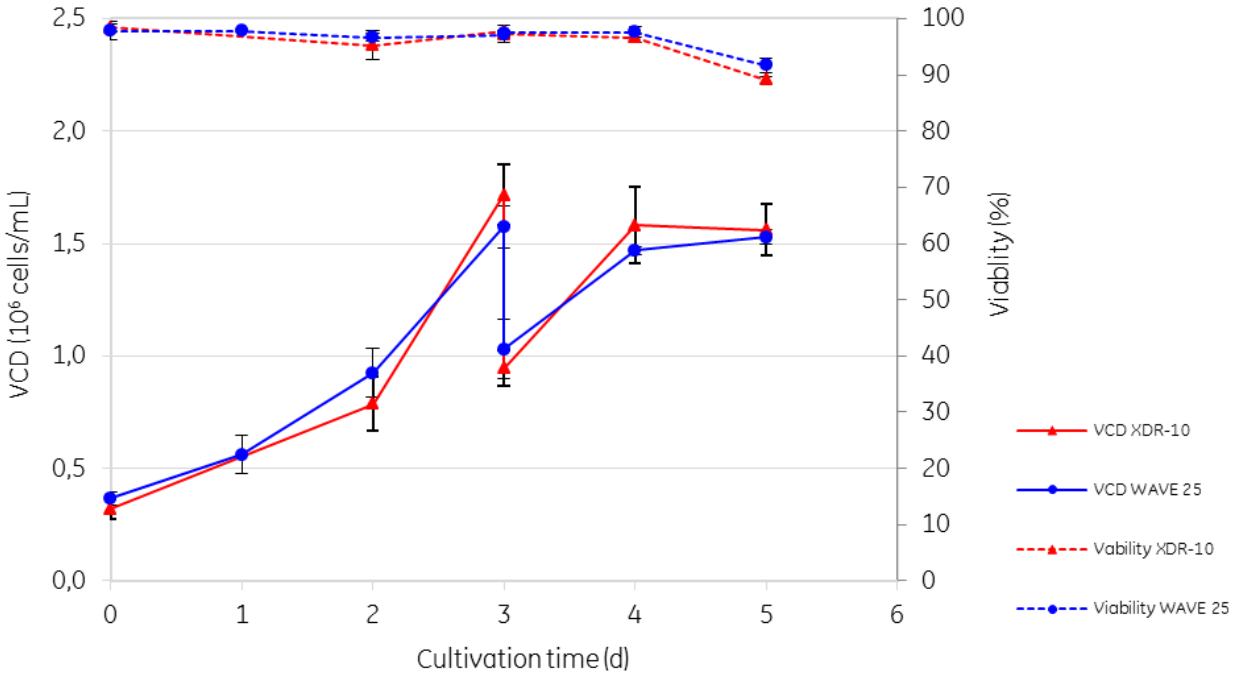
Adenovirus productivity in ReadyToProcess WAVE™ 25



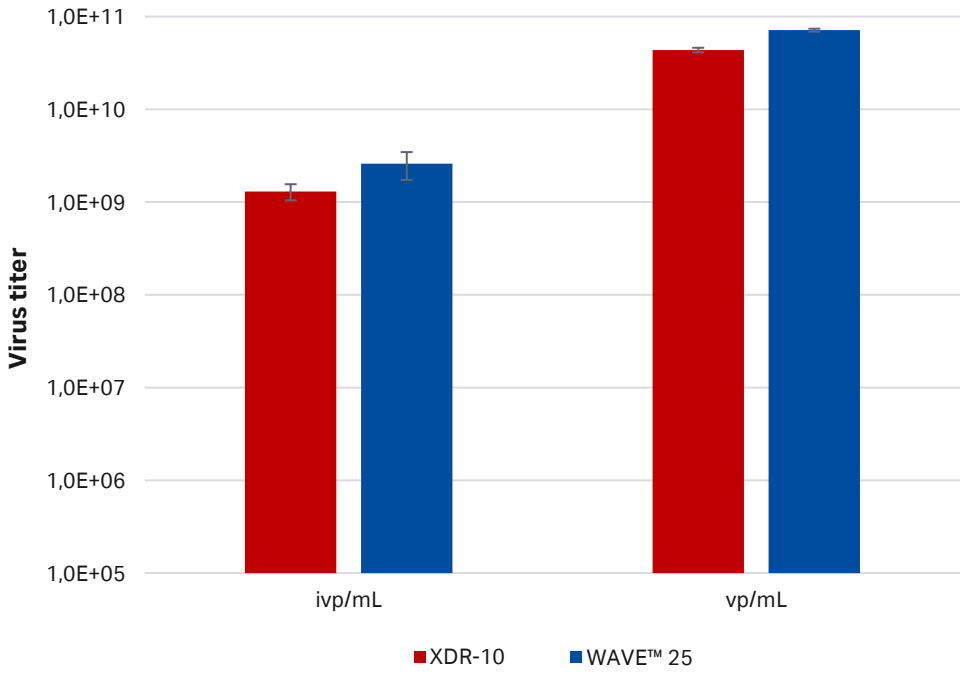
ivp = infectious virus particles, vp = virus particles
VCD = viable cell density

Comparable adenovirus production in ReadyToProcess WAVE 25 bioreactor and Xcellerex XDR-10 bioreactor

Cell growth and viability



Adenovirus productivity, both bioreactor types



ivp = infectious virus particles, vp = virus particles
VCD = viable cell density

Downstream purification

Evaluation and optimization of each step in small scale

Downstream

- **Cell lysis**
  DNA fragmentation
- **Clarification**
- **Conc. and buffer exchange**
- **Capture**
- **Polishing**
- **Conc. and buffer exchange**
- **Sterile filtration**

Harvest: Need of a lysis detergent to replace Triton X-100

Downstream

Cell lysis
DNA fragmentation

Clarification

Conc. and buffer exchange

Capture

Polishing

Conc. and buffer exchange

Sterile filtration

Screening of alternative lysis detergents compliant with environment and health regulations (REACH)

Detergent	Properties	REACH status	
Brij™-35	Non-ionic	✗	
CHAPS	Zwitterionic	✓	
IGEPAL™ CA630 (Nonident NP-40)	Non-ionic	✗	
Octyl glycoside	Non-ionic	✓	
Sodium deoxycholate	Ionic(-)	✓	
Tergitol™ NP-40 (INP40)	Non-ionic	✗	
Triton™ X-100	Non-ionic	✗	
Tween™ 20	Non-ionic	✓	←
Tween 80	Non-ionic	✓	←
Zwittergent™ 3-14	Zwitterionic	✓	←

