ThermoFisher SCIENTIFIC

Viral vector CDMO services

• API • BIOLOGICS • **VIRAL VECTOR SERVICES** • EARLY & LATE PHASE DEVELOPMENT • CLINICAL TRIAL SOLUTIONS • LOGISTICS SERVICES • COMMERCIAL MANUFACTURING

patheon

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Viral vector services (VVS)

Experience. Capacity. Breadth of technical expertise and capabilities

With over 20 years of experience manufacturing a broad range of viral vector products, VVS has the experience needed to handle your unique product. With more than 555,000 square feet spread across more than 50 suites and growing, you can be sure we have the capacity you need. In addition, our breadth of integrated services ensure smooth transitions and expertise across your value chain.

Experience	Capacity	Capabilities
• 20+ years of cGMP experience • 160+ viral vector products produced • 700+ viral vector cGMP clinical and commercial lots • 3 commercial licenses with more expected	• More than 555,000 square feet • 50 drug substance suites • 12 drug product suites • 4 late-phase/commercial manufacturing facilities • Experience with 12+ AAV serotypes • 10 manufacturing modalities	• Full-service viral vector CDMO • Experience with 12+ AAV serotypes • 10 manufacturing modalities • Leverage Thermo Fisher's technology, cell lines, equipment, products, and logistics • Access to a breadth of integrated services

While the viral vector market is dominated by adeno-associated viruses (AAV) and lentiviral vectors (LV), there is also a range of less commonly used vectors. If you have a novel system, we're excited to learn about it. Regardless of your vector strategy, you can be confident that we have the experience and resources to smoothly manage any project.

Vector manufacturing modalities*		
AAV	Adherent + Suspension	Suspension + HSV
	Producer cell line + Adherent	Suspension + Baculovirus
ADENOVIRAL	Adherent + Suspension	
HERPESVIRAL	Adherent + Suspension	
LENTIVIRAL	Packaging/producer cell line	Adherent + Suspension
RETROVIRAL	Packaging/producer cell line	Adherent + Suspension

- Mammalian cells
- Mammalian cells transient transfection
- Mammalian cells infection
- Insect cells

* Additional manufacturing modalities also available; inquire for more information

Viral vector capabilities overview

Broad capabilities, flexible equipment options, and robust analytics

Broad capabilities

From process development and process characterization to manufacturing, QC, and fill-finish, VVS has the broad capabilities and expertise needed to develop and manufacture your viral vector product.

Process development and characterization capabilities			
Upstream processing	**Downstream processing**	**Assay development and analytics**	**Process sciences**

• Molecular and viral cloning
• Seed train and vector production via transfection, viral infection, and stable production
  • Cell lines (mammalian, insect, PCL, adherent, or suspension)
  • Technologies (Flatstock, iCELLis, SUB, Perfusion)
• Full process customization and development (ambr, DOE, iCELLis Nano, scale-up)
	• Purification of common and novel vector types
	• Chromatography-based
	• Optimization as needed
	  • Increase yield/recovery
	  • Full capsid separation
	  • Specific purity requirements
	• Broad range of purification technologies
		• Assay establishment, customization, or development
		• Platform assays for various vector types
		• Process development testing support
		• Preclinical material testing
		• High-throughput analysis for rapid support
			• Analytical support
			• Process establishment and engineering
			• Process characterization
			  • Risk assessments, CQAs, product profile
			  • Scale-down model qualification
			  • Satellite campaign batches

Manufacturing capabilities			
MS&T and process validation	**Manufacturing**	**QC**	**Fill-finish**
• Manufacturing support studies • Process validation plan and strategy • FMEA • Validation support studies • PPQ	• Suspension and adherent modalities • Clinical and commercial-scale capacity • Broad range of technologies and equipment • Cell and viral banking	• Compendial assay verification, assay qualification, and validation • DS and DP in-process and batch release testing • cGMP stability studies • Reference standard qualification • Assay bridging and product comparability studies	• Formulation evaluation • Semiautomated and automated fill lines (Bausch + Strobel, Optima) • Prequalified vial configurations • Primary vial labeling and packaging • Up to 5,000 vial fill capacity per lot

Flexible equipment options

Sites are equipped with flexible options to scale adherent or suspension manufacturing processes, upstream and downstream processing, and fill and finish. In addition, suites can be configured to meet additional process requirements, ensuring maximum flexibility to accommodate your unique needs.

