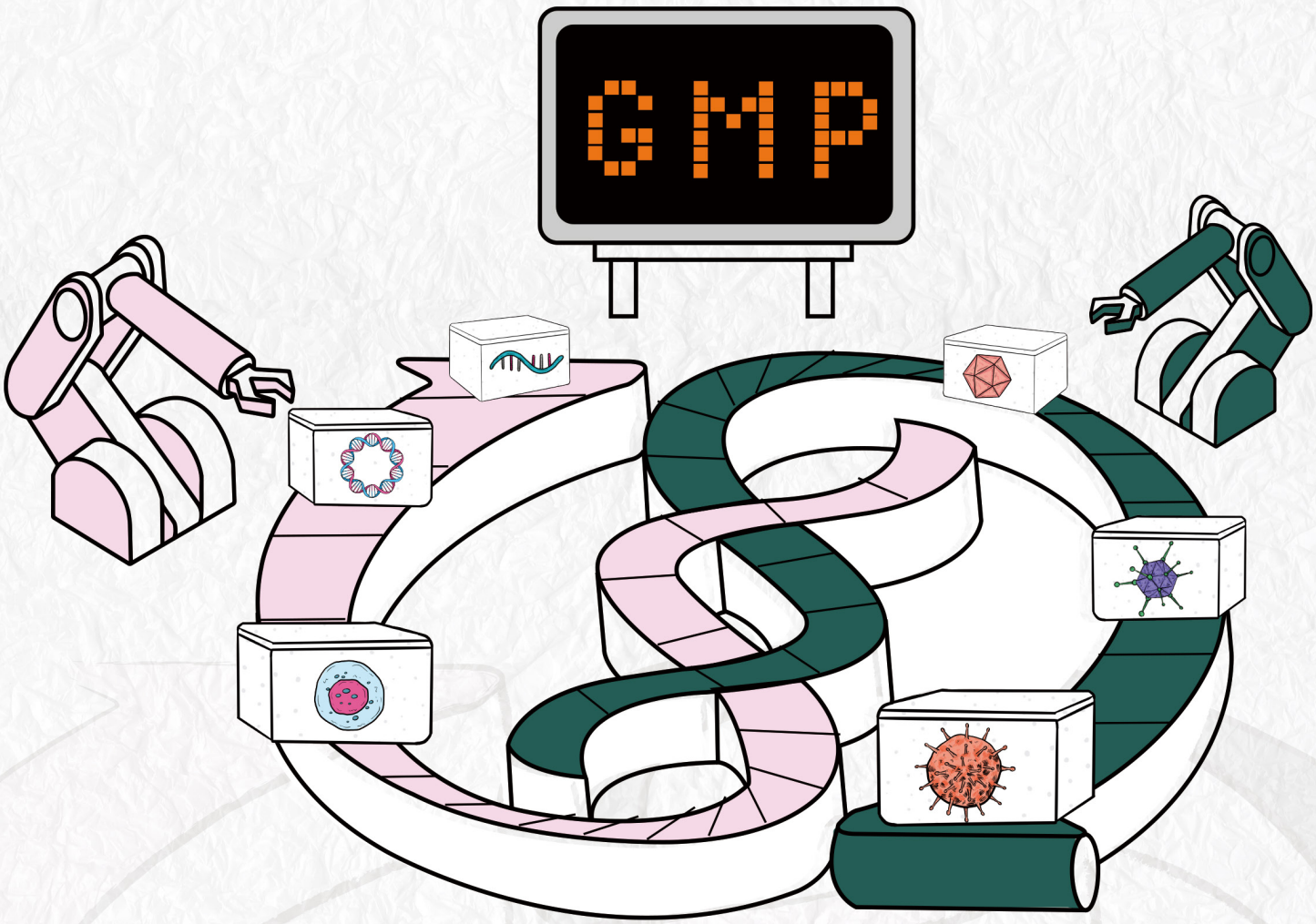
VectorBuilder

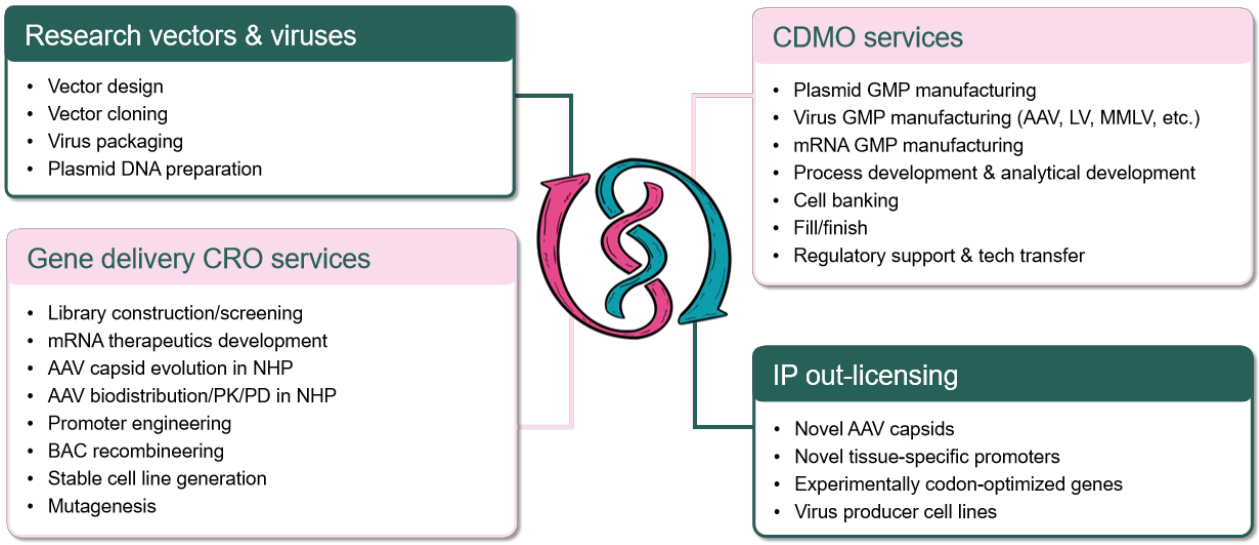
CDMO Services

Revolutionize Gene Delivery from Research to Therapy

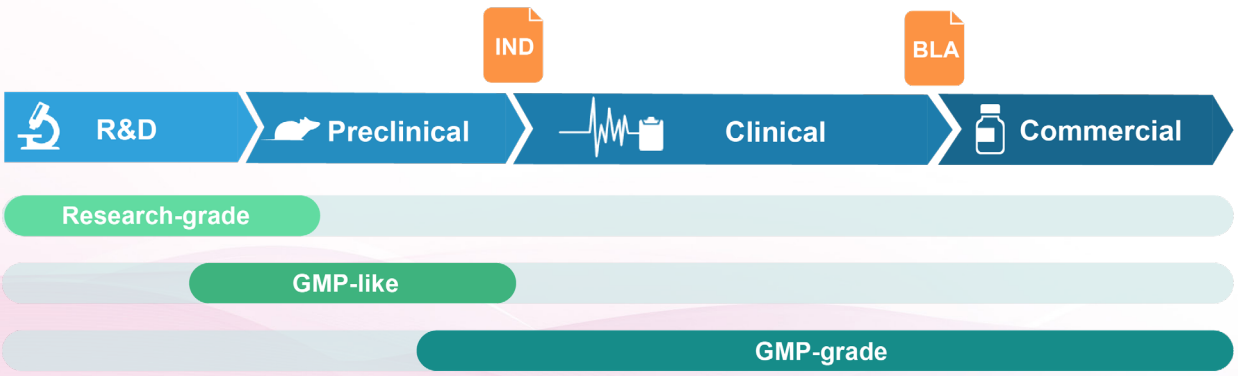


About VectorBuilder

As a global leader in gene delivery technologies, VectorBuilder offers a full spectrum of gene delivery solutions covering virtually all research and clinical needs from basic research to therapy. We have supported tens of thousands of laboratories and biotech/pharma companies across the globe along their entire drug-discovery pipelines, going from research-grade vectors for early discovery, to GMP-like vectors for preclinical testing, to full GMP-grade vectors for clinical trials. Our 4 major business segments include research vectors & viruses, gene delivery CRO services, CDMO services, and IP out-licensing.



VectorBuilder is a full-service CDMO with extensive experience in cGMP vector manufacturing. Operating several state-of-the-art facilities, we have supported many customers along their entire drug-discovery pipelines with