✓ = low risk of being added to authorization list

✗ = high risk for being added to authorization list

✗ = on authorization list

Harvest: Tween 20 is a good alternative to Triton X-100 for lysis

Downstream

Cell lysis
DNA fragmentation

Clarification

Conc. and buffer exchange

Capture

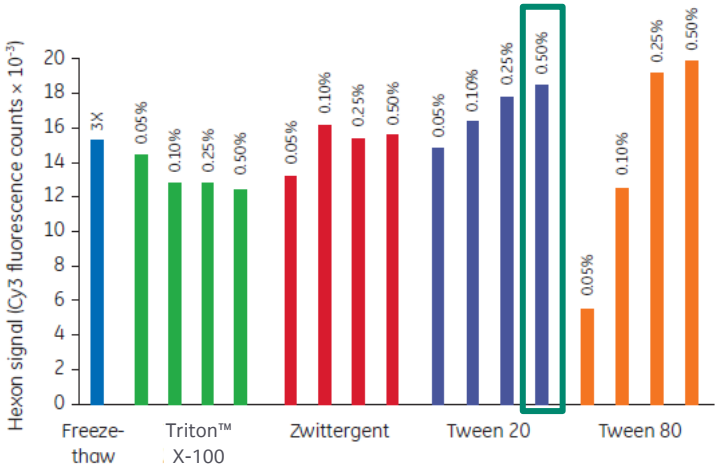
Polishing

Conc. and buffer exchange

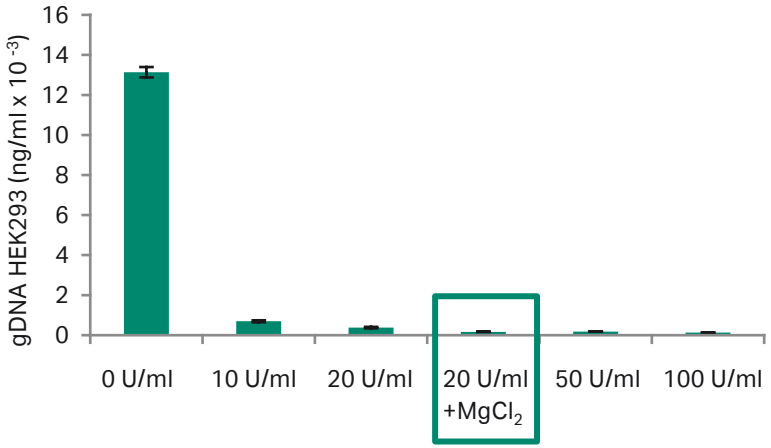
Sterile filtration

LC-MS = Liquid chromatography – Mass spectrometry

Released viral protein
Detergent conc. 0.05-0.5%, 1 h



DNA fragmentation, Benzonase 4h



Outcome:

- 0.5% Tween™ 20 + 20U/mL Benzonase™ and 1 mM $MgCl_2$
- Incubation in bioreactor for 4 hours at 37˚C with mixing
- Virus infectivity was not affected
- LC-MS method for residual Tween 20 analysis

Clarification: Evaluation of normal flow filtration

Downstream

- Cell lysis DNA fragmentation
- **Clarification**
- Conc. and buffer exchange
- Capture
- Polishing
- Conc. and buffer exchange
- Sterile filtration

GF = Glass fiber

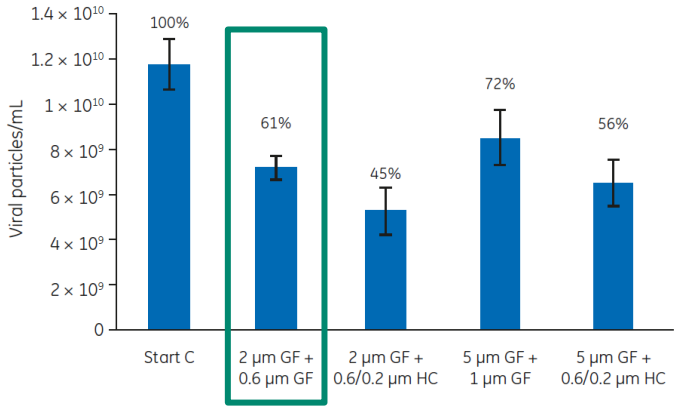
Filter evaluation using ø 47 mm filter discs with different pore sizes

Impurity removal and capacity

Filter train	Total protein reduction (%)	gDNA reduction (%)	Capacity 2nd filter (L/m^2)
2 µm GF + 0.6 µm GF	37	88	> 77*
2 µm GF + 0.6/0.2 µm HC	42	98	95
5 µm GF + 1 µm GF	30	85	> 60*
5 µm GF + 0.6/0.2 µm HC	38	97	62

* Feed volume was consumed over second filtration step, but the pressure was stable at 0.5 bar at the end of the filtration.

Virus titer recovery (qPCR)



Outcome:

- 2 µm + 0.6 µm GF filter
- Selection based on the overall results for capacity, impurity removal, virus recovery, and turbidity level

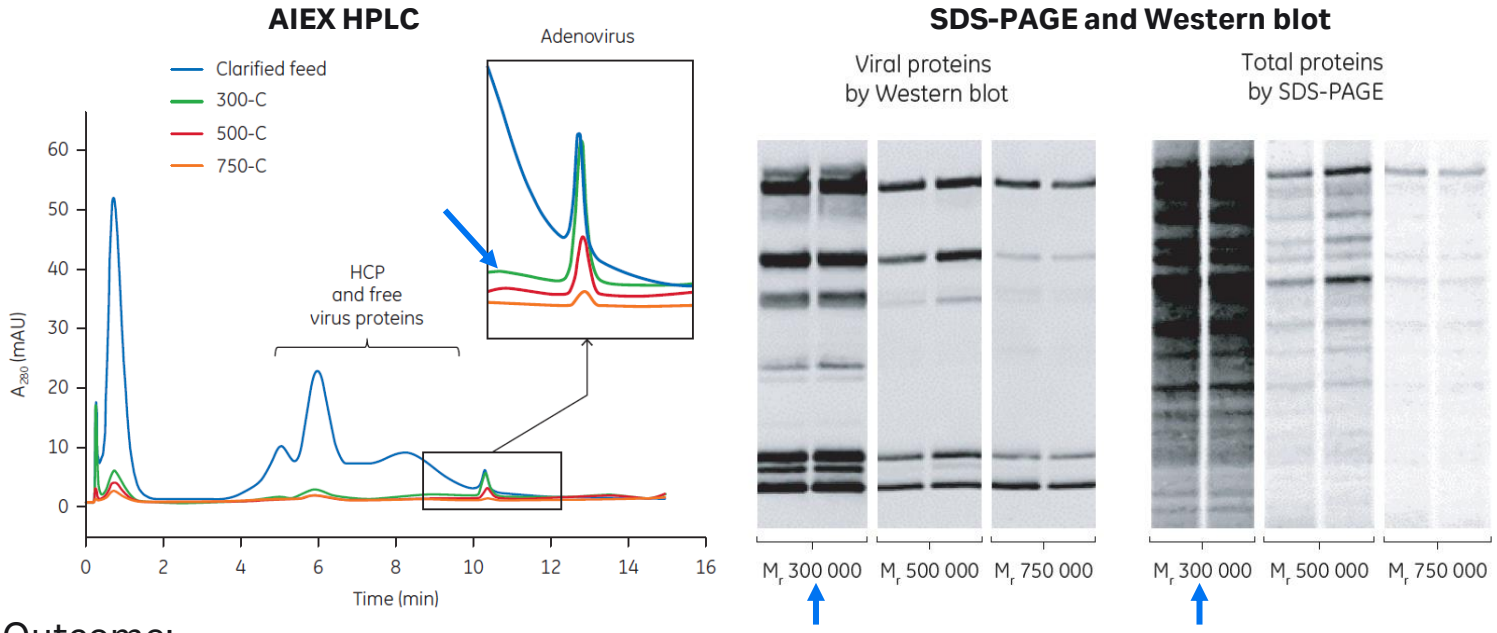
Concentration and buffer exchange: Tangential flow filtration

Downstream

- Cell lysis
  DNA fragmentation
- Clarification
- **Conc. and buffer exchange**
- Capture
- Polishing
- Conc. and buffer exchange
- Sterile filtration

UF= Ultrafiltration
DF= Diafiltration
AIEX = Anion exchange chromatography

Analysis of retentate



Outcome:

- 300-C hollow fiber
- 10X UF/5X DF, 20 mM Tris, 300 mM NaCl, pH 8. Shear rate 3000 s^{-1}
- Highest virus recovery and absence of virus in permeate

Concentration and buffer exchange: Tangential flow filtration

Downstream

- Cell lysis DNA fragmentation
- Clarification
- **Conc. and buffer exchange**
- Capture
- Polishing
- Conc. and buffer exchange
- Sterile filtration

	300-C	500-C	750-C
Protein removal %	73	92	100
Total DNA removal %	53	91	95
Recovery % based on virus infectivity (ivp/mL)	55	25	9