<table>
<tr><th rowspan="2">Platform</th><th>PD/Phases 1 and 2</th><th colspan="4">Late-phase/commercial</th></tr>
<tr><th>Gosselies, Belgium</th><th>Lexington, MA</th><th>Cambridge, MA</th><th>Plainville, MA</th><th>Seneffe, Belgium</th></tr>
<tr><td>Adherent</td><td>24CS10 and 15HS36</td><td>iCELLis 48HS36 or 40CS10</td><td>iCELLis 500 40CS10 or 48HS36</td><td>Flex</td><td>24CS10 and 15HS36</td></tr>
<tr><td>Suspension HEK293</td><td rowspan="3">Up to 2 x 200 L</td><td rowspan="3">Flex up to 1,000 L</td><td>2 x 200 L</td><td rowspan="3">Up to 4 x 200 L
Up to 2 x 2,000 L</td><td>Up to 2 x 200 L</td></tr>
<tr><td>Suspension Sf9/ Baculovirus</td><td>Up to 2,000 L</td><td>Up to 2 x 1,000 L</td></tr>
<tr><td>Suspension other</td><td>Up to 2 x 200 L
Up to 2,000 L</td><td>Up to 2 x 200L
Up to 2 x 1,000L</td></tr>
<tr><td>Fill-finish equipment</td><td>N/A</td><td>Bausch + Strobel KSF5105
Up to 2,500 vials</td><td>Bausch + Strobel KSF5105
Up to 500 vials (10 mL)
Up to 2,500 vials (2 mL)</td><td>Optima VFVM 7000
Up to 5,000 vials</td><td>Bausch + Strobel KSF5105
Up to 10,000 vials</td></tr>
</table>

Alternative scales, technologies, and platforms (i.e., perfusion-based systems) available.

Robust analytics

Analytical development and testing is critical to ensuring the development of robust processes and products that meet regulatory requirements. By using in-house resources and methods and continually investing in new technologies, we have created an agile response to adhere to changing regulatory and customer requirements. Consistent method execution ensures streamlined batch release testing, further accelerating the release of your product.

Critical quality attributes	Assay and testing methods	
Strength/potency	• Vg titer • Infectious titer • Transduction assays	• Capsid titer • Potency assays • Infectivity
Impurities/purity	• Residual DNA (host, plasmid, helper) • Residual HCP	• Aggregation • E:F capsid (AUC)
Safety	• Adventitious agents • Sterility/bioburden • Mycoplasma	• Endotoxin • rcAAV/rcL/rcA
Other assays/particles	• Particle concentration (HPLC) • Capsid ELISA • Total protein/DNA	• Genome integrity • A260/280

Tech transfer and process development

Phased approaches and collaborative readiness assessments ensure smooth transitions

Technology transfer from a sponsor company to its CDMO of choice can be one of the most critical stages of development. A full understanding of available data and product requirements is necessary to ensure comprehensive gap and risk assessments and development of product-appropriate batch records, SOPs, and product specifications. A phased approach can help ensure a smooth tech transfer process—and subsequent process performance qualification activities—so that cGMP manufacturing can start as soon as possible.

Phased approaches to (A) technology transfer and (B) process performance qualification

A.

Information transfer	Information assessment	Execution
• Project schedule • Team roles • Available data transfer • Initial facility fit • Raw materials assessment	• Detailed gap and risk assessment • Bill of materials • Detailed process descriptions • Sample plan • Process development/ characterization/pilot runs (if needed)	• Batch records • SOPs • Spec development • ENG and GMP run execution

B.