GMP manufacturing of plasmid DNA, IVT mRNA, and viral vectors such as lentivirus, AAV, adenovirus, MMLV, and other viruses. Besides GMP manufacturing, our CDMO services include process development, analytical development, cell banking, fill/finish, and regulatory support. We have provided IND-enabling vectors to a worldwide client base in the US, Europe, Japan, China, and South Korea.



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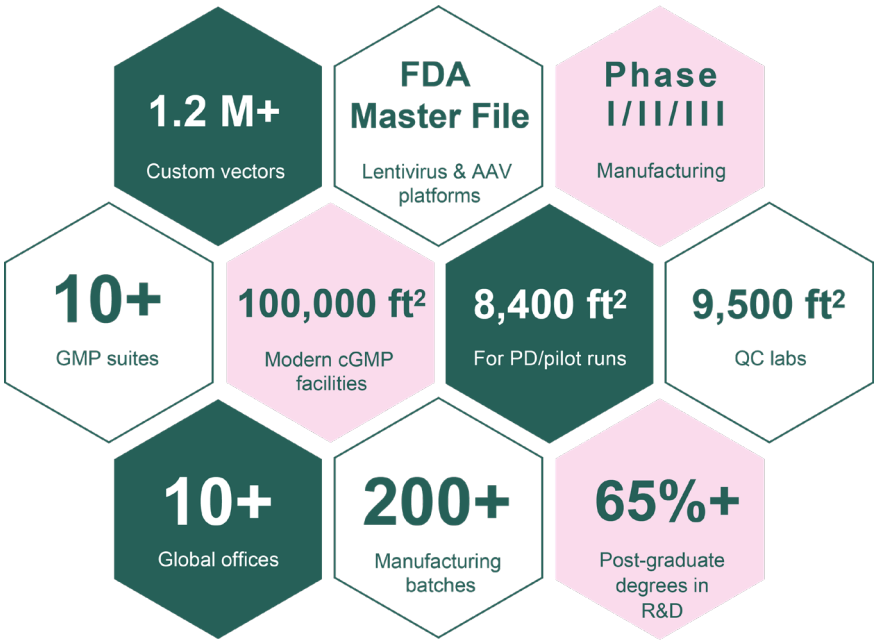
Our CDMO Capabilities

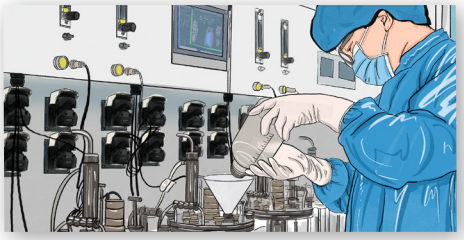
Our comprehensive quality system is embedded in every aspect of our GMP manufacturing process that spans facilities, supplies, production, fill/finish, storage, in-process and release QC, and personnel. Our company culture places great emphasis on quality, innovation, continuous improvement, and “white-glove” customer service. As such, we can consistently meet and exceed customer expectations. We also strive to achieve rapid turnaround and affordable prices while maintaining high quality and full regulatory compliance.



