Facilitating the Transition to Late-Stage Gene Therapy Manufacturing

Robert Levendosky, PhD., Manager, Analytical Development

June 9, 2026

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Pharma Services

We Champion Missions That Matter to Help People Live Better and Healthier Lives

VISION

To be the world's most trusted, reliable, and innovative drug development and delivery partner by upholding the highest industry standards and exceeding customer expectations, while driving strong, sustained growth for the company.

MISSION

To develop, manufacture and supply products that help people live better and healthier lives.

VALUES

Patient First, People, Integrity, Customer Dedication, Innovation, Excellence

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Cell & Gene Therapy Site Network

From Building Blocks to End Products

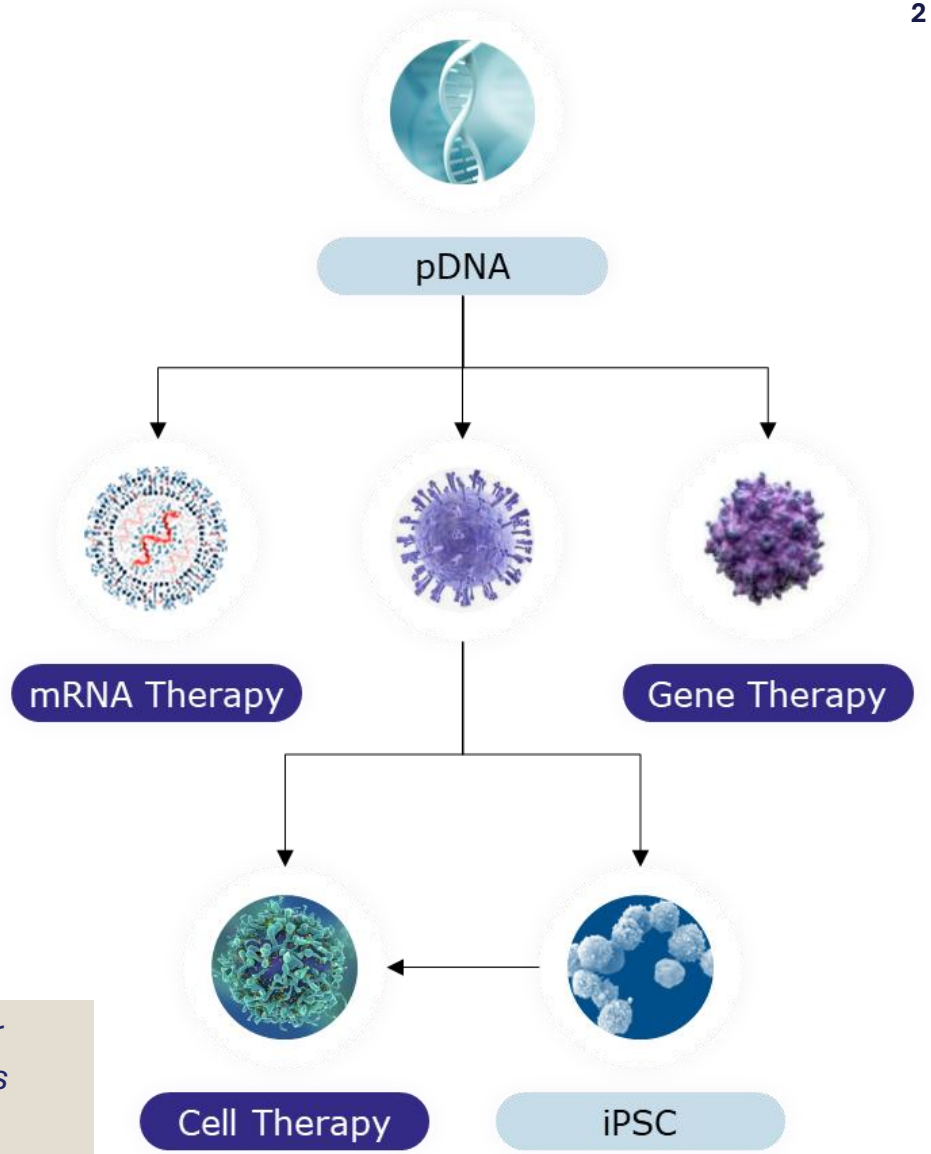
Plasmid DNA*

Gene Therapy

Cell Therapy

Biologics Analytical

Global network of plasmid DNA and viral vector facilities offering cell & gene therapy developers access to the latest manufacturing technology; total plasmid & viral vector footprint of over 500,000 sq. ft across the globe.



*BWI-2 Plasmid facility in progress – target online by end of CY2026

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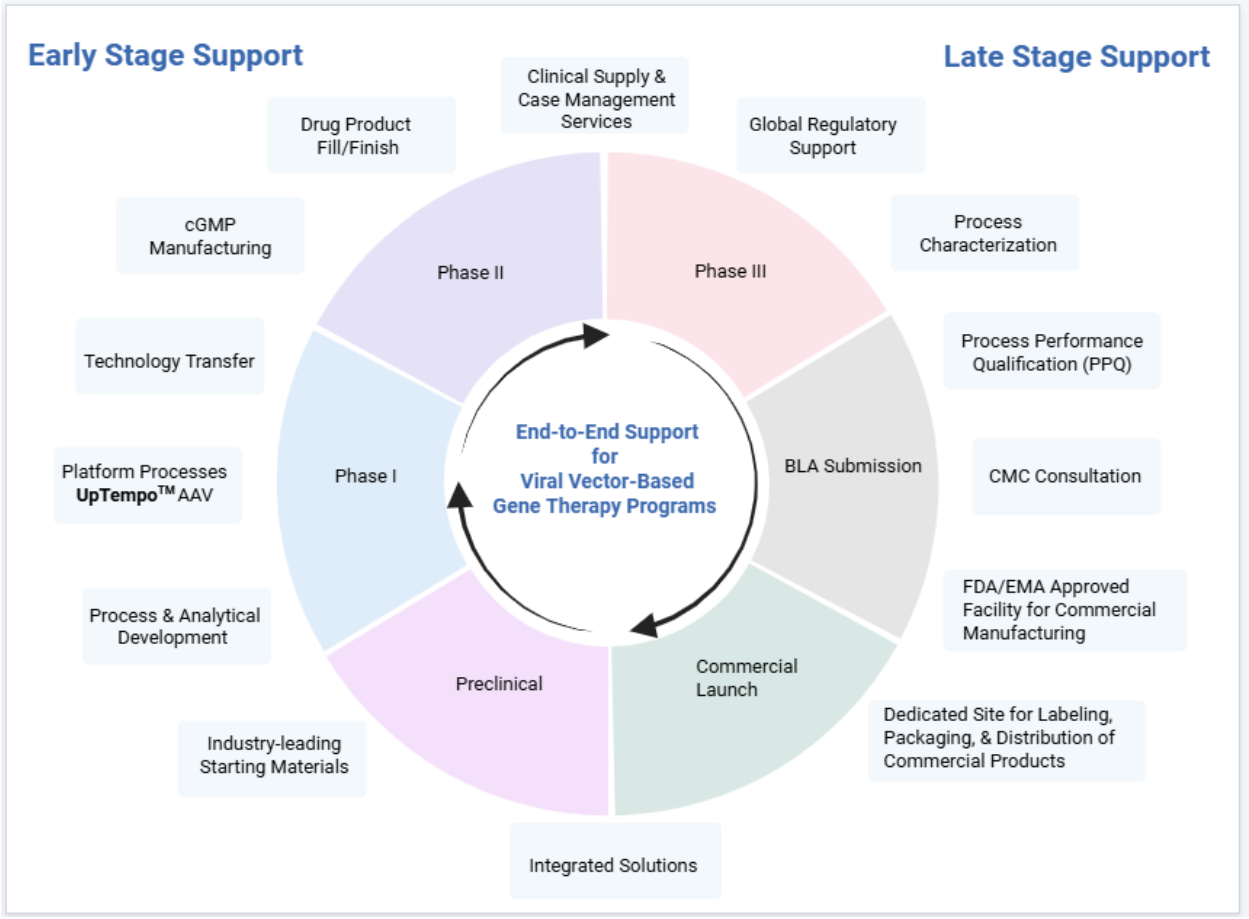
Catalent Support for Product Life Cycle

pre-clinical to commercial stage

Support preclinical and clinical stage programs at any stage of development

Provide end-to-end support from critical starting materials to clinical supply services