Phase 1	Phase 2	Phase 3A	Phase 3B

Process definition
• Process characterization/ process understanding
• Shipping studies
	Process validation
	• PVMP
	• PPQ runs
	• Support PQs
	  • Buffer/media hold studies
	  • Clean hold time studies
	  • Buffer/media mixing studies
		Continued process verification (short-term)
		• Controlled by CPV plan
		• Generation of intermediate process control limits
		• Finalization of process control limits
			Continued process verification (long-term)
			• Controlled by trending program
			• Process monitoring for control
			• Evaluation for process health

Global capacity

Global footprint of over 650,000 square feet ready to develop and manufacture your viral vector products

We have the flexibility to deploy capacity, talent, and tech transfers across sites to ensure efficient processes and robust product.

The Lexington, Cambridge, and Alachua sites are all equipped with the latest tools to support process and analytical development, as well as preclinical and clinical manufacturing and in-house QC laboratories for rapid lot release testing.

The addition of the Plainville site effectively doubled our US manufacturing capacity. The site was designed for large-scale manufacturing and offers a flexible and scalable configuration of laboratory and production suites co-located with adjacent warehousing and office space. Plainville R&D is heavily focused on developing the next generation of production platforms intended to facilitate rapid transitions from early development to commercial-scale manufacturing.

The Gosselies and Seneffe, Belgium, sites joined our viral vector services network in 2021. Gosselies is focused on process and analytical development with small- to mid-scale cGMP production capabilities of up to 200 L, whereas the Seneffe site is dedicated to clinical and commercial viral vector production, fill-finish, and manufacturing with mid- to large-scale cGMP production of up to 2,000 L.

More than 500,000 square feet of development and manufacturing facilities in North America

Cambridge, MA	Lexington, MA	Plainville, MA
• 140,000 sq. ft. (3 buildings) • Scale-up labs • 10 cGMP DS suites • 2 cGMP DP suites • 2 host cell suites • QC labs • First commercial license (lentivirus) obtained in Q1 2021 with additional licenses expected to follow • Process characterization and validation	• 65,000 sq. ft. facility • MS&T labs for process transfer, validation, and characterization • 8 cGMP DS suites • 1 cGMP DP suite • QC labs • Flexible facility supporting range of manufacturing technologies	• 290,000 sq. ft. facility, cGMP-ready in 2022 • Up to 25 cGMP DS suites • Up to 4 cGMP DP suites • Full-scale engineering lab • Centralized support services • State-of-the-art digital manufacturing technology

More than 40,000 square feet of development and manufacturing facilities in Europe

Gosselies, Belgium	Seneffe, Belgium
• 4,000 sq. ft. of classified cGMP space • 4,300 sq. ft. of R&D space • 2 cGMP suites with upstream and downstream processing capabilities • Process and analytical development • Clinical viral vector production	• ~34,000 sq. ft. dedicated to upstream and downstream processing and fill-finish • 4 cGMP manufacturing lines that can be run in parallel • 2 fill-finish suites (1 clinical, 1 commercial) • Quality control labs • Robust reliability and performance with production and fill-finish operations run at the same site

Regulatory services

Document review and preparation to support your regulatory filings

The advanced therapies regulatory landscape is continually evolving, and what is acceptable today may not be acceptable tomorrow. With over 15 years of experience supporting customers with global regulatory interactions (US, EU, and Canada), CMC regulations, guidelines, and inspections, we have developed an approach that is well-suited to evolving requirements. Working in concert with our process development and manufacturing technical experts, our regulatory services team can help reduce the number of intermediaries and filing lead times by providing document review, gap analyses, and document preparation to support your regulatory filings.

