GMP-GRADE PRODUCTS

FOR NUCLEIC ACID THERAPEUTIC MANUFACTURING

NEW ENGLAND Biolabs®

For over 50 years, NEB® has been a world leader in the discovery and production of reagents for the life science industry. When it is time to scale up and optimize reaction components, our standalone reagents are readily available in formats matching our GMP-grade* offering, enabling a seamless transition to large-scale therapeutic manufacturing.

To better serve the needs of customers in regulated markets, in 2018 NEB opened a state-of-the-art, 43,000 sq. ft. production facility in Rowley, MA for the manufacture of GMP-grade products – approximately 15 minutes from our main campus in Ipswich, MA, USA. This purpose-built facility includes Quality Control and Production functions ranging from a shipping/receiving area and dedicated warehouse, to separate inoculation preparation, fermentation, purification and filling suites.

From research to therapeutic production, NEB's GMP-grade portfolio will meet your needs.

NEB's portfolio of research-grade and GMP-grade reagents support microgram scale research production to gram scale therapeutic mRNA production. Our optimized HiScribe kits and components enable convenient *in vitro* transcription (IVT) workflows. When it is time to scale up and optimize reaction components, our standalone reagents are readily available in formats matching our GMP-grade offering, enabling a seamless transition to large-scale therapeutic manufacturing.

To inquire about custom formats or GMP-grade product manufacturing, contact us at
www.neb.com/contactcustomizedsolutions

** "GMP Grade" and "GMP-grade" are branding terms NEB uses to describe products manufactured or finished at NEB's Rowley facility. The Rowley facility was designed to manufacture products under more rigorous infrastructure and process controls to achieve more stringent product specifications and customer requirements. Products manufactured at NEB's Rowley facility are manufactured in compliance with ISO 9001 and ISO 13485 quality management system standards. However, at this time, NEB does not manufacture or sell products known as Active Pharmaceutical Ingredients (APIs), nor does NEB manufacture its products in compliance with all of the Current Good Manufacturing Practice regulations.*

BENEFITS OF **GMP-GRADE PRODUCT MANUFACTURING** AT NEB

NEB's expertise in enzyme manufacturing positions us to best anticipate your needs and minimize the risk of transferring manufacture of your materials to our GMP-grade production facility. Examples of customer requirements that are achieved by our GMP-grade products include:

- Bioburden and/or endotoxin specifications on reagents
- Certified animal-free origin and manufacturing process
- Qualified equipment, utilities, QC test methods and instrumentation to deliver the highest levels of lot-to-lot consistency
- Validated QC methods designed to provide customers with quantitative values where appropriate

Infrastructure & Approach

- Purpose-built for GMP-grade manufacturing
- Increased manufacturing output
- ISO 8 clean rooms, ISO 5 filling hoods
- Environmental monitoring of the facility
- Animal-free facility

Manufacturing Processes

- Lateral transfer of historical RUO (Ipswich) to GMP-grade (Rowley) enabling seamless customer scale up without impact from NEB materials
- Characterized master cell banks
- Ampicillin-free processes
- Dedicated chromatography resins
- 0.22 micron-filtered final product

Product Attributes/Testing

- Validated QC methods utilizing quantitative analytical instrumentation
- Verified compendial test components where applicable
- TSE/BSE statements – animal-free raw materials, processes and formulation
- Established reference standard program and stability program for each product
- QC release testing with stringent specifications for impurities such as RNase, Endo and Exonucleases, genomic DNA, bioburden and endotoxin

QA & Regulatory

- ISO 9001 and ISO 13485 certification
- Batch history files/batch records
- Defined CQAs and CPPs
- Enhanced change management and lot disposition processes
- Customer support for regulatory submissions and required risk asssesments/evaluations including but not limited to melamine, residual solvents, glycerol-containing compounds, elemental impurities and residual antibiotics