VectorBuilder currently has about 100,000 ft² of modern GMP facilities with advanced designs and state-of-the-art equipment. Our facilities include:

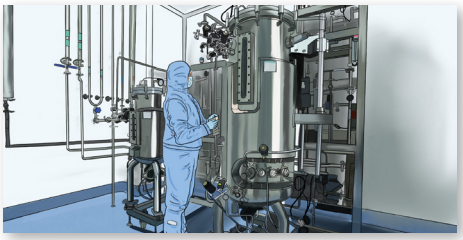
- 10+ GMP manufacturing suites
- Fill/finish suites
- QC laboratories and analytical development suites
- Process development suites
- GMP warehouse

CDMO Services Overview



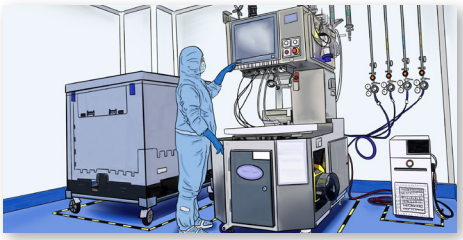
Process & Analytical Development

We develop and optimize GMP manufacturing processes for a variety of gene therapy vectors. We can develop and validate all the in-process and release QC assays required for the production of GMP-grade gene therapy vectors.



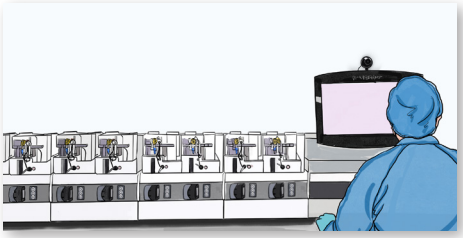
Plasmid Manufacturing

We can manufacture GMP-grade plasmid DNA at various scales, employing antibiotic-free and animal component-free production methods.



Viral Vector Manufacturing

We can produce GMP-grade AAV and lentivirus using our platform technologies. We also have experience producing other types of viral vectors such as adenovirus, MMLV, HSV, and vesicular stomatitis virus (VSV).

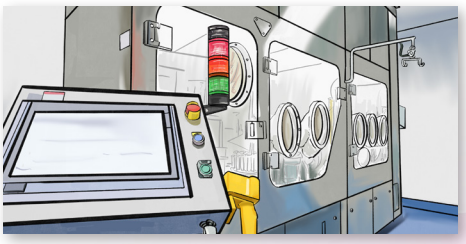


IVT RNA and LNP Manufacturing

We provide optimal in vitro transcription vector designs, large-scale IVT mRNA manufacturing, and LNP encapsulation followed by thorough quality control tailored to a wide range of research and clinical needs.

Cell Banking

We can generate GMP-grade Master Cell Banks (MCBs) and Working Cell Banks (WCBs) for E. coli, mammalian cells and insect cells, derived either from our in-house validated cell lines or customer-provided cell lines.



Fill/Finish

We can do manual or automated aseptic filling of the DS/DP into glass vials (0.25 ml to 2 ml) or cryo bags. We have the capacity to complete >3000 vials per batch.

Process Development

VectorBuilder has a dedicated process development team that is highly experienced in developing optimal manufacturing processes for GMP-grade gene therapy vectors. We consider many factors in our process development, including biological properties of the vector, quality and safety requirements, production quantity and scalability needs, regulatory requirements in the intended market, and the customer's cost and timeline target.

Upstream Process Development

- ***Cell line development***
  E. coli, mammalian cell lines, insect cell lines
- ***E. coli fermentation scale-up and scale-out***
  Fermentation systems range from flasks to up to 100 L stirred fermenters.
- ***Mammalian and insect cell culture scale-up and scale-out***
  Adherent systems: flasks, Cell Factory, fixed-bed bioreactors (up to 600 m^2)
  Suspension systems: flasks, wave bioreactor (up to 50 L), single-use bioreactors (up to 200 L)
- ***Media screening and optimization***
  Antibiotic-free, serum-free, animal-free, chemically defined
- ***High-density cell culture optimization***
  E. coli, mammalian cells, insect cells
- ***Transfection/infection optimization***
  Rep/Cap and helper plasmid optimization, plasmid DNA ratio, transfection reagent, infection MOI, cell density, etc.