Enable developers to de-risk programs ensuring accelerated pathways to the clinic & approval



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Agenda

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II. Beginning the Transition to Late-Stage

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Delivering Excellence in AAV Manufacturing

Supporting gene therapy innovators at all stages of development

Pre-IND & Early-Stage Capabilities

Partnering with early-stage innovators through **close collaboration, agile solutions, & accelerated timelines**

AAV UpTempo™ Platform

- Production of clinical material in as little as 9 months
- Proprietary HEK293 cell line, off-the-shelf AAV plasmids
- Pre-qualified analytical assays
- Fully transferable process

Advanced Technologies: Improved Vector Yield & Quality

- Next-generation AAV RepCap plasmids (RepCapExcels™)
- Upstream process intensification

Full Life-Cycle Support

- Plasmid manufacturing to clinical supply services
- High-quality R&D material for preclinical animal studies, toxicology batches for GLP studies & clinical cGMP manufacturing
- Manufacturability assessment (lead candidate screening), release testing & ICH stability studies

Late & Commercial Stage Capabilities

Extensive experience & proven success in **commercial AAV manufacturing** enabling late-stage partners to seamlessly advance their programs

Late-Stage Experience

15+ late Phase/PPQ programs

Commercial Track Record

2500+ Upstream & 300+ BDS batches manufactured & released

State-of-the-Art Facilities

- Commercial manufacturing at BWI
- Packaging/ Distribution at Philadelphia

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AAV Manufacturing Platform

Manufacturing time savings places Analytics on critical path

Off the Shelf Plasmids → **Clonal HEK293 Cell Line** → **Platform Process** → **Analytical Suite** → **Speed to Clinic**

Simplified Supply Chain	Streamlined Development	Templated Records
Standardized raw materials	*Parallel process & analytical development activities*	*Templated documents ease production record generation & review*
• Suspension-based process at 2 x 200L or 500L scale • Catalent or External Cell Line (one choice) • Materials on hand, ready to use	• Limited process optimization informed by QbD • Scale-up/ Demo runs for generation of Reference Standard and Tox Material	• Variables table guides limited updates to Master Batch Records • Established buffer SMPs • Pre-set sampling plan • Processes familiar to tech staff, reducing start time & deviations

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Typical Phase I AAV Platform Process

Simplified Supply Chain	Streamlined Development	Templated Records
• Standardized raw materials • 2 x 200L or 500L process • Materials pre-stocked	• Limited, QbD-driven development • Demo runs for generation of Reference Standard and Tox Material	• Variables table guides limited updates to Master Batch Records

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Typical Phase I AAV Analytics Platform

Activities familiar to tech staff, reducing start time and duration

Off the Shelf Plasmids → **Clonal HEK293 Cell Line** → **Platform Process** → **Analytical Suite** → **Speed to Clinic**

Client Specific Assays	Verification Ready Residuals Assays	Qualified Client Reference Material
Templated Qualification Documents	*Pre-qualified Residuals*	*Qualify Client Reference Material in Platform Assays*
• Client specific work instructions. • Minimum required dilution and dilutions defined. • Full ICH parameters for assay and reference material.	• Minimum required dilution defined. • Demonstrate dilutional linearity or spike recovery	• Establish reference acceptance criteria from ruggedness experiments.

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Typical Early-Phase cGMP Readiness

Assay and Reference Material Qualification

- Genome Titer and ID
- Particle Titer
- Aggregation
- Protein Purity
- vg Packaging
- rcAAV
- Potency or Infectivity

Compendial Verification

- pH/Appearance
- Osmolality
- Endotoxin
- Bioburden
- IVAA
- Mycoplasma
- Sterility
- Subvisible Particulates

Residuals Verification

- Host Cell Protein
- Host cell DNA
- E1A
- Plasmid
- Nuclease
- Detergent
- Poloxamer 188
- Affinity Ligand Leakage
- Transfection Reagent

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Critical retains and Data for comparability can be leveraged

50L or greater	• Assay development • Tox batch testing
Lockdown/ Toxicology	• Toxicology study • Stability and stressed stability
Reference Standard Supply Run	• Reference for cGMP assay readiness • cGMP release and stability
Engineering Run	• Robustness studies • Assay validation and PPQ testing

Tox batch often same run as Ref Std supply

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III. Transitioning to the Late-Stage Process

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Drug Substance Lifecycle – Process Design, Validation, and Verification

Process & Method Optimization

- Robust, scalable process to deliver commercial quantities with operational ease
- Analytical method readiness for validation

Process Design (Characterization)

- Establish scale-down models
- Determine scope of studies to evaluate potential Critical Process Parameters (CPPs)
- Identification of CPPs, NORs, PARs, and mitigation plan for identified risks

Process Validation (PPQ) Campaign

- Demonstrate consistency and reproducibility of process and control strategy in PPQ campaign
- Initiate stability studies
- Issue a validation summary report
- Inspection and filing preparation

Commercial Manufacturing, Lifecycle Management, and Verification

Risk Assessments (RA) or FMEAs

- Data-mining for process performance and operational ranges
- Detailed assessment of product quality attributes (QTPP, specifications), process parameter, and raw material RAs

Process Validation Readiness

- Establish process control strategy
- Complete method validation
- Prepare the validation master plan
- Establish PPQ protocols and batch records
- Master validation risk assessment

Catalent Biologics' process validation philosophy uses a multi-stage lifecycle approach consistent with FDA and EMA regulatory guidelines, and ICH guidance

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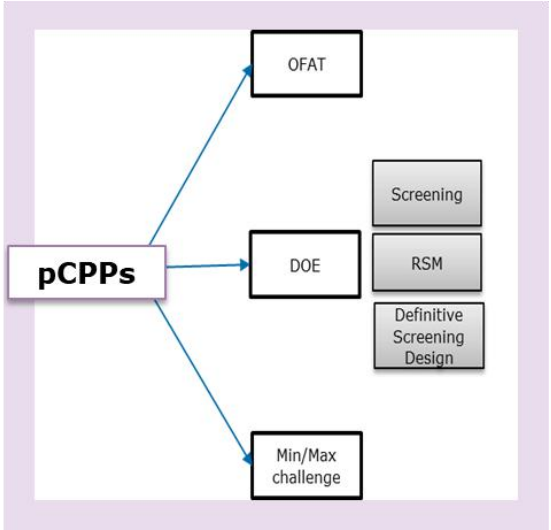
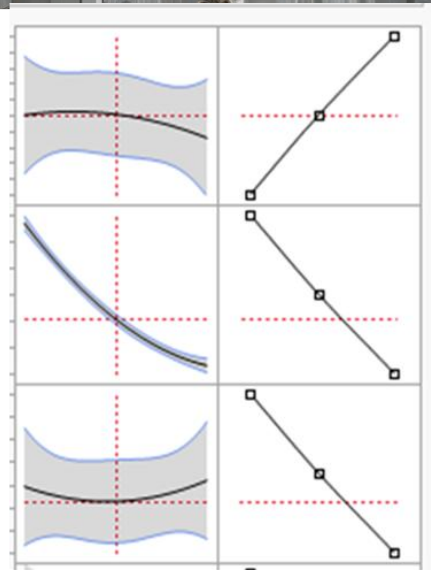
Process Characterization

- FMEA and pCPPs
- Scale Down Model Qualification
- Seed train studies
- DOE studies, unit op specific
- OFAT studies
- Intermediate Hold Studies: 2 – 8C and RT
- Filtration max load
- TFF overconcentration
- RMRA - Supply chain risk mitigation (Media, FBS)
- EOPCB qualification
- Media Hold Studies
- Re-processing studies
- Process capability & residual spiking studies
- DP Mixing Studies
- Viral Clearance
- Statistical support in-house





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IV. Characterization Tools to Ease Process Characterization

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Technology for Advanced Characterization

Genome packaging is paramount. Faster method to interrogate packaging quality would benefit vector design, process impact, & characterization studies.