Document review

- Registration file review gap analysis
- Registration file comparison versus
  - Donor site
  - Thermo Fisher site current practices and regulatory standards
- Summary form on CTD quality/CMC file review and preparation

Document preparation

- Complete CMC dossier
- New application—ICH region (EU and US)
- Abridged export files—non-ICH region
- MoH inquiry responses—ICH region partial CMC dossier
- Regulatory feedback (EU and US)

Technical support

- **Site-related**
  - Master referentials
  - Manufacturer license/GMP certificate
  - Site master documents
- **Product-related**
  - Original declaration—therapy and components
  - Registration questionnaire
  - Permits
  - Document legalization

Regulatory services

- 15 years of experience
- ICH region (EU and US)—ICH Common Technical Document (CTD) Module 3
- Range of services
  - Document preparation
  - Document review
  - Technical support

Patheon Quick to Clinic™ viral vector program

De-risk your therapy development and advance to the clinic more quickly

Patheon™ Quick to Clinic™ viral vector services is a high-performance, scalable, end-to-end manufacturing service for adeno-associated viral (AAV) and lentiviral (LV) vectors. This service enables you to deliver your gene therapy to the clinic by de-risking timelines and global regulatory filings without additional or surprising out-of-pocket costs.

De-risk your therapy development and advance to the clinic more quickly

Patheon Quick to Clinic™ viral vector services

Moving gene therapies from preclinical studies to clinical and commercial manufacturing is a complex journey that requires significant financial investment—and it's filled with risks and challenges.

Thermo Fisher Scientific offers a high-performance, scalable, end-to-end manufacturing service for adeno-associated viral (AAV) and lentiviral (LV) vectors. This service enables you to deliver your gene therapy to the clinic by de-risking timelines and global regulatory filings without additional or surprising out-of-pocket costs.

End-to-end, flexible viral vector manufacturing services

Accelerated timeline

- Raw materials fully released with licenses secured
- Prequalified analytics
- Streamlined batch release
- Supported by a large network of Thermo Fisher Scientific gene therapy products

Global regulatory filing

- Industry expertise in regulatory CMC management and compliance
- Phase-appropriate regulatory support included
- Drug master file (DMF)

Cost-effective and transparent price

- All-inclusive upfront price that includes pass-through costs (raw materials), licenses*, cell banking, and more
- No additional drug substance process development and release testing costs**
- Improved cash flow with spread out payment structure

* May require additional licensing for proprietary AAV serotype

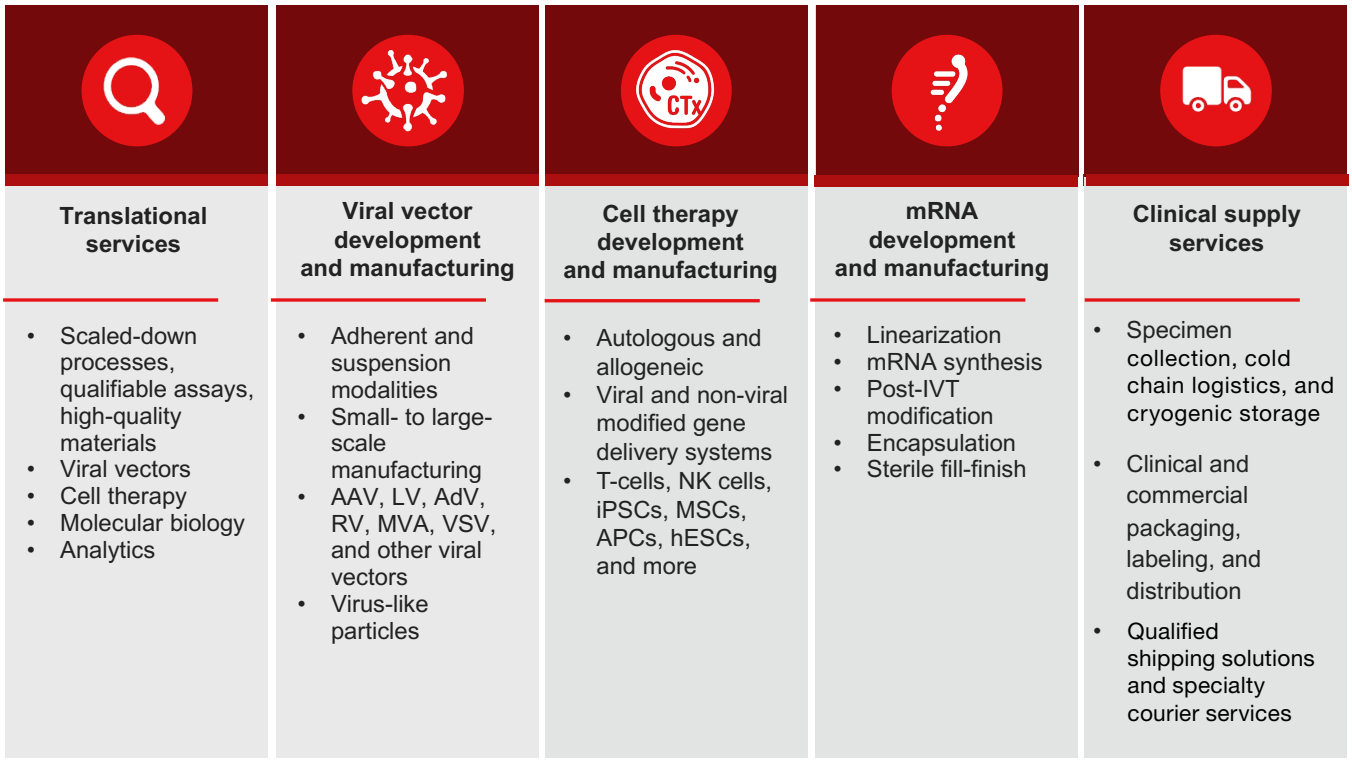
** Standard Patheon™ Quick to Clinic™ process with the flexibility to add plasmid manufacturing, DP fill and release testing at a fee