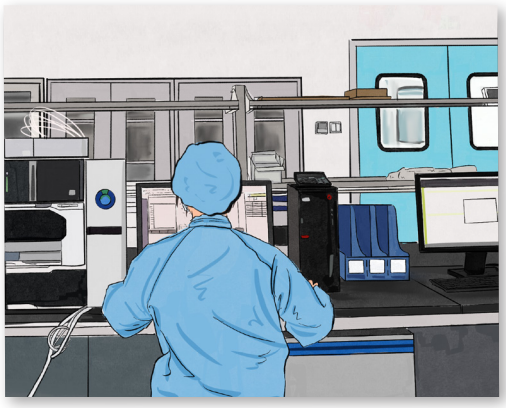
Vector Optimization

- ***Rich collections of fully validated vector components***
  Backbones, promoters (constitutive, tissue-specific, inducible, synthetic), ORFs, linkers, tags, shRNA and CRISPR target site libraries, etc.
- ***Large-scale screening platforms***
  Tissue-specific promoter/enhancer screening, capsid evolution, shRNA screening, CRISPR screening, Rep/Cap promoter optimization, CAR antibody screening, etc.
- ***Viral genome engineering***
  De novo construction of novel viral vectors, including utilizing BAC and YAC recombineering to build vectors containing large viral genomes such as coronavirus and herpes simplex virus (HSV).

Downstream Process Development

- ***Harvest and lysis optimization***
  Harvest time, cell lysis method, nuclease treatment, etc.
- ***Purification optimization***
  Chromatography: size exclusion, ion exchange, affinity, mixed mode
  Gradient centrifugation: sucrose, CsCl, iodixanol
- ***Clarification, concentration and buffer exchange***
  UF/DF (tangential flow, hollow fiber, depth filtration)

Analytical Development



VectorBuilder can provide the full range of analytical development services capable of developing, optimizing, qualifying and validating in-process and release QC assays tailored to individual gene therapy vectors. We can also provide drug stability studies to ascertain vector shelf life under various storage and transport conditions.

QC Attribute	QC Assay
General/physical properties	Appearance, concentration, pH, extractable volume, osmolality, aggregation
Identity	Restriction enzyme digestion, sequencing, agarose gel electrophoresis, SDS-PAGE, immunoassay
Strength/potency	Physical titer: qPCR, ddPCR, immunoassay, OD260/280 Infectious titer: plaque assay, TCID50 Expression of the transgene: transduction test, Western blot, RT-qPCR, flow cytometry
Purity	**Product related** • Full/empty viral particle ratio: TEM • Supercoiled plasmid ratio: agarose gel electrophoresis, HPLC **Host cell related** • Host cell protein: immunoassay, SDS-PAGE, silver stain, Micro BCA, BCA, HPLC • Host cell DNA: qPCR, agarose gel electrophoresis • Host cell RNA: agarose gel electrophoresis, RT-qPCR, fluorometric quantification **Process related** • Residual plasmid DNA: qPCR • Residual benzonase: immunoassay • Residual BSA: immunoassay • Residual PEI: HPLC • Residual antibiotic: immunoassay
Safety	Sterility: direct inoculation, membrane filtration sterility test Endotoxin: kinetic chromogenic assay (KCA) Mycoplasma: qPCR, culture method, indicator cell culture method Replication competent virus: qPCR, immunoassay, Southern blotting Adventitious virus: qPCR, in vitro cell culture Presence of viral oncogenes such as E1A and SV40: qPCR

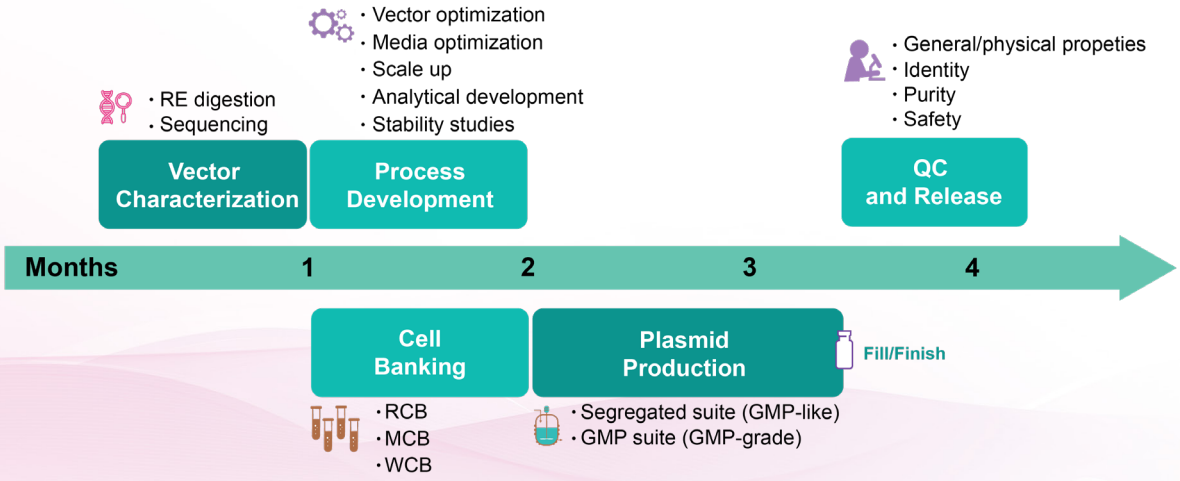
Plasmid Manufacturing

We can provide optimal vector designs tailored to a wide range of research and clinical needs. For plasmid DNA manufacturing, we offer several grades that cover different downstream needs including drug discovery research, pre-clinical studies, clinical trials, and commercialization.