Current Limitations of AUC

- Sample prep time & purity requirements
- Vol & concentration requirements
- Assay lead time and analysis complexity
- Cost
- Data offer limited view of vector quality
- Cell-based potency methods high labor/ low throughput

Desirable Method Attributes

- In-process sample compatibility
- Low vg requirement
- Rapid, better throughput
- Low operational complexity
- Low cost
- Multiple CQA outputs per method
- Potency correlate/ orthogonal method

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NanoMosaic (NM) Nanoneedle Technology

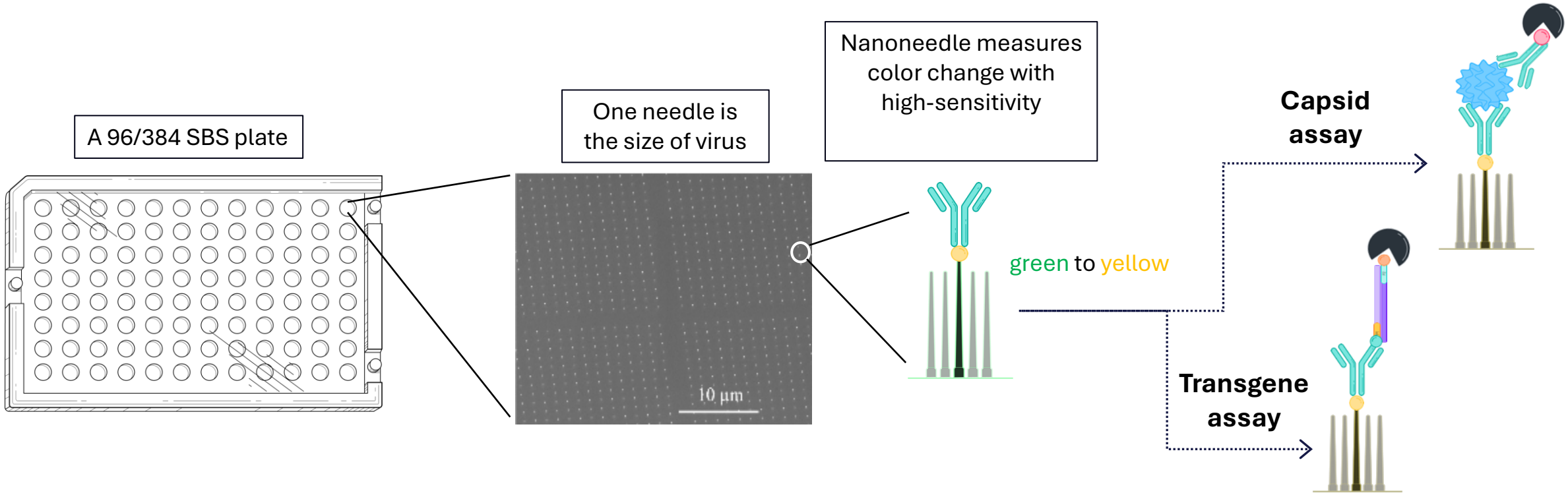

Figure provided by NanoMosaic

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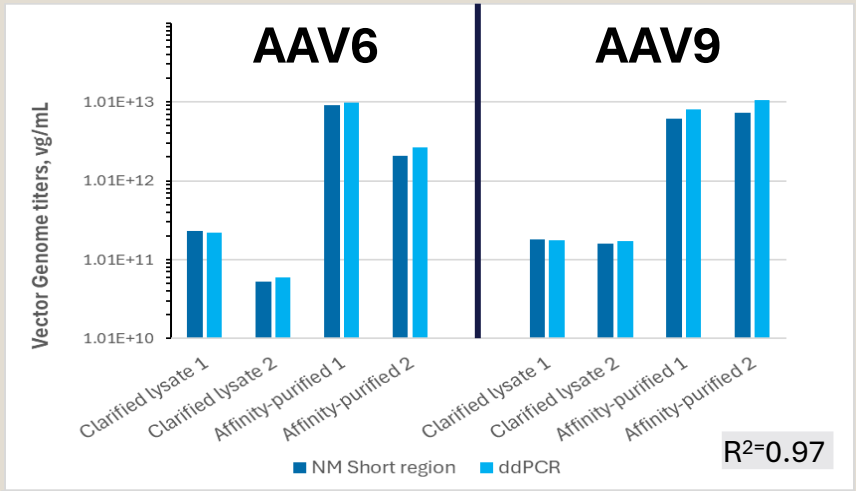
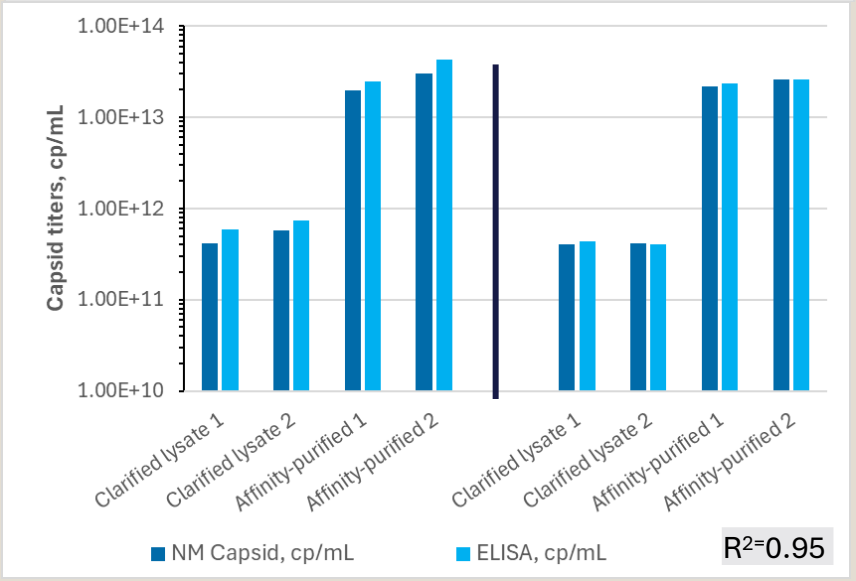
High Correlation Between NM Nanoneedle and Traditional Methods (ddPCR, ELISA)

- Sample 1 & 2 prepared with two different pRepCap plasmids
- Direct measurement in crude extracts/ cell lysate enables speed
- Opens opportunities for early GOI vector development and upstream characterization