- Highest virus recovery with 300 C filter
- Recovery low likely due to low sample volume relative to filter area
- Improved recovery in larger scale (vp: 92 % and ivp: 100 %)
- Improved impurity removal in larger scale (total protein and DNA 80 %)

vp = virus particles
ivp = infectious virus particles

Capture: Screening for highest dynamic binding capacity

Downstream

- Cell lysis
  DNA fragmentation
- Clarification
- Conc. and buffer exchange
- **Capture**
- Polishing
- Conc. and buffer exchange
- Sterile filtration

1 mL HiTrap™ columns:

Capto™ Q

Capto Q ImpRes

Capto adhere

Capto adhere ImpRes

Capto DEAE

Q Sepharose™ Fast Flow

Q Sepharose XL

DEAE Sepharose Fast Flow

ANX Sepharose fast Flow

ReadyToProcess™ Adsorber Q nano, 1 mL

Outcome:

- High-throughput plate format screening not compatible with analytics
- Capto Q ImpRes with smaller bead size and ReadyToProcess™ Adsorber Q membrane showed highest capacity for virus

Capture: Optimization of elution conditions

Downstream

- Cell lysis DNA fragmentation
- Clarification
- Conc. and buffer exchange
- **Capture**
- Polishing
- Conc. and buffer exchange
- Sterile filtration

HCP = host cell protein

Step or gradient elution

Capto™ Q ImpRes with gradient elution

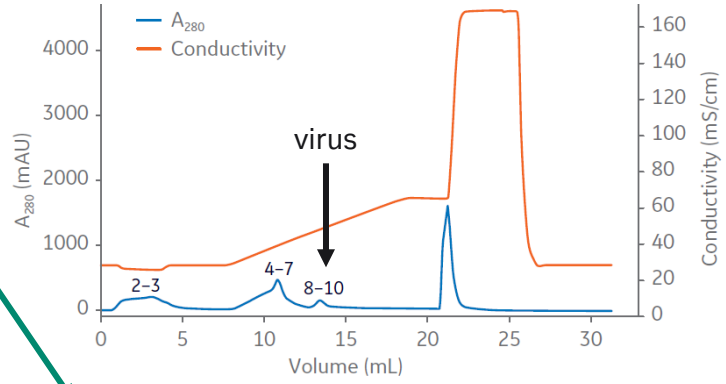
20 mM Tris pH 8, 300–700 mM NaCl

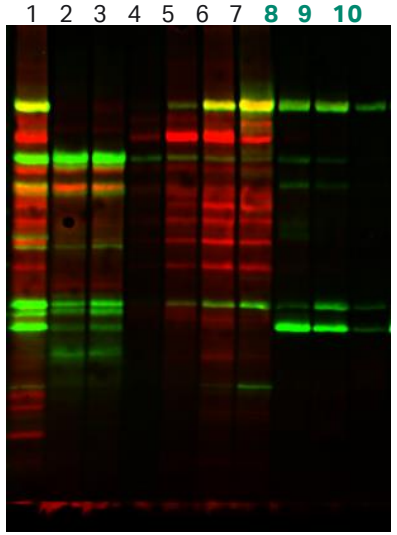
- Highly efficient HCP removal
- Gradient elution improved DNA reduction

ReadyToProcess™ Adsorber Q with step elution

20 mM Tris pH 8, 720 mM NaCl

- Gradient elution not an option, no resolution between virus and impurities





1: start material
2: flowthrough
3: wash
4 to 7: first elution peak (HCP)
8 to 10: elution peak (virus)

Red = HCP
Green = viral proteins

Polishing: Comparing size exclusion and Capto Core 700

Downstream

- Cell lysis DNA fragmentation
- Clarification
- Conc. and buffer exchange
- Capture
- **Polishing**
- Conc. and buffer exchange
- Sterile filtration

Evaluation of capture and polishing combinations, 1 mL HiTrap™ columns

Capture	Polishing	Load	Recovery of total virus particles (%)*	Total protein (µg/dose)	Total DNA (ng/dose)	hcDNA (ng/dose)
Capto™ Q ImpRes	Sepharose™ 4 Fast Flow	0.1 CV	39/57	< LOD	< LOD	< LOD
	Capto Core 700	26 CV	65/100	< LOD	< LOD	< LOD

** Two numbers indicates that the same sample was analyzed twice.*

Outcome:

- Similar impurity removal performance
- Capto core enables higher sample load volume capacity (up to 30 CV)
- DNA removal after ReadyToProcess™ Adsorber Q capture (step elution) was less efficient for both SEC and Capto Core (data not shown)

Concentration and formulation: Tangential flow filtration and sterile filtration

Downstream

Cell lysis
DNA fragmentation

Clarification

Conc. and buffer exchange

Capture

Polishing

Conc. and buffer exchange

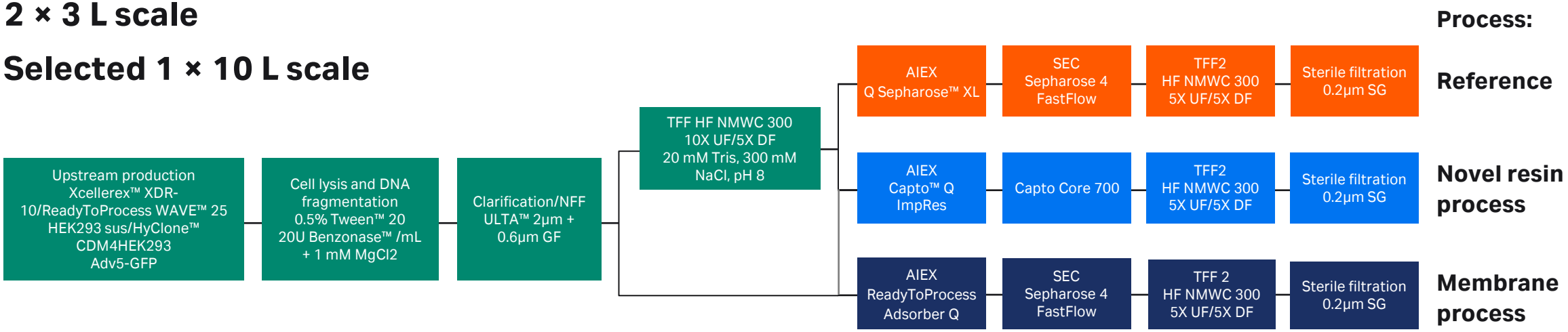
Sterile filtration

- Smaller sample volume require scaled down filter area compared to first tangential flow filtration step
- Same parameters but lower concentration factor
- Buffer exchange by diafiltration into final bulk storage solution: 20 mM Tris™, pH 8, 25 mM NaCl, 2 mM $MgCl_2$ and 2.5 % glycerol
- Sterile filtration using 0.2 µm SG filter (PES-polyethersulphone)

Evaluation of process variants in larger scale

2 × 3 L scale

Selected 1 × 10 L scale



Adv5 = Adenovirus type 5
GFP = Green fluorescent protein
HF = Hollow fiber
TFF = Tangential flow filtration
UF= Ultrafiltration
DF= Diafiltration
AIEX = Anion exchange chromatography
SEC= Size exclusion
SG = Sterile grade

Results for process variants: Analysis of final bulk

Process variant	Recovery vp %	Recovery ivp %	HCP ng/mL	Total protein µg/dose	gDNA ng/dose
Reference process, Run 1	31/38*	36	17	11/13	< LOD
Reference process, Run 2	35/64	53	27	38/20	3
Reference process average	**42**	**45**	**22**	**20**	**< LOD -3**
Novel process, Run 1	46/68	39	< LOD	13/11	< LOD
Novel process, Run 2	17	40	< LOD	10	< LOD
Novel process, Run 3 (10 L)	38/25	50	< LOD	4/10	< LOD
Novel resin process average	**39**	**43**	**< LOD**	**10**	**< LOD**
Membrane process, Run 1	30/44	63	169	30/16	< LOD
Membrane process, Run 2	41/50	28	155	20/3	< LOD
Membrane process average	**41**	**46**	**162**	**17**	**< LOD**