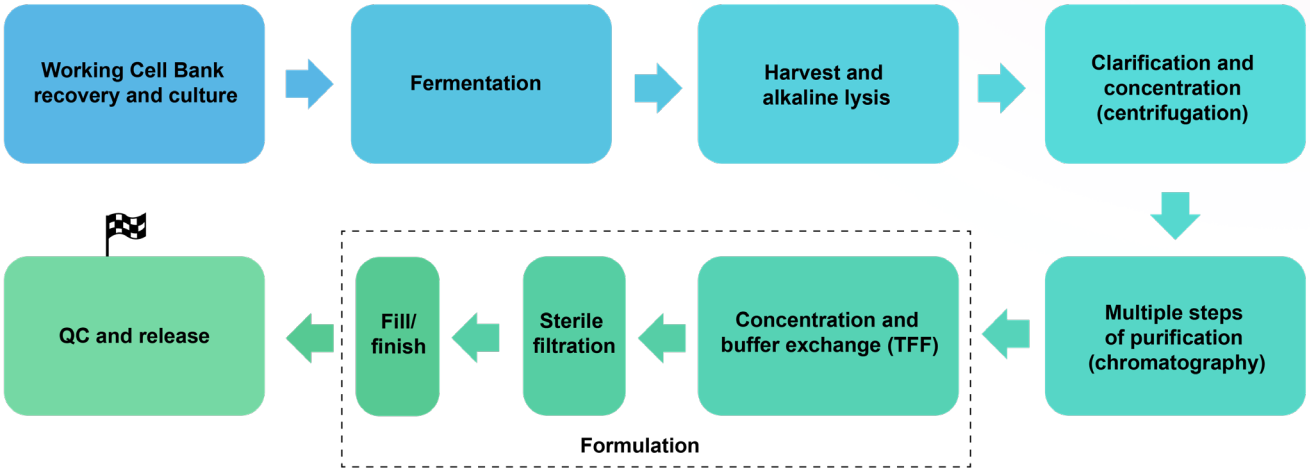
Plasmid DNA Offered

	Research-grade	GMP-like	GMP-grade
Applications	Basic research, drug discovery, preclinical studies	Preclinical studies	Preclinical studies, clinical studies, and commercialization
Production scales	10 ug to several 100 mg	10 mg to 1 g per batch	10 mg to 5 g per batch
Turnaround	1-8 days	1-3 months	A few months to half a year
Quality system	ISO9001	ISO9001 while adopting key features of GMP system	ICH quality guidelines for GMP manufacturing
Document deliverable	COA upon request	1. COA 2. Manufacturing summary 3. TSE/BSE statement upon request	1. COA 2. TSE/BSE statement 3. CTD documents 4. Others upon request

Workflow for GMP Production of Plasmid DNA



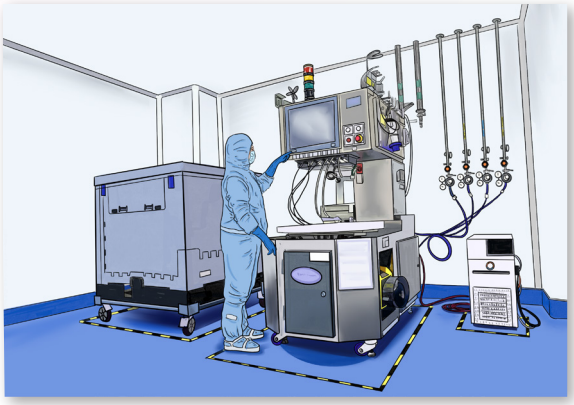
Technology Platform



QC and Release Criteria

QC Item	Method	GMP-like	GMP-grade
Plasmid concentration	UV spectrophotometry	≥500 ug/ml	≥500 ug/ml
pH	pH meter	Report result	Report result
Restriction digest	Agarose gel electrophoresis	Identical to expected restriction pattern	Identical to expected restriction pattern
Sanger sequencing	Sanger sequencing of the entire plasmid	Identical to reference sequence	Identical to reference sequence
A260/A280	UV spectrophotometry	1.80-2.00	1.80-2.00
ccc plasmid DNA ratio	EtBr stained agarose gel electrophoresis	≥80%	≥80%
Residual protein	BCA or equivalent	≤2.00%	≤2.00%
Residual RNA	Fluorescence analysis or equivalent	≤5.00%	≤5.00%
Residual host cell DNA	Quantitative PCR or equivalent	Report result	≤5.00%
Endotoxin	Kinetic chromogenic assay	≤50 EU/ml	≤10 EU/ml
Sterility	Direct innoculation	No growth	No growth

Viral Vector Manufacturing

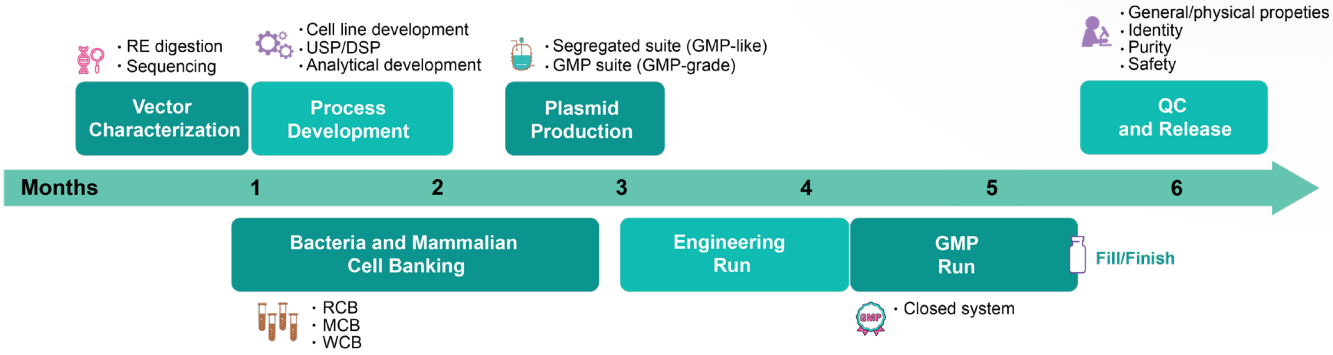


We can provide viruses of different scales and quality attributes to meet the full range of demands along the gene therapy drug development pipeline. We have established and validated platform technologies for large-scale GMP manufacturing of adeno-associated virus (AAV) and lentivirus.