Vector Genomes



Total Particles



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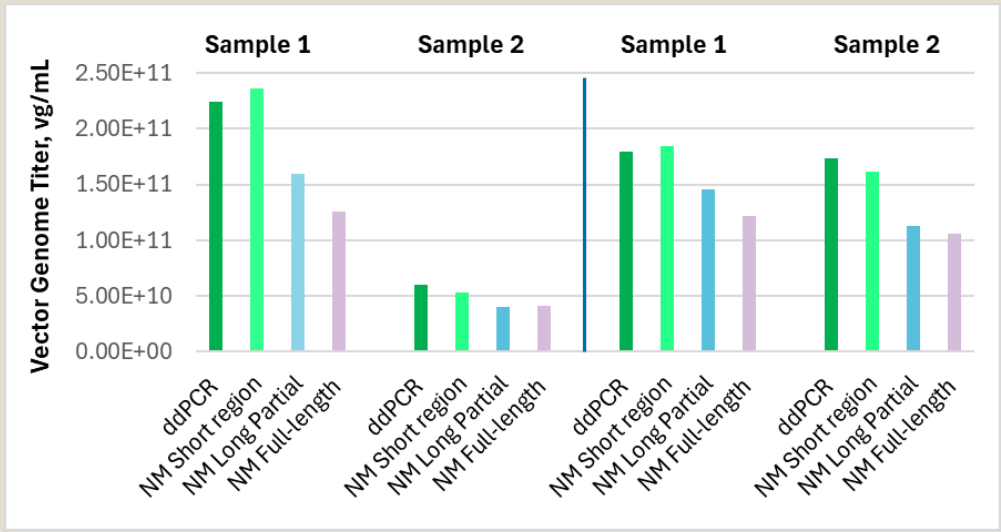
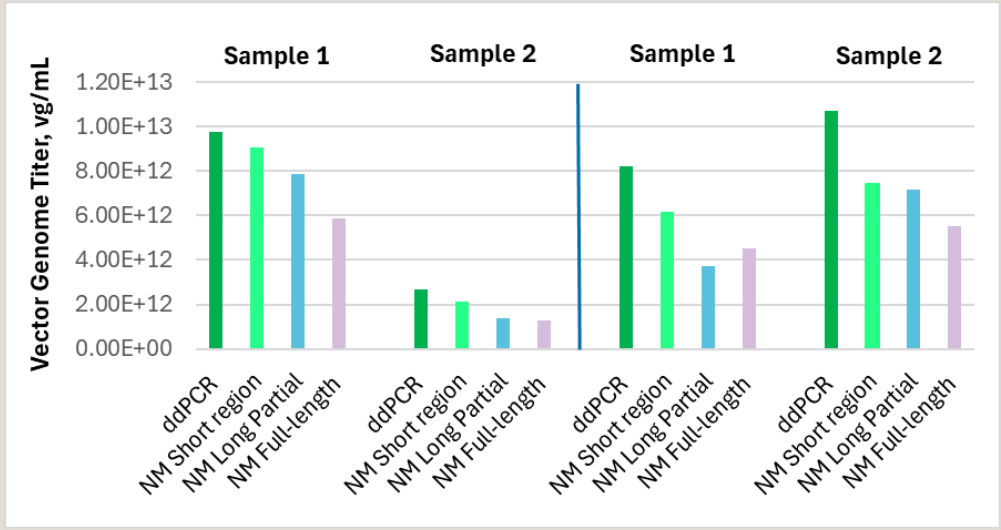
Molecular Specificity to Easily Detect True Full Length GOI

Nanoneedle technology allows accurate differentiation between full-length and truncated transgene components.

Clarified Lysates



Affinity batch-purified samples



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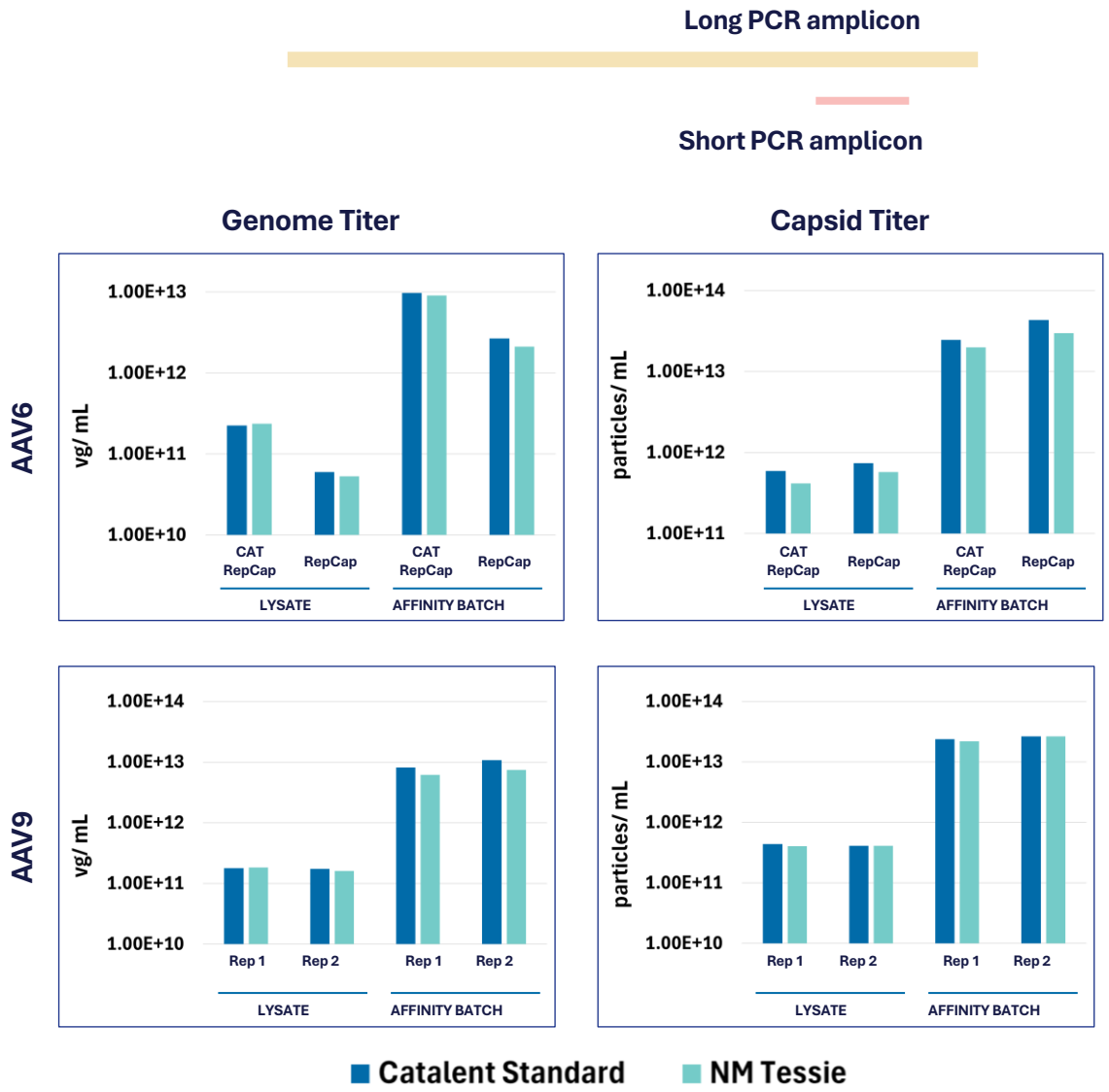
Tessie Speeds Decision Making in Upstream Optimization

- **Enable multiple attributes with a single testing platform**
- **Probe vg intermediates and truncations**
- **Assay lower concentration samples**
- **Eliminate sample processing steps**