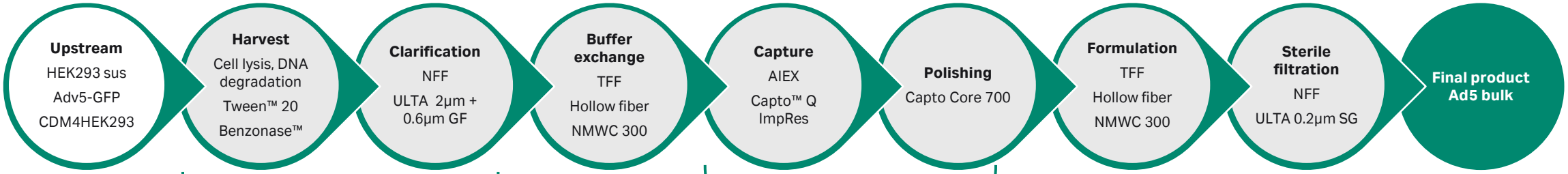
< LOD = below limit of detection
vp = Total virus particles (qPCR)
ivp= Infectious virus particles (IN Cell)
HCP = host cell proteins

* Two numbers indicates that the same sample was analyzed twice

Purity targets

- Dose size assumption: 10^{11} virus particles
- Host cell proteins: < 20 µg/dose
- Host cell genomic DNA: < 10 ng/dose
- Total virus particles/infectious virus particles ratio < 30

Adenovirus process — Cytiva products used in process development



Xcellerex™ XDR-10

ReadyCircuit™

ÄKTA™ flux 6

ÄKTA pure 150

ÄKTA flux s

ULTRA™ SG Filters

Biacore™ T200

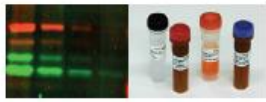
ReadyToProcess Wave™ 25

ReadyMate™ Aseptic Connector

ReadyToProcess™ hollow fibers

Capto Core™ 700

ReadyToProcess hollow fibres



Amersham™ QuickStain CyDye™ labeled antibodies

HyClone™ CDM4HEK293

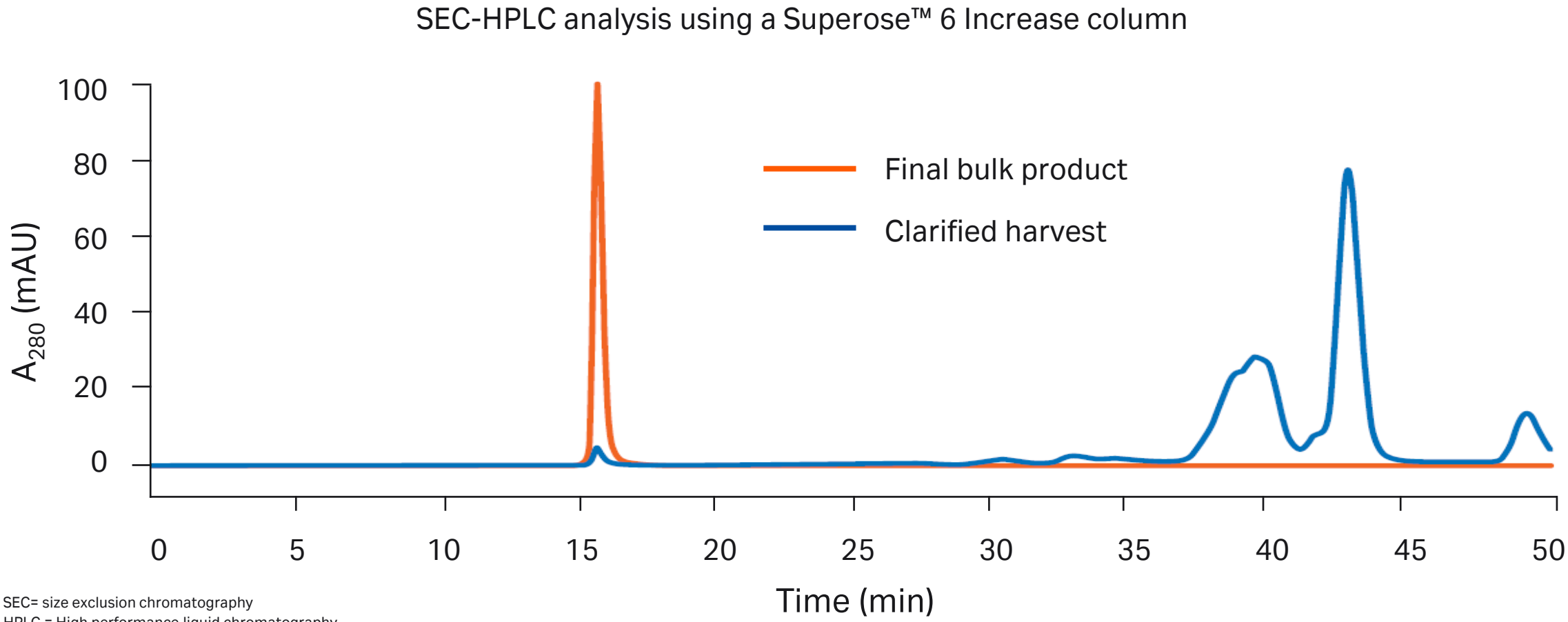
ULTRA NFF Filters

Pre-packed columns and resins

IN Cell Analyzer

Characterization

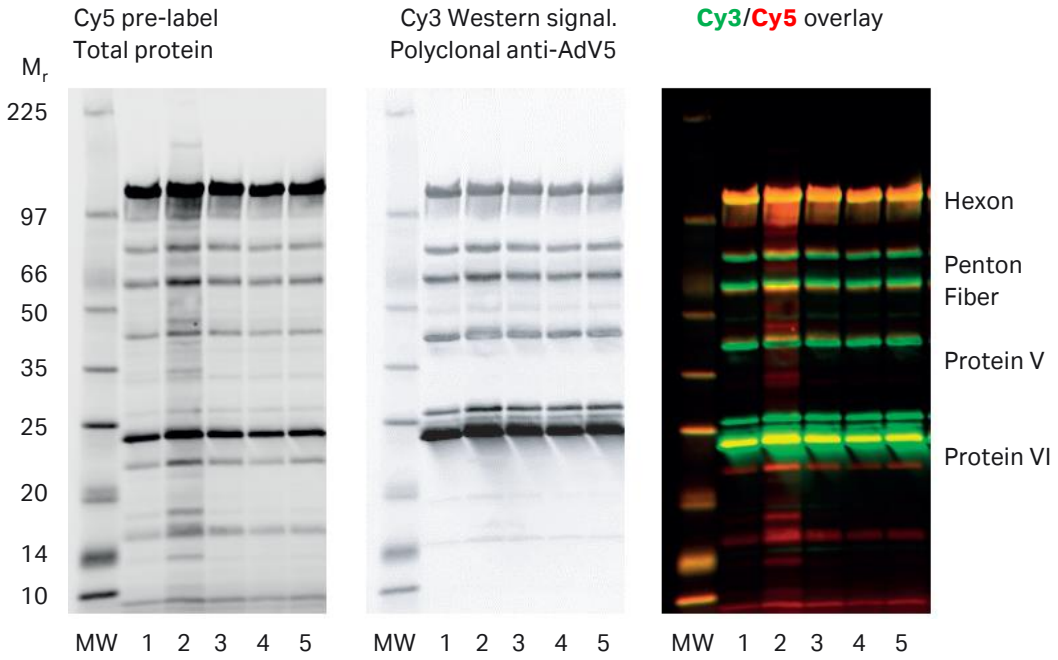
Efficient adenovirus purification and impurity reduction