Learn more at
www.neb.com/GMP

GMP-GRADE PRODUCTS FOR NUCLEIC ACID THERAPEUTICS MANUFACTURING **AT THE SCALE (µL to L) YOU NEED**

	GMP-GRADE PRODUCT NAME	GMP-GRADE PRODUCT DESCRIPTION
 **AMPLIFICATION**	Q5® Hot Start DNA Polymerase	Composed of a novel polymerase fused to the processivity enhancing Sso7d DNA binding domain, improving speed, fidelity and ultra-low error rates
	phi29 DNA Polymerase	Replicative polymerase from the *Bacillus subtillis* phage phi29 and has exceptional strand displacement and processive synthesis properties with inherent 3´→5´ proofreading exonuclease activity
 **mRNA SYNTHESIS**	T7 RNA Polymerase	RNA Polymerase used for *in vitro* mRNA synthesis, and is highly specific for the T7 phage promoter
	Inorganic Pyrophosphatase (*E. coli*)	Catalyzes the hydrolysis of inorganic pyrophosphate to form orthhophosphate
	RNase inhibitor (Murine)	Specifically inhibits RNases A,B and C
	DNase I (RNase-free)	DNA specific endonuclease used for removal of contaminating genomic DNA from RNA samples and degradation of DNA templates in transcription reactions
	Vaccinia Capping Enzyme	Adds the m7G-cap (Cap-0) to the 5´ end of the triphosphorylated and dephosphorylated RNA
	Faustovirus Capping Enzyme	
	Cap 2'-O-Methyltransferase	Adds a methyl group at the 2´-O position of the first nucleotide adjacent to the cap structure at the 5´ end of the RNA
	HiScribe® T7 RNA Polymerase Mix	Separate components available in GMP-grade format
	HiScribe 10X T7 Reaction Buffer	
 **NUCLEIC ACID THERAPEUTICS MANUFACTURING**	ATP	
	CTP	
	GTP	
	UTP	
	BsaI-HF®v2 COMING SOON	Type IIS restriction enzyme optimized for protocols requiring DNA cutting by BsaI
	BspQI	Type IIS restriction enzyme and isoschizomer of LguI and SapI used to linearize plasmid DNA for mRNA therapeutics
	Deoxynucleotide (dNTP) Solution Mix	An equimolar solution of ultrapure aATP, dCTP, dGTP and dTTP (25mm each)
	T4 DNA Ligase	Catalyzes the formation of a phosphodiester bond between juxtaposed 5´ phosphate and 3´ hydroxyl termini in duplex DNA or RNA. Joins blunt end and cohesive end termini as well as repair single stranded nicks in duplex DNA and some DNA/RNA hybrids
	T4 DNA Ligase Reaction Buffer	
	T5 Exonuclease	Double-stranded DNA specific exonuclease and single-stranded DNA endonuclease, initiates at the 5' termini of linear or nicked double-stranded DNA
	TelN Protelomerase	Cuts dsDNA at a TelN recognition sequence and leaves covalently closed ends at the site of cleavage

NOT SURE WHETHER YOU NEED **RESEARCH-GRADE (RUO)** OR **GMP-GRADE** PRODUCTS?

		RUO	GMP*
mRNA PRODUCTION	Ability to produce gram to kilogram quantities of mRNA		✓
	Support production of commercially approved mRNA product(s)		✓
	Comparability reports supporting migration from RUO to GMP-grade products for clinical production		✓
PRODUCT CUSTOMIZATION	Examples include but are not limited to: High-concentration enzymes, formulation, fixed protein concentrations, packaging and fill size	✓ Contact our Customized Solutions Team to discuss	✓ Contact our Customized Solutions Team to discuss
INFRASTRUCTURE	Animal-free facility		✓
	Risk-based Validation Programs	✓	✓
	Expanded validation requirements for facility/utilities/environment/cleaning/process equipment/computer systems		✓
	ISO 8 Clean Rooms, ISO 5 Filling Hoods		✓
	Multiple production sites for business continuity	✓	✓
MANUFACTURING PROCESSES	Ampicillin-free processes	Contact our Customized Solutions Team to discuss	✓
	Animal-free processes and final formulation	Contact our Customized Solutions Team to discuss	✓
	Characterized master cell banks		✓
PRODUCT ATTRIBUTES/ TESTING	Comprehensive panel of product contamination assays performed and Terminal filtration of final product	✓	✓
	Validated assays with quantitative results		✓
	Compendial assays applied to all products, including bioburden and endotoxin levels, where applicable		✓
	TSE/BSE statements		✓
	Animal-free raw materials, processes and formulation	Contact our Customized Solutions Team to discuss	✓
QA & REGULATORY	ISO 9001 and ISO 13485 certified	✓	✓
	Batch history files/batch history records	✓	✓
	Consolidated batch history file/batch records and defined critical quality attributes and critical process parameters and QA reviews		✓
	Change management and lot disposition by Quality Unit	✓	✓
	Regulatory support package including but not limited to the following risk statements – melamine, antibiotic, mutagenic and elemental impurities, nitrosamine and residual solvents		✓
	Validated shipping configurations	✓	✓
	Temperature tracking devices for all GMP-grade shipments		✓
SUPPORTED APPLICATIONS		Research use or preclinical applications	For further processing in clinical or commercial cGMP applications

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x/f/yNEB137_V7.0_0625