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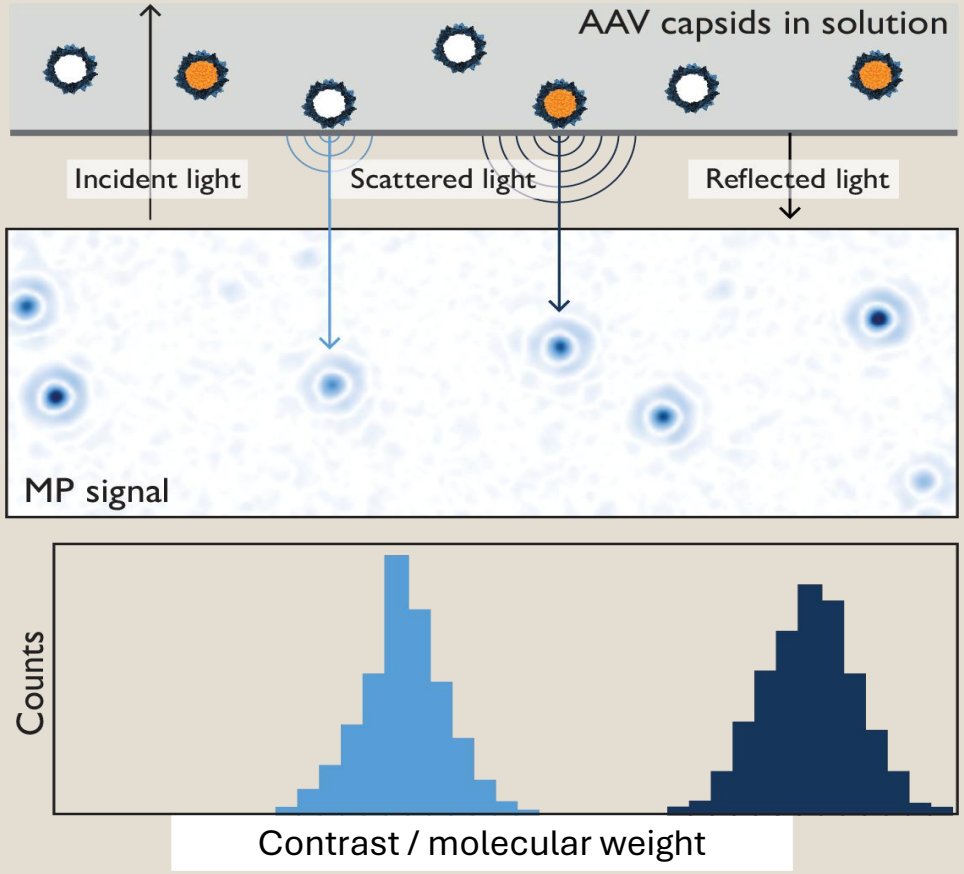
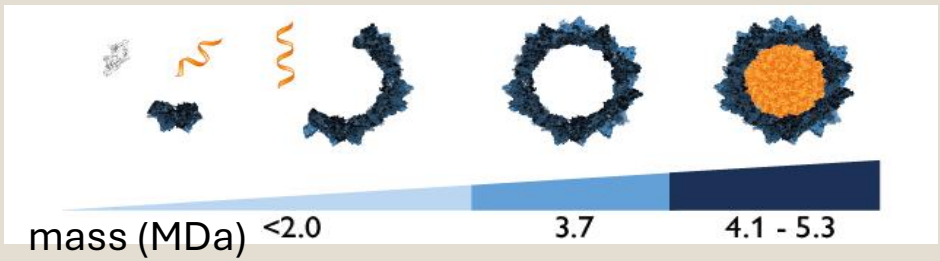
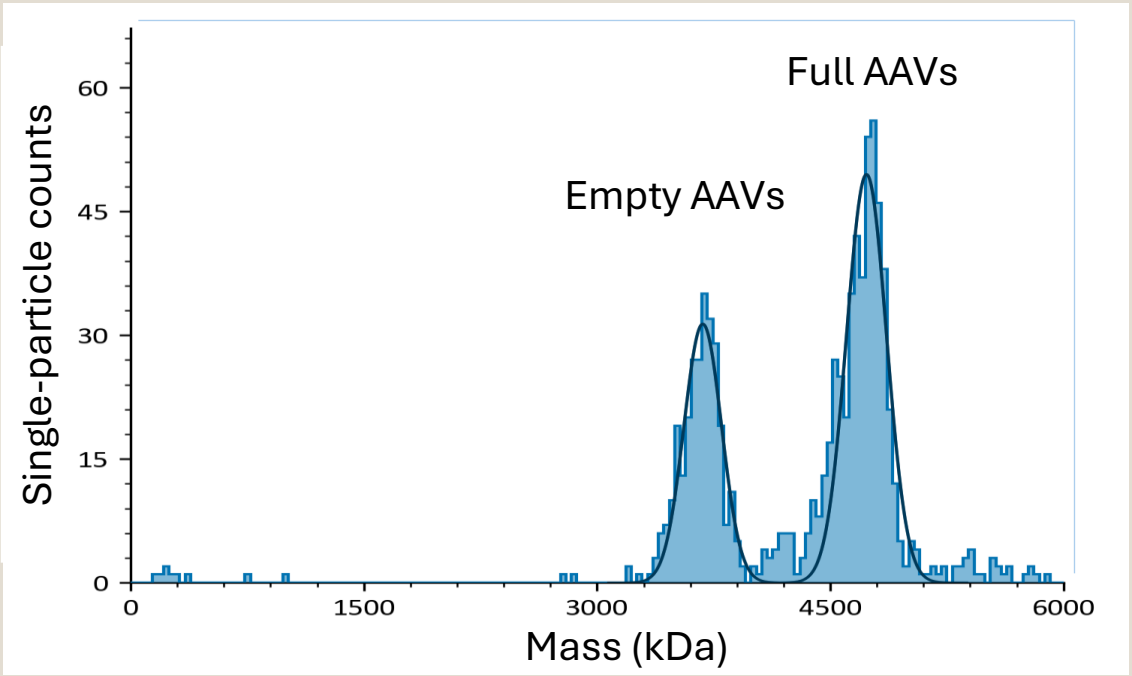
Refeyn Mass Photometry Measures the Mass of Single Particles

Benefits







Slide courtesy of Refeyn

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V. Transitioning to Late-Stage Analytics

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Analytical QBD Milestones and Lifecycle

PD Testing | Tox Lot Testing | Clinical lot release testing | PPQ Testing | Commercial Testing

Confirm comparable results, readiness, and ruggedness

Unvalidated methods transferred via co-qualification

1 Transferred Method Assessment

2 Method Establishment

3 Method Development/ Optimization

4 Method Transfer to QC

5 Method Validation

Validated Methods Established

Determine if method can be established without further development

A QbD approach to determine optimal parameters; confirm ruggedness

Protocol defines applicable parameters from USP/ICH Q2 (R1)

Validated methods are confirmed as comparable then transferred to QC via protocol and training program

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Late-Stage Analytical Assays for Consideration

Strength	Identity/ Purity	Process Related Impurities

• Particle Titer
  • **UV - SoloVPE**
• **Potency – Protein of Interest**
  • ELISA
  • Western
  • Flow Cytometry
	• **Genome Integrity**
	  • **Sanger/ NGS**
	  • **CE**
	• **Peptide Mapping**
	• **PTM**
	• **cIEF**
		Residuals:
		• **Transfection Reagent**
		• **Transfection Enhancer**
		• **DNA Sizing & Quant**

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Late-Phase Analytical Activities recommended Prior to cGMP/PPQ

Assay Validation

- Genome Titer and ID
- Particle Titer
- Potency
- Product related impurities
- Process related impurities
- rcAAV
- Excipients
- IPC

Verification

- Compendial methods
- Safety

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Potency Assays Should be Implemented or Improved

	ddPCR – TCID50	mRNA Transcriptional Assay by qPCR	ELISA or Flow Cytometry
Advantages	Assess absolute gene copy number	Assess inserted or transferred gene construct functionality	Evaluates translational activity
	No standard curve required	Verification of cell transcriptional activity	Determines population of cells expressing transgene
Limitations	Low dynamic range	Requires normalization using a housekeeping gene	No amplification detectability limitations
	Unable to indicate if gene construct is inserted functionally	Multi-step assay	Could be difficult to standardize