SEC= size exclusion chromatography
HPLC = High performance liquid chromatography

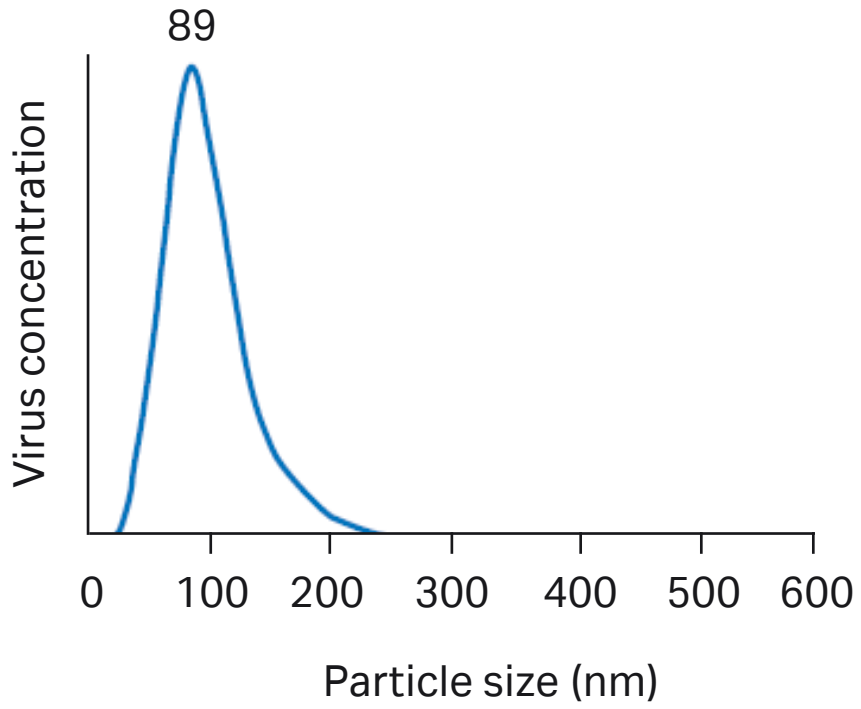
Confirmation of viral protein pattern and particle size

SDS-PAGE and Western blot
Expected viral protein pattern in final bulk

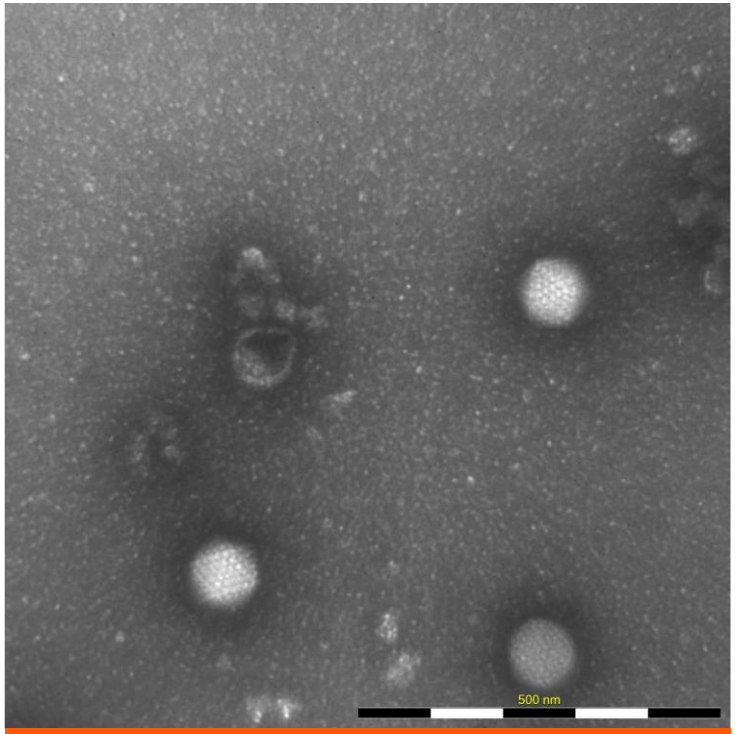


1–2: Reference process
3–5: Novel resin process

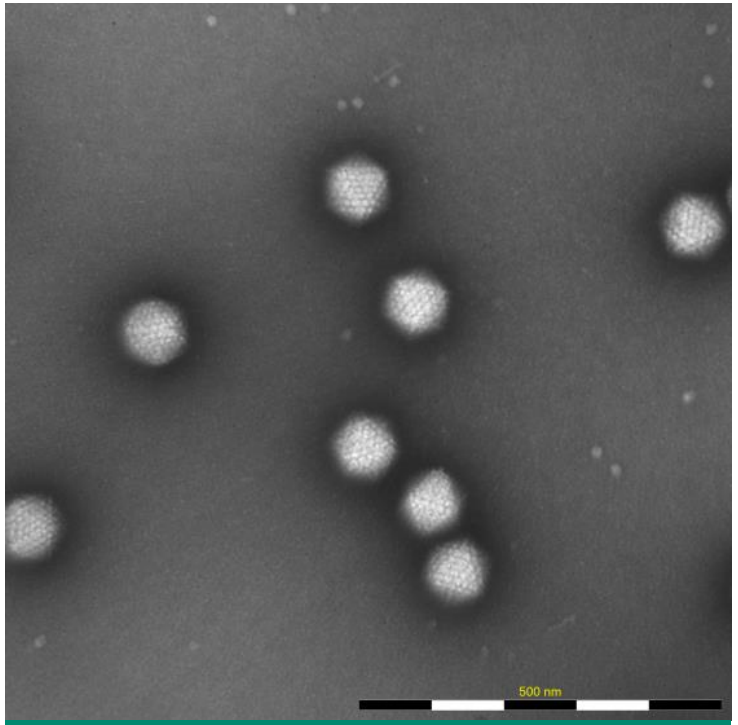
Nano tracking analysis
Expected size of virus particles in final bulk



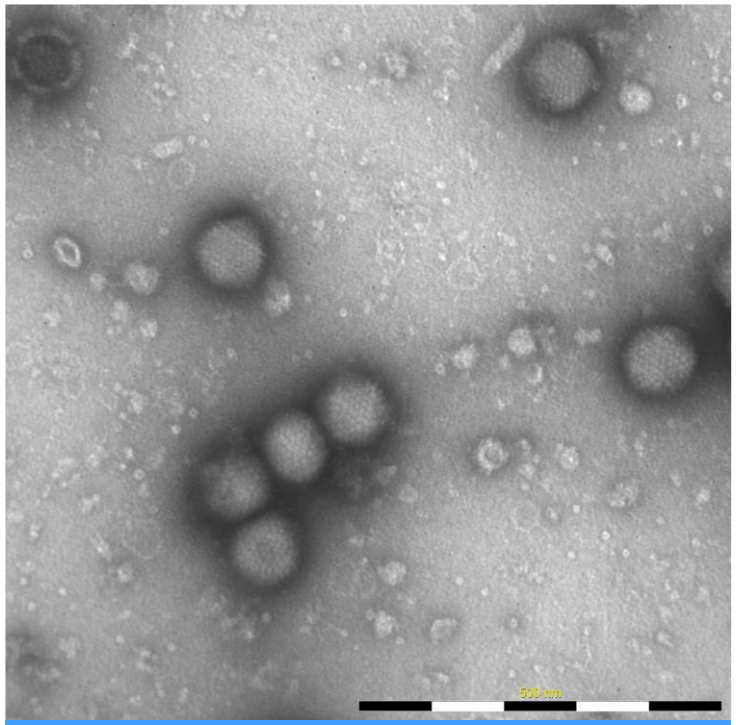
Electron microscopy shows improved impurity removal with novel resin process