Advanced therapies integrated services

Integrated services de-risk development and manufacturing to get you to clinic faster

Integrated services can reduce risk in both development and manufacturing by streamlining handoffs and allowing key processes to run in parallel.

One key risk area that is often overlooked is the early establishment of manufacturing controls when transitioning from early discovery work to clinical manufacturing. That's why we've added early translational services to help streamline your translational research and rapidly identify lead therapeutic drug candidates. Translational services utilizes established, scalable processes with the advanced analytical testing that is characteristic of future cGMP workflows to support candidate drug selection.



Translational services

- Scaled-down processes, qualifiable assays, high-quality materials
- Viral vectors
- Cell therapy
- Molecular biology
- Analytics

Viral vector development and manufacturing

- Adherent and suspension modalities
- Small- to large-scale manufacturing
- AAV, LV, AdV, RV, MVA, VSV, and other viral vectors
- Virus-like particles

Cell therapy development and manufacturing

- Autologous and allogeneic
- Viral and non-viral modified gene delivery systems
- T-cells, NK cells, iPSCs, MSCs, APCs, hESCs, and more

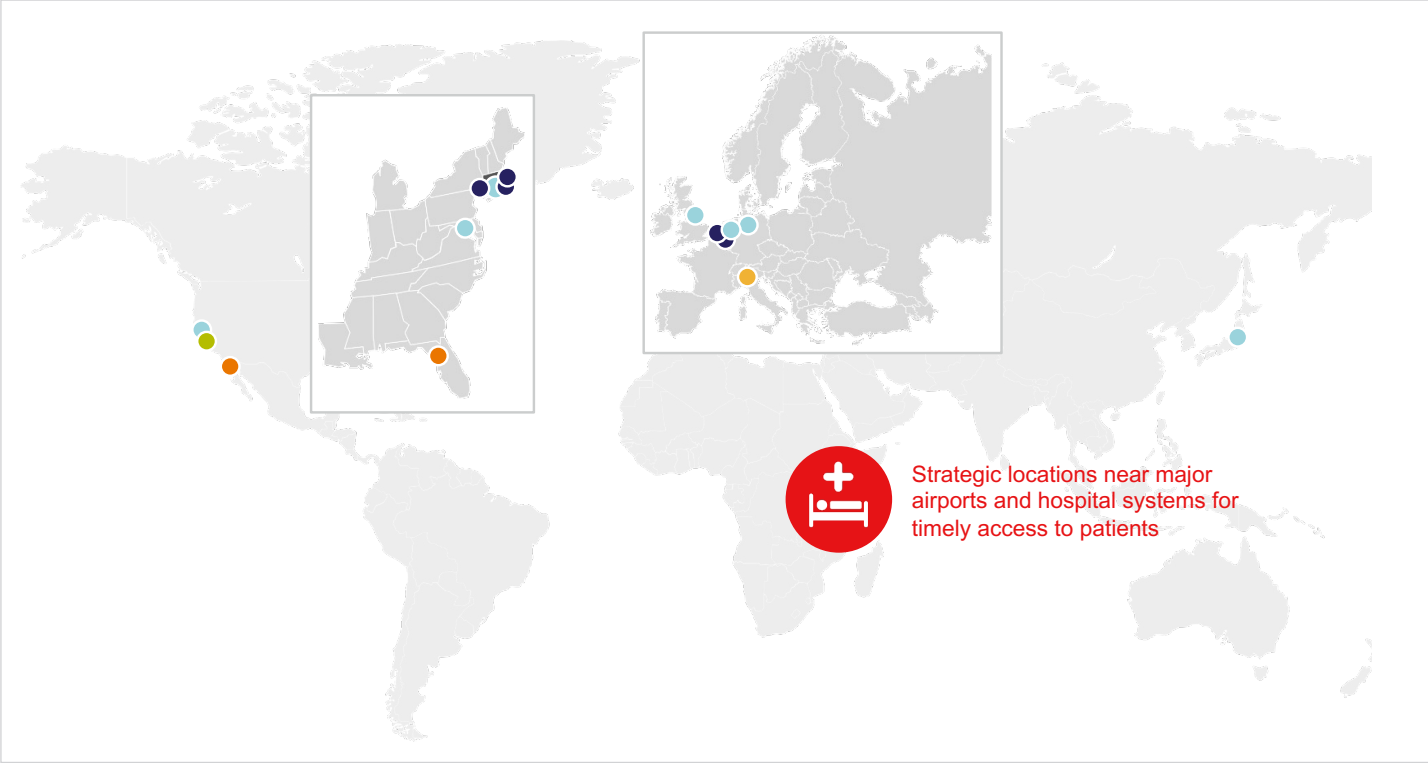
mRNA development and manufacturing

- Linearization
- mRNA synthesis
- Post-IVT modification