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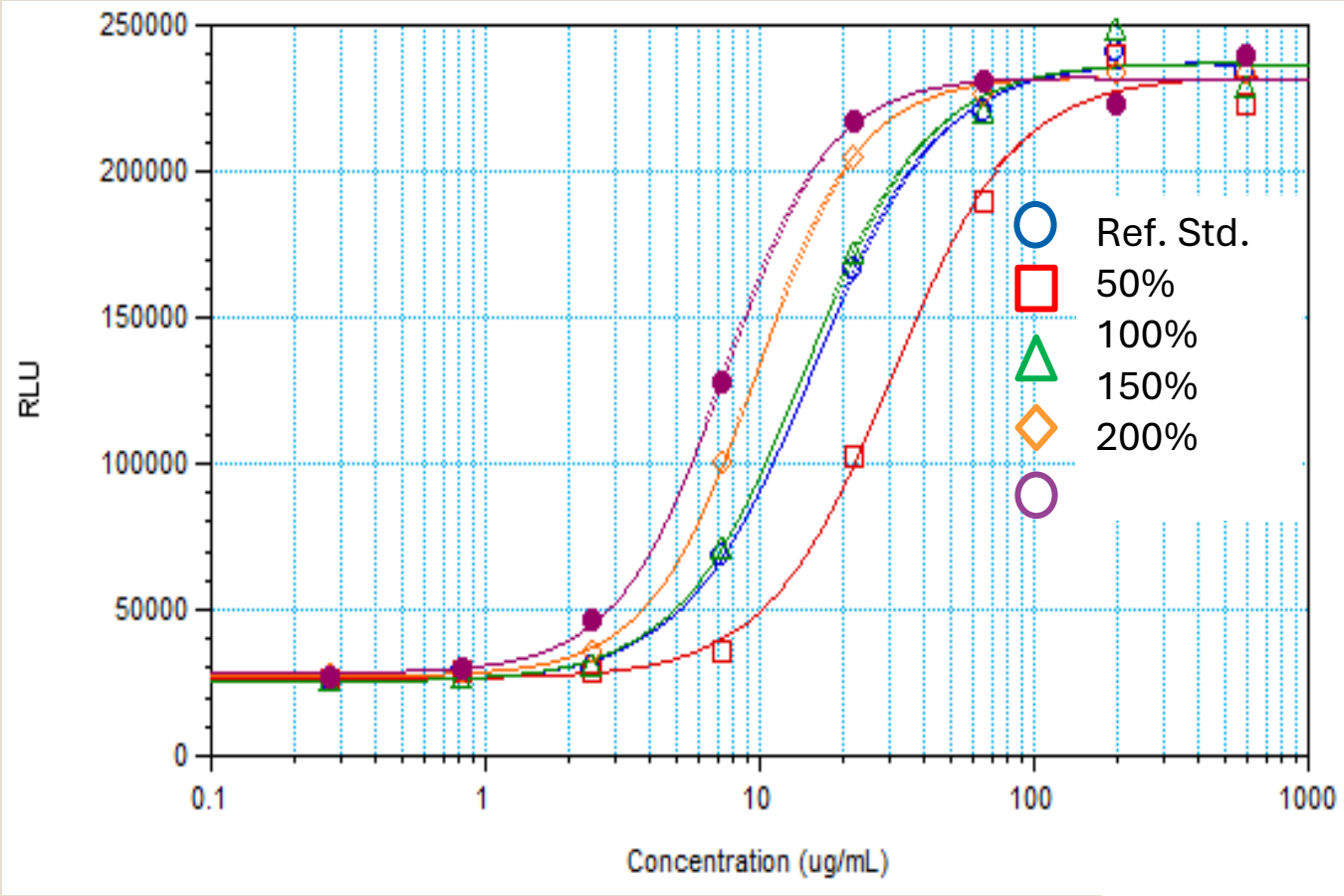
Monitoring of Protein Expression via Relative Potency

Drug dilution series generate biological responses

Good parallelism & responses across the assay range

Example of well-balanced curves, with defined upper & lower asymptotes, more than one point at the linear range, utilizing a reporter gene.



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Late-stage Challenges provide Opportunities

Time to complete assay validations prior to PPQ testing is short.

Challenge

- Sufficient reference material may not be available to support activities.
- Platform verifications may not have fully utilized client product.
- Performance characteristics of transferred assays may be insufficient for validation.
- Duration of PPQ activities is shorter for some rare indications as fewer lots are required.

Opportunity

- Leverage PC material for experimentation.
- Transition to cGMP reference material lot during validation.
- Product specific validation.
- Solidify client ownership of methods.
- Confirm verification of IPC's.
- Determine product specific QL.

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Late-stage Challenges provide Opportunities

DOE driven approach to robustness ultimately saves time

Challenge

- Lack of early-stage DOE data.
  - screening DOEs which utilize your product may not be available.
  - optimization DOEs which utilize your product may not be available to define ranges.
- Logistical and Material constraints
  - Sufficient material may not be available for extensive evaluation of *related factors*

Opportunity

- Leverage invalid assay tracking and LIRs to inform of sources of variability.
- Execute DOE driven screening for sources of variability.
- Execute DOE driven experiments to assess assay robustness and interactions of robustness factors.

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Late-stage Challenges provide Opportunities

Data Trending Provides Key Insight into Assay Performance

Challenge

Data trending

- Assays may have a high invalid rate due to narrow acceptance criteria.
- Valid assay executions may exhibit significant variability due to broad acceptance criteria
- Sufficient details of assay execution may not be available for multi-variate analysis.

Opportunity

Leverage reference and sample results to evolve assay control strategy.

- Invalid assay data can inform sources of variability.
- Valid data can be analyzed to narrow assay acceptance criteria.
- Lack of execution detail can be overcome by performing screening DOEs to inform sources of assay variability.

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VI. Process Validation and PPQ

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Process Validation & PPQ Flow for US/DS/DP

Validation Master Plan (Client Specific)

- Overarching plan for PPQ highlighting Validation strategy
- Includes additional studies/at-scale verification studies, etc.

Ancillary Studies

- Can be performed concurrent with engineering, clinical or PPQ batches
  - Resin Reuse, Mixing or Hold Studies, etc.

Control Strategy

- Identify CQAs and associated CPPs, KPPs, NKPPs, IPCs, etc.

PPQ Protocols

- Sampling plan included in Master Production Record & Protocol
- Defines how process parameters/in-process controls are monitored/challenged
- Includes data entry of process parameters/IPCs + sample testing

PPQ Readiness Checklist (Internal Document)

- Internal Catalent document to verify equipment, facility qualification, method validation, training, document readiness, material readiness, etc.

CPV (upon commercial manufacturing)

- Client specific plan(s) created to detail strategy

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PPQ Activities

Pre-PPQ/PPQ Planning

- Upstream Process FMEA
- Downstream Process FMEA
- DP Process FMEA
- PC Study Design Plan
- Upstream Process Characterization
- Downstream Process Characterization
- Process Control Strategy & PPQ Acceptance Criteria BDS/DP
- Process Validation Master Plan BDS/DP
- Fill Volume Assessment/Studies
- Container Closure Study
- PPQ Protocol Upstream/Downstream/DP
- DP CCIT/CCOQ
- DP Aseptic Process Simulation
- Autoclave Load Assessment

PPQ Adjacent/Post PPQ Activities

- Intermediate Hold Studies
- Product Mixing Study
- Drug Product Mixing Study
- Cumulative Hold Study
- Reprocessing Validation
- At Scale Buffer/Media Mixing Studies
- At Scale Buffer/Media Hold Studies
- BDS/DP Shipping Validation
- PPQ Report
- DP Filling Homogeneity

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VII. Quality & Regulatory Affairs

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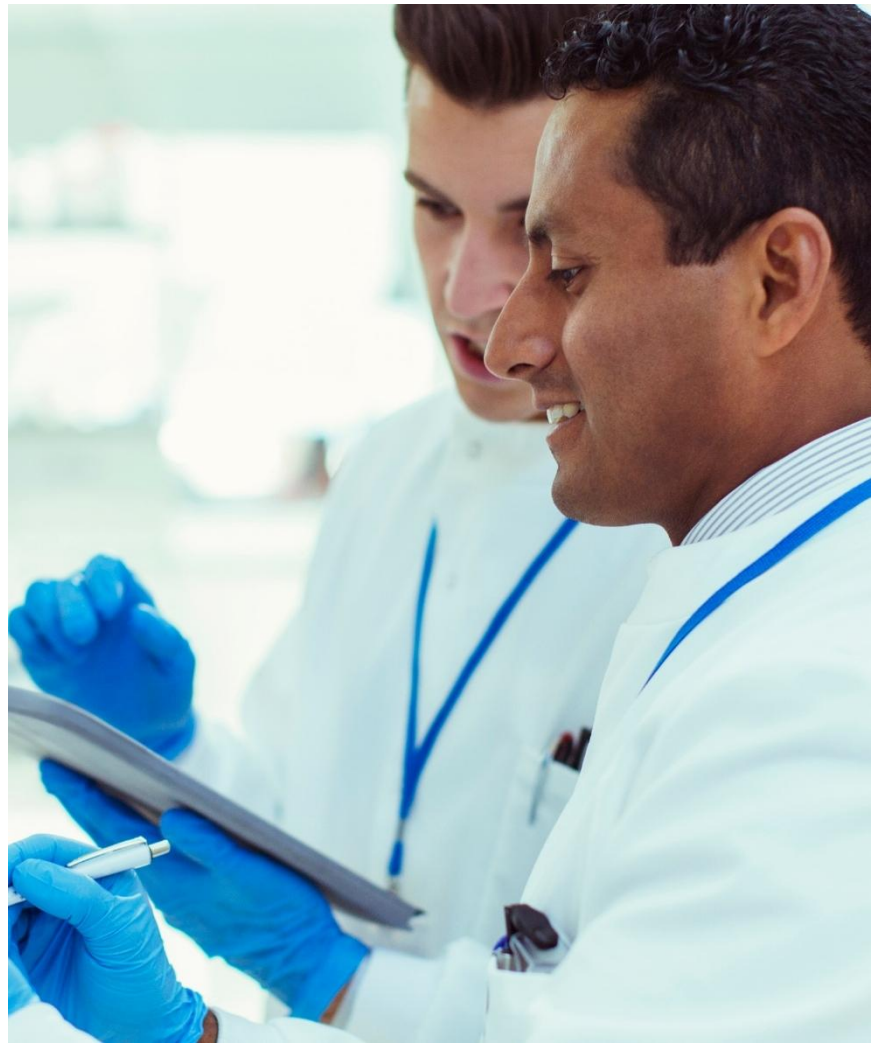
Regulatory Experience