Reference process
Sepharose™ Q XL
Sepharose 4 Fast Flow



Novel resin process
Capto™ Q ImpRes
Capto Core 700

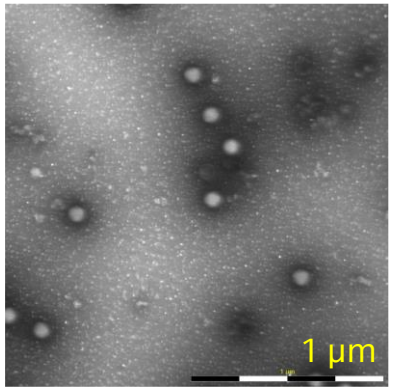


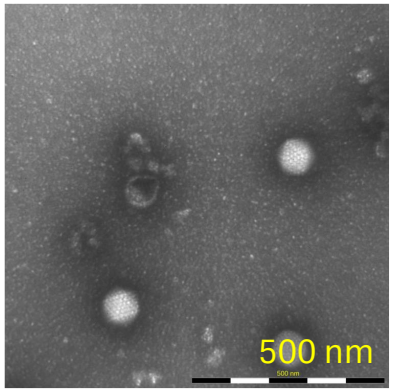
Membrane process
ReadyToProcess™ Adsorber Q
Sepharose 4 Fast Flow

Transmission electron microscopy performed by Vironova AB using MiniTEM™ system, Stockholm, Sweden

Electron microscopy shows improved impurity removal with novel resin process

Reference process





Process workflow

Upstream production

Cell lysis and DNA fragmentation

Clarification

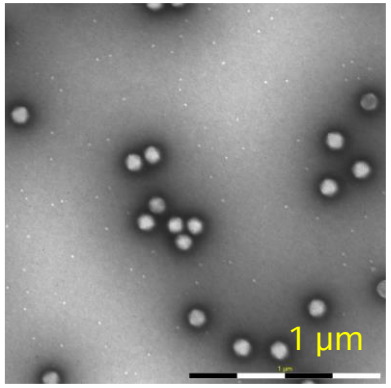
Concentration and buffer exchange

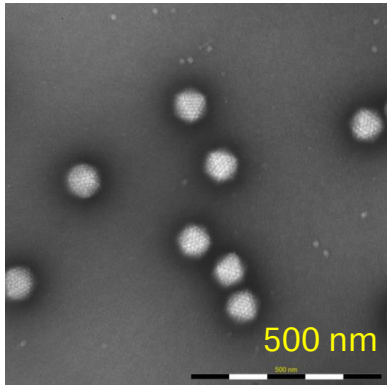
Reference process	Novel process
Capture: Q Sepharose™ XL	Capture: Capto™ Q ImpRes
Polishing: Sepharose 4 Fast flow	Polishing: Capto Core 700

Formulation

Sterile filtration

Novel process



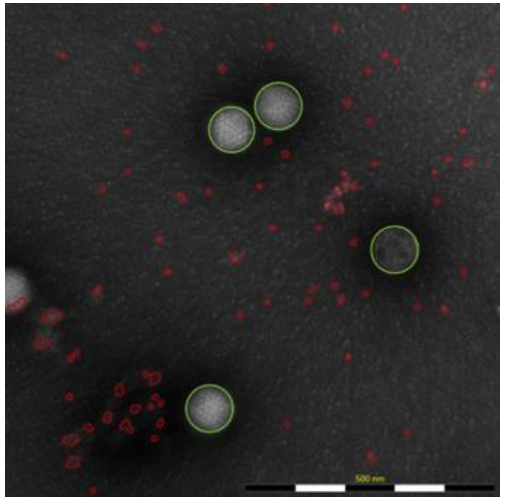


Transmission electron microscopy imaging performed by Vironova AB using MiniTEM™ system, Stockholm, Sweden

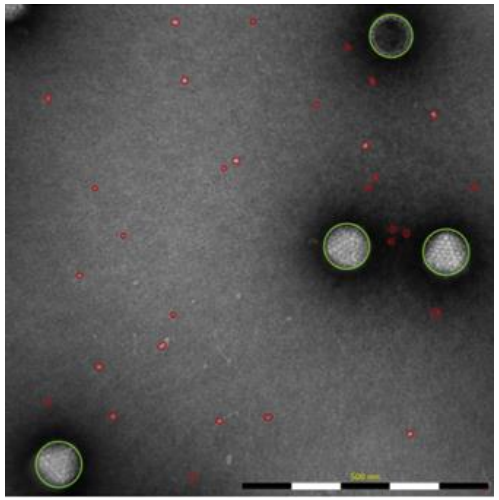
Purity comparison by image analysis

Final bulk samples from novel resin process contain less impurities

Reference process



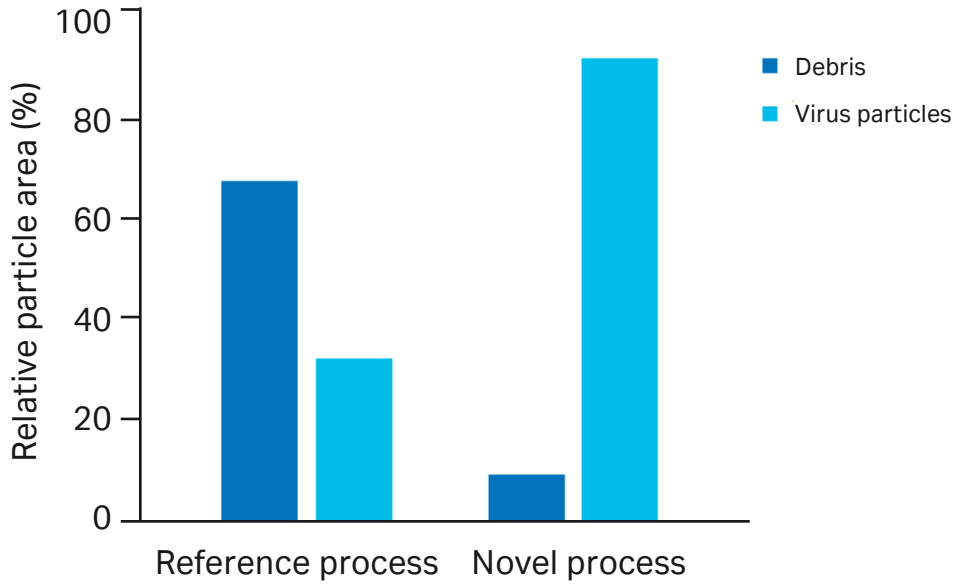
Novel resin process



Purity analysis by automated image analysis of approx. 200 images.

Transmission electron microscopy performed by Vironova AB using MiniTEM™ system, Stockholm, Sweden