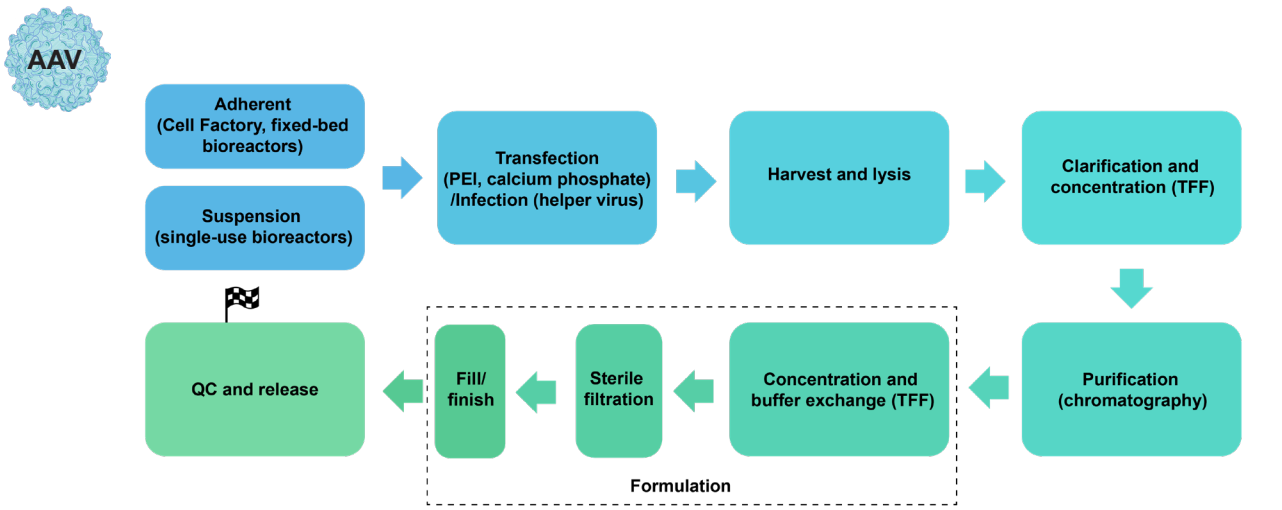
Viral Vectors Offered

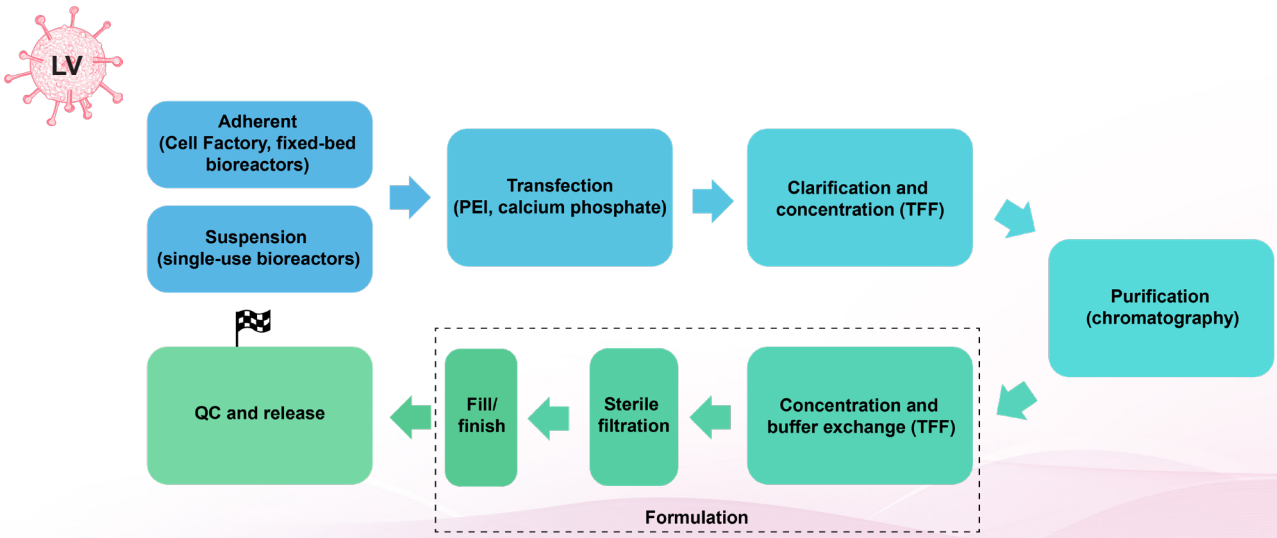
		Research-grade	GMP-like	GMP-grade
Applications		Basic research, drug discovery, preclinical studies	Preclinical studies	Preclinical studies, clinical studies, and commercialization
Production scales	**AAV**	$5x10^{10}$ to 10^{14} GC	$5x10^{13}$ to 10^{17} GC per batch	10^{14} to 10^{17} GC per batch
	Lentivirus	>$2.5x10^{7}$ TU	10^{9} to 10^{12} TU per batch	$5x10^{9}$ to 10^{12} TU per batch
Turnaround	**AAV**	10-50 days	4-5 months	6-12 months
	Lentivirus	8-16 days	4-5 months	6-12 months
Quality system		ISO9001	ISO9001 while adopting key features of GMP system	ICH quality guidelines for GMP manufacturing
QC and release tests		Titer measurement, SDS-PAGE, endotoxin testing, mycoplasma detectection, etc.	Depending on individual project needs	Full panel QC assays, analytical development upon individual project needs