Range of Services

Support from pre-IND through post-approval

- Regulatory advice
- Full CMC dossier authoring
- Submission & document review
- eCTD & publishing support
- Full regulatory strategic planning
- Updates & maintenance
- Regulatory triage & health authority meetings
- Due diligence
- Gap assessment & advisement



Catalent handles over 200 submissions annually

- 8 Pre-approval inspections
- 3 General inspections

Since 2020, our Maryland gene therapy facilities have been inspected by international regulatory bodies, leading to product approvals and GMP certifications where relevant.

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Regulatory Inspection History

DATE		INSPECTION TYPE	SITE	KEY HIGHLIGHTS
2026	April	No inspection	Harmans (BWI)	Product Approved
2025	August	Ministry of Industry and Trade of the Russian Federation	Harmans (BWI) and BioPark (BPK)	Product Approved
	April	FDA CBER Pre-License Inspection for 1 Product	Harmans (BWI)	Product Approved
	April	FDA General Surveillance Inspection	BioPark (BPK)	Inspection Closed
	March	EMA Pre-Approval Inspection for 1 Product	Harmans (BWI) and BioPark (BPK)	GMP Certificate Issued
	February	PMDA	Harmans (BWI)	Product Approved
2024	November	FDA CBER Routine Surveillance Inspection	Harmans (BWI)	No 483 issued – No Action Indicated
	July	ANVISA Pre-Approval Inspection for 1 Product	Harmans (BWI) and BioPark (BPK)	Product Approved
2023	March	FDA CBER Pre-Approval Inspection for 1 Product	Harmans (BWI)	Product Approved
	February	FDA CBER Pre-Approval Inspection for 1 Product	BioPark (BPK)	Product Approved
	January	FDA Routine Surveillance Inspection	Harmans (BWI)	No 483 issued – No Action Indicated
2021	November	FDA CBER General Inspection	Harmans (BWI)	Voluntary Action Indicated
2020	December	PMDA Pre-Approval Inspection for 1 Product	Harmans (BWI)	Product Approved
	December	EMA Pre-Approval Inspection for 1 Product	Harmans (BWI)	Product Approved
	June	FDA CBER Pre-Approval Inspection for 1 Product	Harmans (BWI)	Product Approved

Site has supported commercialization of three approved AAV gene therapies

VIII. Catalent OneBio® Suite

An integrated Solution for Development, Manufacturing and Clinical Supply

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OneBio® Integrated Offering

Fundamental Benefits

INTEGRATED OFFERING VALUE PROPOSITION

Speed to Patient	One Supply	Expertise	Global Footprint	One GMP Umbrella
Leverage our platform processes and comprehensive capabilities to shorten development timelines	Reduce the burden of managing multiple partners and inventory across the production chain	Broad development, tech transfer, and manufacturing knowhow; single point of contact	De-risk manufacturing strategy through multiple sites; data visibility across sites	Single quality oversight; all modalities under one system

Enable continuity along the development journey from pre-clinical to commercial launch and lifecycle management

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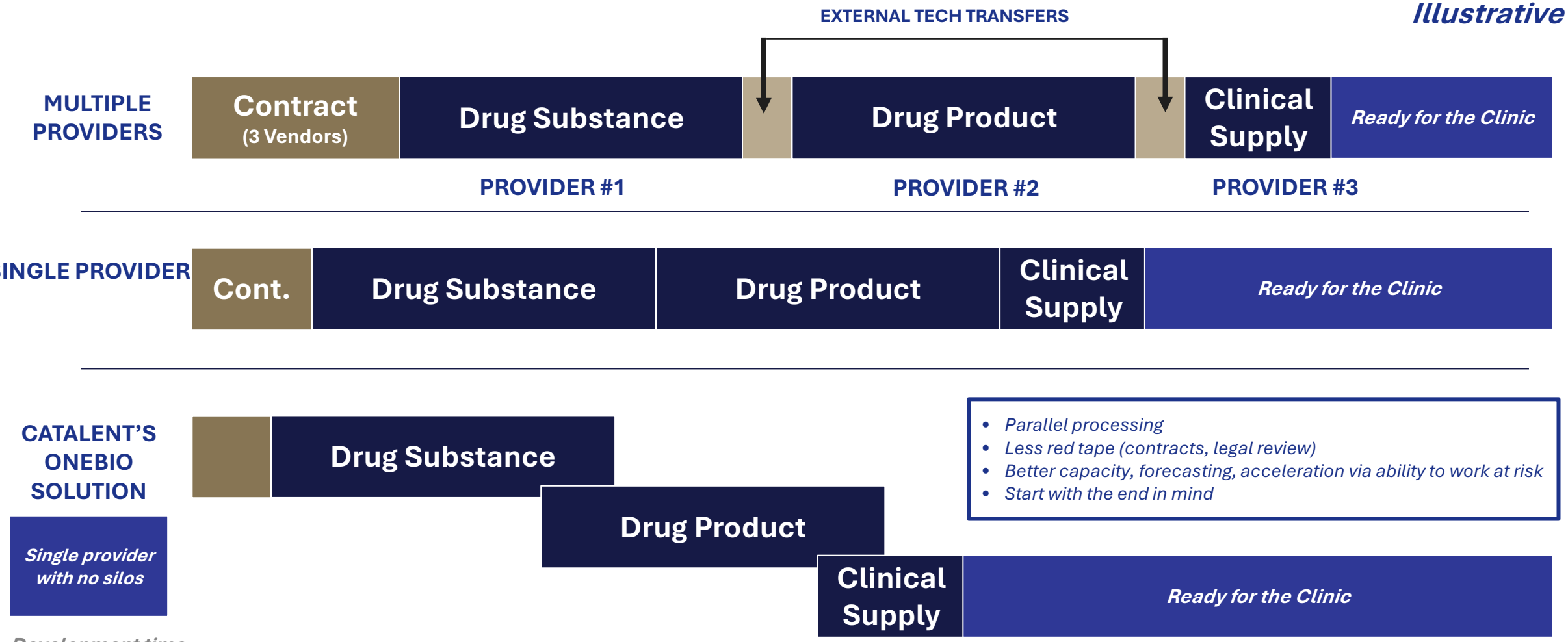
Significant Gains can be Realized by Leveraging a Single Partner

Illustrative



- *Parallel processing*
- *Less red tape (contracts, legal review)*
- *Better capacity, forecasting, acceleration via ability to work at risk*
- *Start with the end in mind*

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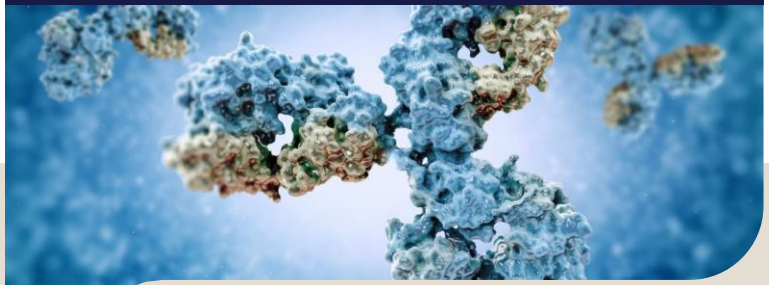
Biologics Analytical Services- We Have The Proven Expertise To Take Your Biologic To Clinic Or Market Quickly And Reliably