Debris-to-virus ratio

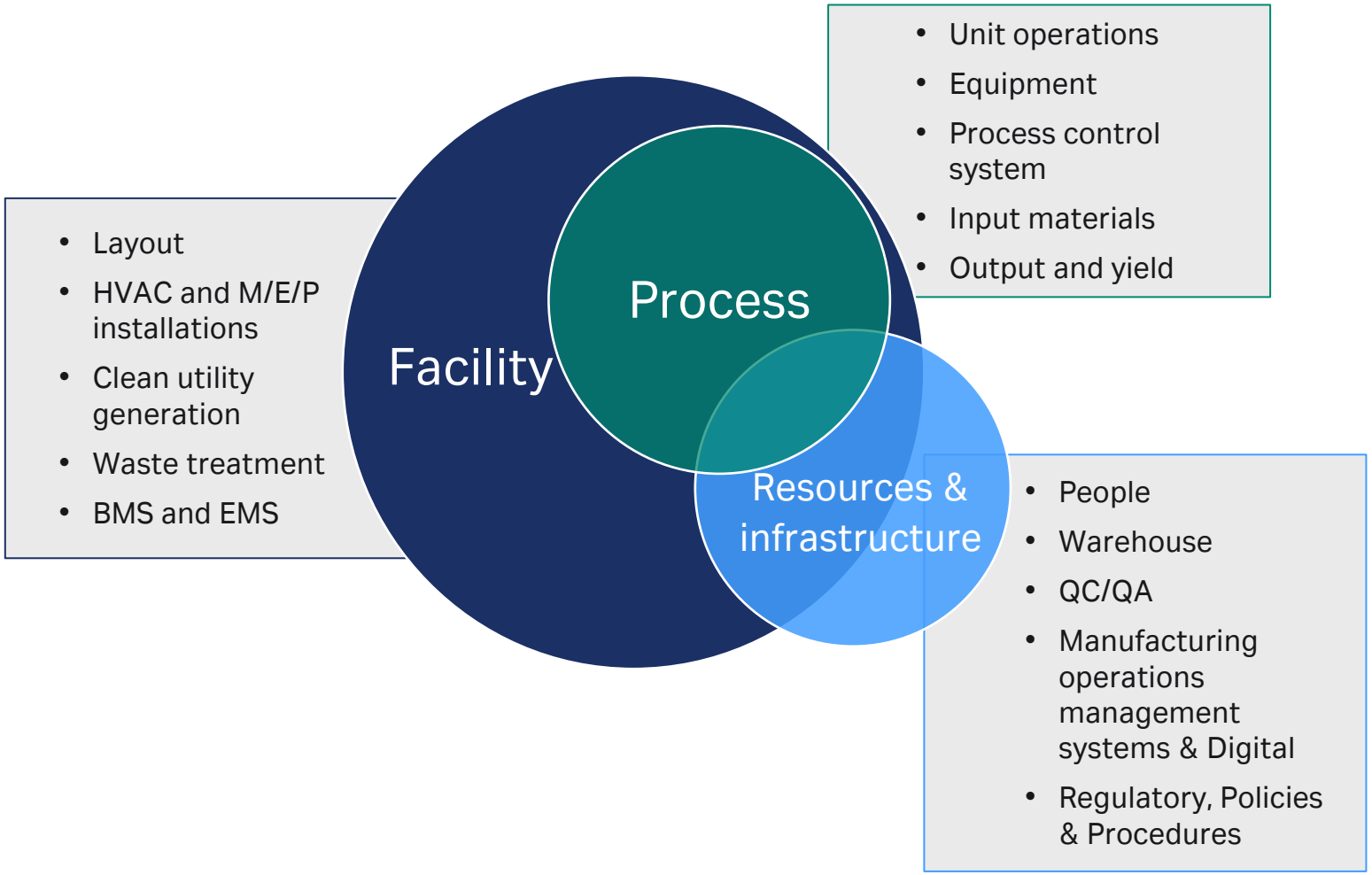


Biomanufacturing options
Adenovirus vector vaccines

Enterprise Solutions

The process is central to biomanufacturing

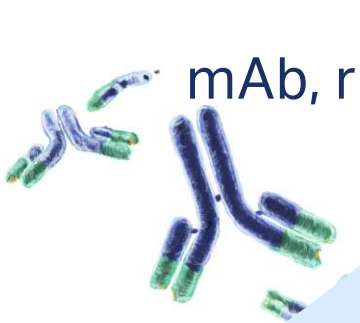
- A biomanufacturing enterprise includes process, facility, resources and infrastructure
- These elements are integrated and influence each other
- Focus should be put on understanding the product and its manufacturing process
- FlexFactory and KUBio offerings are built around a process mass balance. Process design services are available from Cytiva to support process understanding



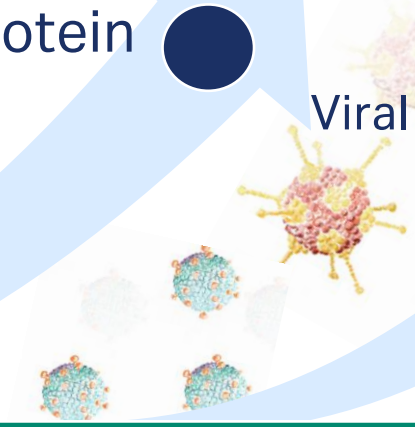
Enterprise Solutions
Adapting and evolving in a more diverse industry

FlexFactory™ platform

- Equipment
- Consumables
- Automation
- Services



mAb, rProtein



Viral vectors and vaccines

pDNA

mRNA

Oligo

-2010 | 2018–2020 | 2021-

KUBio™ and KUBio™ box facilities
Modular biomanufacturing environments

KUBio™ facility BSL-1

KUBio™ facility BSL-2

KUBio™ facility Cell therapy

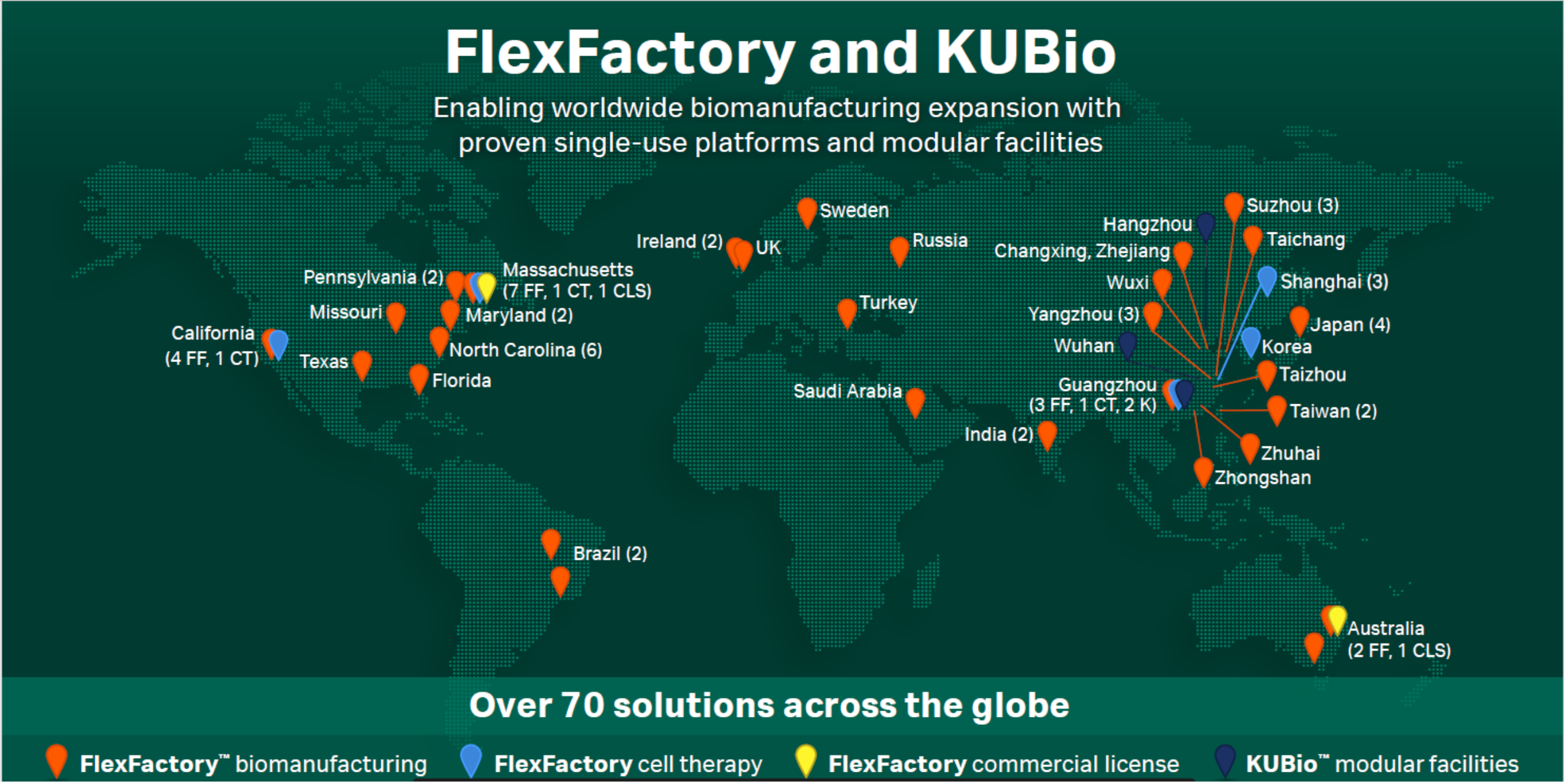
KUBio™ box Viral vectors

KUBio™ box

New manufacturing scales and product modalities

FlexFactory and KUBio

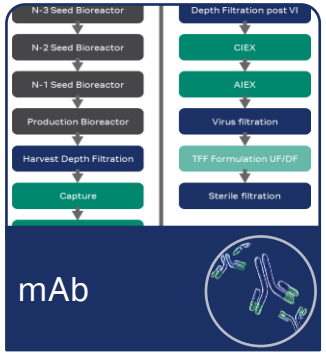
Enabling worldwide biomanufacturing expansion with proven single-use platforms and modular facilities