- Encapsulation
- Sterile fill-finish

Clinical supply services

- Specimen collection, cold chain logistics, and cryogenic storage
- Clinical and commercial packaging, labeling, and distribution
- Qualified shipping solutions and specialty courier services

Advanced therapy development, manufacturing, and supply chain services across the globe



- **Cell therapy**
  - San Francisco, California, US
- **Cell and gene therapy clinical services**
  - Bishop's Stortford, United Kingdom
  - Bleiswijk, Netherlands
  - Franklin, Massachusetts, US
  - Rockville, Maryland, US
  - Tokyo Japan
  - Vacaville, California, US
  - Weil am Rhein, Germany, DE cryocentre
- **mRNA**
  - Monza, Italy
- **Translational services/science and technology**
  - Alachua, Florida, US
  - San Diego, California, US
- **Viral vector**
  - Cambridge, Massachusetts, US
  - Gosselies, Belgium
  - Lexington, Massachusetts, US
  - Plainville, Massachusetts, US
  - Seneffe, Belgium

For more than 20 years, Thermo Fisher has been providing the experience, capacity, and breadth of technical expertise and capabilities needed to bring your viral vector product to market

Experience and expertise in gene therapy

- 20+ years viral vector (VV) cGMP track record
- 4 late-phase/commercial manufacturing facilities
- More than 50 drug substance and 12 product suites
- Experience with AAV (natural and novel stereotypes), LV, Adenoviral, Herpesviral, Retroviral, and viral vaccine