Workflow for GMP Production of Viral Vectors



Technology Platforms

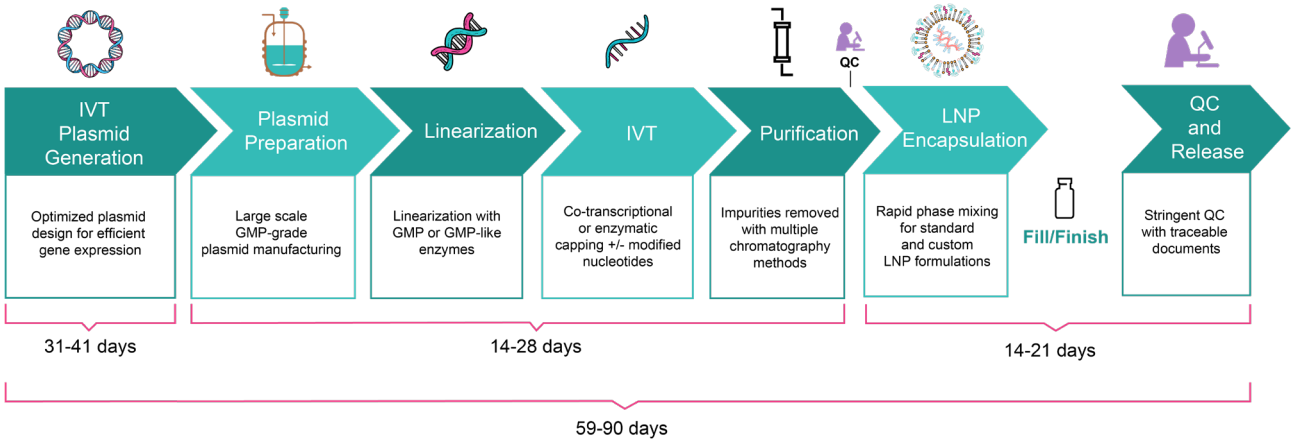




IVT RNA and LNP Manufacturing

VectorBuilder offers a full range of CRO and CDMO services for in vitro transcription (IVT) mRNA manufacturing and lipid nanoparticle (LNP) therapeutic development. Relying on our revolutionary vector design platform and extensive experience, we can provide optimal in vitro transcription vector designs, large-scale IVT mRNA manufacturing, and LNP encapsulation followed by thorough quality control tailored to a wide range of research and clinical needs. We offer several grades that cover different downstream needs including drug discovery research and pre-clinical studies.

Workflow for Production of IVT mRNA



IVT mRNA and LNP Offered

	Research-grade	GMP-like
Applications	Basic research, drug discovery, and preclinical studies	Preclinical studies such as animal testing of drug safety and metabolism
Production scales	mRNA: 0.1-10 mg LNP: 0.1-3 mg	mRNA: 0.01-20 g LNP: 3-20 mg
Turnaround	49-71 days • Vector design & cloning: 26-36 days • Plasmid production & linearization: 14-21 days • IVT mRNA production: 14-21 days • LNP encapsulation: 9-14 days	59-90 days • Vector design & cloning: 31-41 days • Plasmid production & linearization: 14-28 days • IVT mRNA production: 14-28 days • LNP encapsulation: 14-21 days
Quality system	ISO9001	ISO9001 while adopting key features of GMP manufacturing

Quality Control Assays

Product	Attribute	QC Assay
IVT DNA template	Concentration	Spectrometry
	Identity	Gel electrophoresis, Sanger sequencing
	Linearization	Capillary gel electrophoresis
	Residual host E. coli DNA	qPCR
mRNA	Concentration	UV-Vis spectrometry
	Identity	Capillary gel electrophoresis, reverse transcription followed by Sanger sequencing
	Capping efficiency	LC-MS, Capillary gel electrophoresis
	PolyA tail integrity	LC-MS, Capillary gel electrophoresis
	Residual protein	NanoOrange assay
	Residual plasmid	qPCR
	dsRNA	Dot blot
	Endotoxin	Kinetic chromogenic assay (KCA)
LNP	Encapsulation efficiency	RiboGreen assay
	Diameter, PDI, and Zeta potential	Zetasizer

Lipid Nanoparticle Encapsulation

Our production suite can accommodate custom lipid formulations and perform microfluidic mixing, dilution, buffer exchange, sterile filtration, and fill/finish using state-of-the-art equipment.