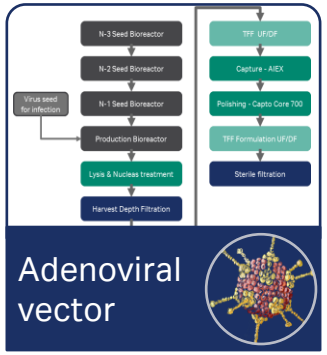


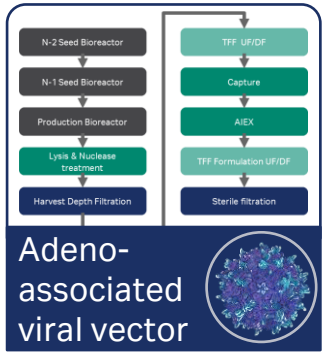
Over 70 solutions across the globe

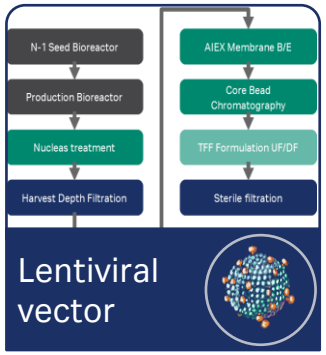
FlexFactory™ biomanufacturing | **FlexFactory** cell therapy | **FlexFactory** commercial license | **KUBio™** modular facilities

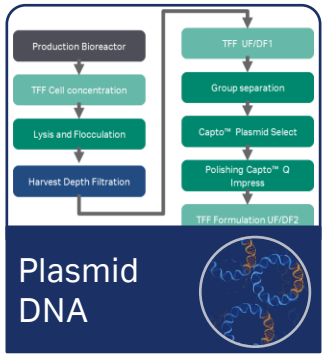
End-to-end support for a portfolio of processes

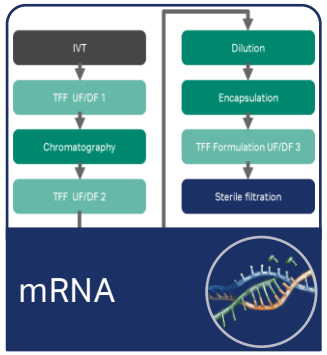












- Process mapping shows that many different processes can be supported end to end with Cytiva equipment
- Process examples at different scales are available as a starting point for customer discussions
- Pall equipment, new acquisitions, and on-boarding of third-party equipment are filling the gaps and expanding the scope
- Optimized based on real-world evidence

Conclusions

Conclusions

Upstream

- The process demonstrates capabilities and products for viral vector processing and fulfills regulatory requirements
- Single-use bioreactors — scalable process technology
- Serum-free culture in chemically defined medium — regulatory advantage
- Process technology compatible with large-scale GMP production (i.e. FlexFactory™ platform)

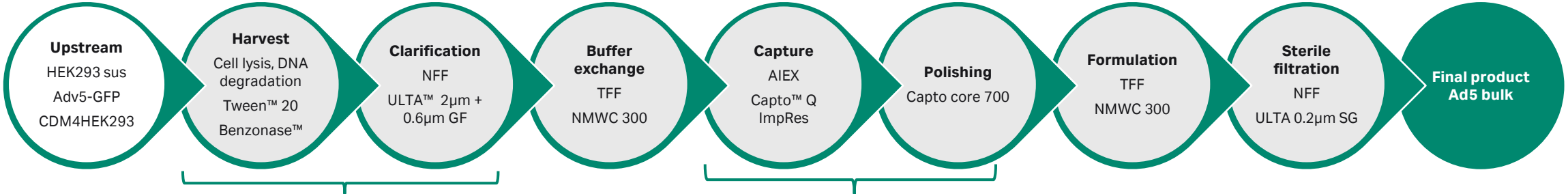
Downstream

- Tween™ 20 is a good alternative detergent for cell lysis
- Modern purification technologies for scalable purification
- Purity of final bulk fulfills regulatory requirements
- Favorable process economy
- Process technology compatible with large-scale GMP production (i.e FlexFactory™ platform)

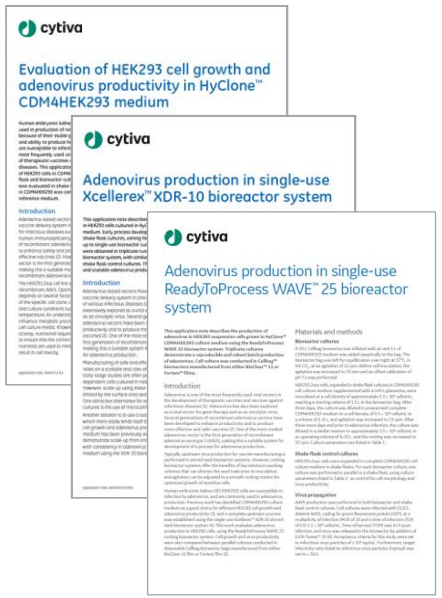
Analytics

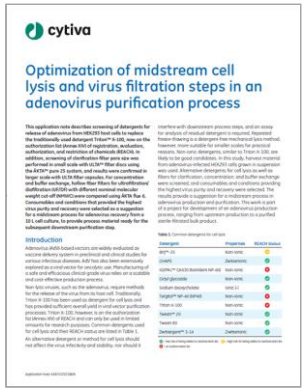
- Critical for success and time consuming
- New Biacore™ assay for virus quantitation. Attractive alternative to commonly used qPCR assay
- New reliable infectious titer assay with IN Cell Analyzer saves time. Attractive alternative to commonly used $TCID_{50}$ assay

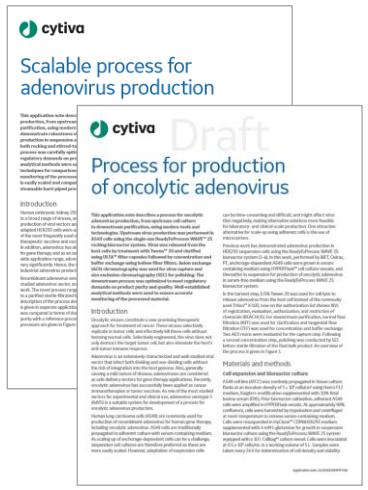
Supporting content for the scalable adenovirus process



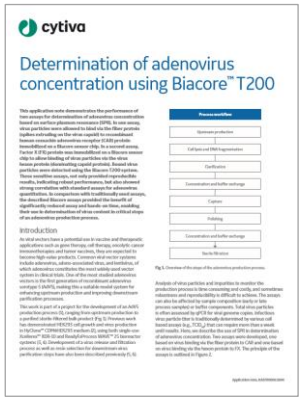
Upstream | Midstream | Downstream | Full process | Analytics | Process economy

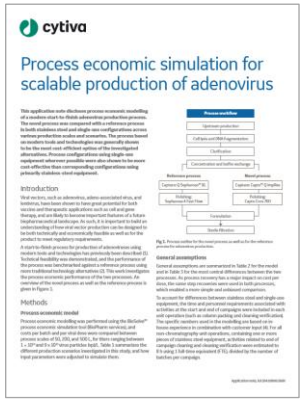






iBET





Link: https://www.cytiva.com/solutions/bioprocessing/knowledge-center/viral-vectors

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