Strong foundation of proven success

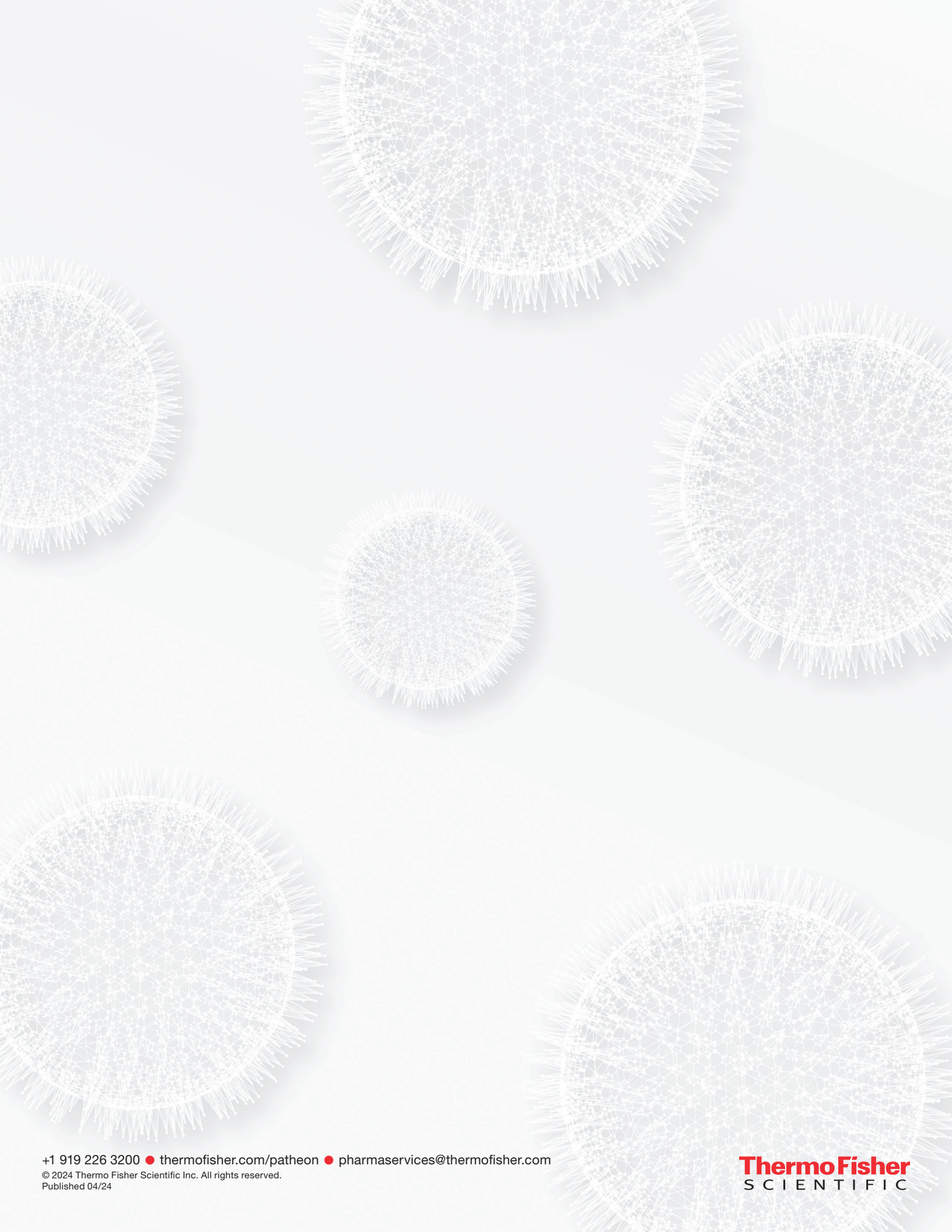
- 3 commercial licensed products
- Multiple regulatory filings in the pipeline
- More than 700+ viral vector cGMP clinical and commercial lots manufactured
- More than 160+ VV products produced
- Expansive global network offering 555,000 square feet capacity

Accelerated product access to patients

- Leading VVS regulatory expert team
- 10 manufacturing platforms
- Leverages based on Thermo Fisher's technology, cell lines, equipment, products, and logistics
- Access to range of advanced therapy CDMO services and global supply chain network

Get started today. Contact your local sales representative or visit patheon.com/vvs to learn more.

Notes



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