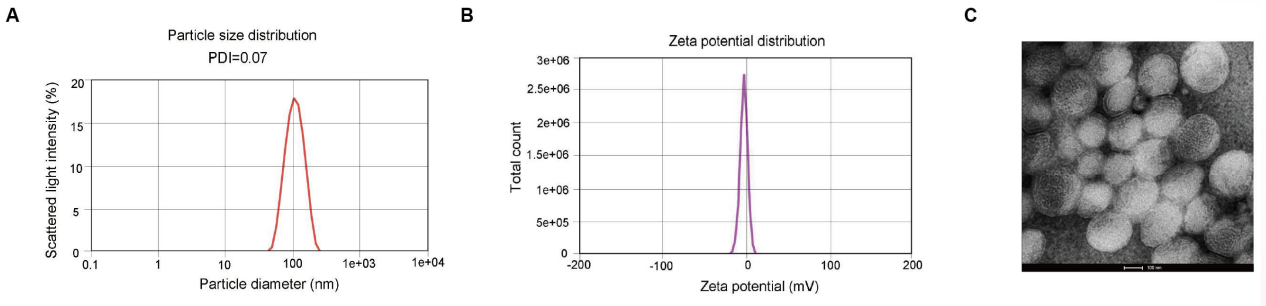


Figure 1. (A) Particle size was determined by dynamic light scattering (DLS) which measures the intensity differences of fluctuated light due to motion of particles. The polydispersity index (PDI) reflects the heterogeneity of a sample on particle size. (B) Zeta potential reflects the stability of LNP. The Zeta potential of the sample is between -1.872 mV and +1.872 mV. (C) TEM of LNPs produced at VectorBuilder.

Off-the-Shelf GMP Products

Virus Packaging Plasmids

VectorBuilder offers GMP-like and GMP-grade lentivirus and AAV packaging plasmids for the manufacturing of pre-clinical and clinical viral vectors for gene and cell therapies. Produced in our state-of-the-art facilities, each plasmid has been optimized to produce high titers of virus and has undergone thorough quality control.

Highlight

- Optimized and validated for high virus yield
- Off-the-shelf plasmids available for immediate use
- Plasmids produced under animal-free and antibiotic-free conditions
- Royalty free
- Drug Master Files available facilitating FDA IND application
- Kanamycin resistance

Lentivirus packaging plasmids

VB-VSV-G
VB-Rev
VB-Gag/Pol

AAV packaging plasmids

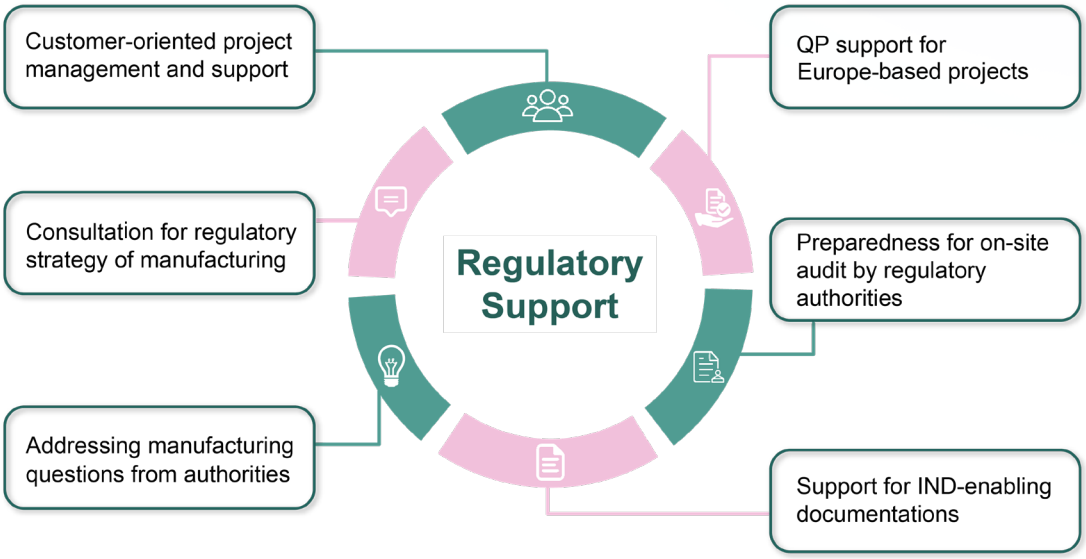
VB-AAV-Helper
VB-AAV2-Rep/Cap
VB-AAV9-Rep/Cap

QC and Release Criteria

QC Item	Method	GMP-like	GMP-grade
Plasmid concentration	UV spectrophotometry	≥500 ug/ml	≥500 ug/ml
pH	pH meter	Report result	Report result
Restriction digest	Agarose gel electrophoresis	Identical to expected restriction pattern	Identical to expected restriction pattern
Sanger sequencing	Sanger sequencing of the entire plasmid	Identical to reference sequence	Identical to reference sequence
A260/A280	UV spectrophotometry	1.80-2.00	1.80-2.00
ccc plasmid DNA ratio	EtBr stained agarose gel electrophoresis	≥80%	≥80%
Residual protein	BCA or equivalent	≤2.00%	≤2.00%
Residual RNA	Fluorescence analysis or equivalent	≤5.00%	≤5.00%
Residual host cell DNA	Quantitative PCR or equivalent	Report result	≤5.00%
Endotoxin	Kinetic chromogenic assay	≤50 EU/ml	≤10 EU/ml
Sterility	Direct innoculation	No growth	No growth

Regulatory Support

We work closely with our customers to provide regulatory support at each critical milestone of their drug development process. These include:



Technology transfer

We can provide technology transfer with best practices including detailed bill of materials, well-documented production process, and fully qualified analytical methods used in the manufacturing of the gene therapy vector.

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