Advanced Science

From antibodies to vaccines to bispecifics and beyond



- **600+** antibodies and **160+** recombinant proteins developed
- **160+** clinical trials utilizing GPEx® cell lines
- **20** commercially approved/ authorized products using GPEx® technology

Integrated Solutions

Accelerated development, fast scale-up and reliable manufacturing

- **9** clinical supply facilities
- **50+** audited depots on 6 continents
- **99%+** on-time delivery for clinical supply

Proven Expertise

Turning your science into better treatments

- **30+** years experience providing analytical services
- **50+** commercially approved products manufactured
- **6,000+** employees

Catalent®

Integrated & Standalone CDMO Solutions To Accelerate Your Biologic To Market

CLINICAL SUPPLY SERVICES & SOLUTIONS
FORMULATION & PROCESS DEVELOPMENT
EXPANDED ACCESS/COMMERCIAL LAUNCH

DRUG SUBSTANCE & DRUG PRODUCT
MANUFACTURING GLOBAL COMPARATOR
SOURCING

CELL LINE DEVELOPMENT

PRE-CLINICAL | PHASE 1 | PHASE 2 | PHASE 3 | COMMERCIAL

INTEGRATED & STANDALONE
ANALYTICAL SERVICES

PRODUCT OPTIMIZATION
SCALE-UP PROCESS
VALIDATION
TECH TRANSFER

LINE EXTENSIONS
LIFECYCLE MANAGEMENT
BACK-UP SUPPLY

MABS & BISPECIFIC ANTIBODIES

PEGYLATED PEPTIDES

BIOCONJUGATES & ADCS

RECOMBINANT FUSION PROTEINS

CELL & GENE THERAPIES

OLIGONUCLEOTIDES, NUCLEIC ACIDS

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Summary

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Summary

- **Catalent meets each program's particular needs to begin preparations for commercial manufacturing.**
- **Pre-PPQ activities set us up for success.**
- **Choosing the proper CDMO partner to meet your needs is critical and relationship management can maximize the partnership.**
- **The OneBio Suite smooths the path from preclinical through commercial manufacturing and testing.**

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Acknowledgements

Viral Vector Process & Analytical Development

Carey Connelly, PhD

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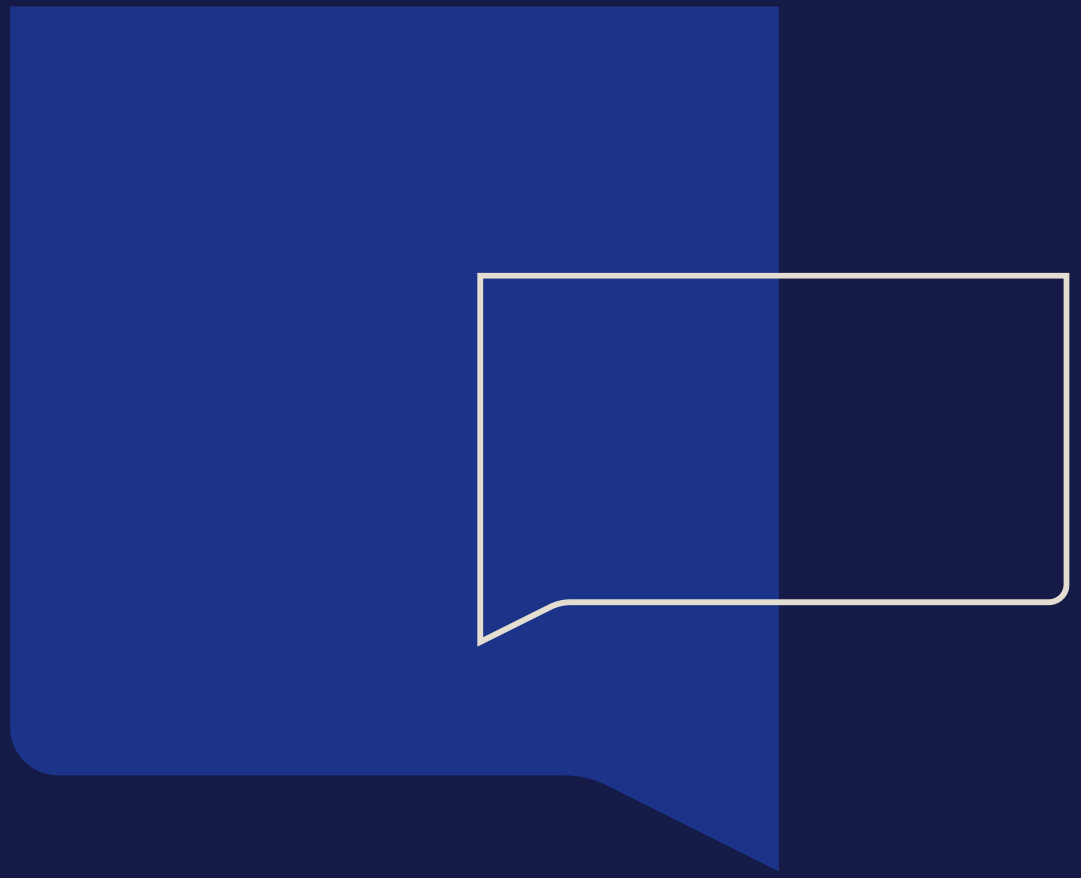

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Thank You
Questions?

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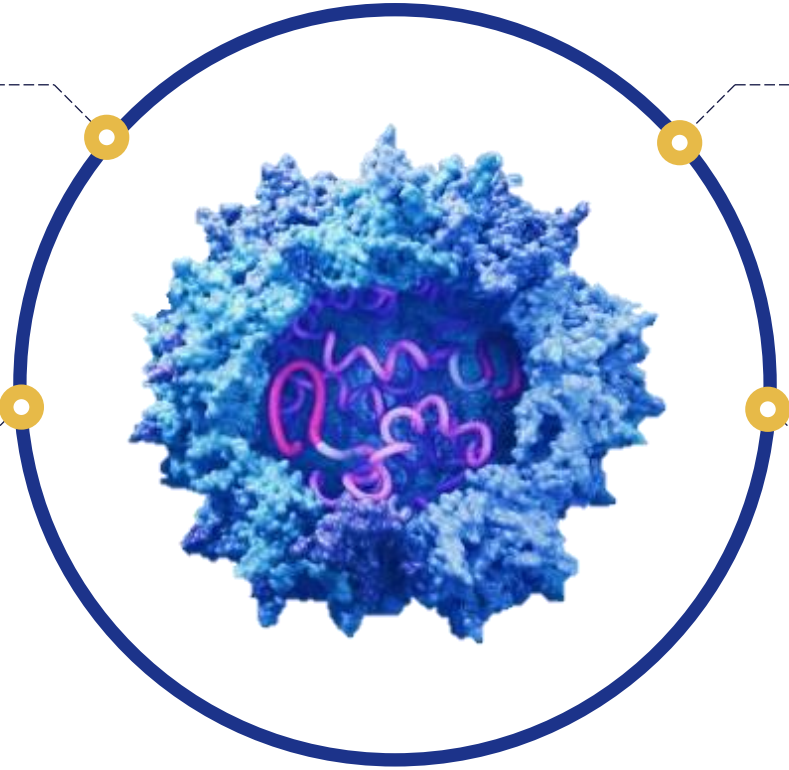
Equipped in Various Assays to Propel Your Program

Potency & Characterization

- Gene copy titer
- Capsid titer
- Capsid ID
- Protein expression
- Infectivity
- Bioassay

Residual Impurities

- HCP and hcDNA
- E1A, E4, REP, and plasmid
- Residual transfection reagents (ie, FectoVIR)
- Residual detergents (ie, PS20, Poloxamer 188)
- Residual Benzonase, PEI
- DNA fragment size



Compendial

- Endotoxin
- Osmolality
- pH
- Appearance
- Particulate matter
- CCIT

Other Analysis

- Bioburden
- Purity
- Aggregation
- Capsid Protein Profiling (LC-MS)
- Transgene mRNA expression

Library of essential methods to accelerate your program immediately

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