

The world leader in serving science



Reagents and custom solutions for mRNA-based therapeutics development

Synthesis | Purification | Formulation | Delivery

ThermoFisher
SCIENTIFIC

Innovation and quality to accelerate your idea

Development and commercialization of emerging mRNA-based products present the market with new challenges, from establishing secure supply chains of critical raw materials to creation of customized solutions. At Thermo Fisher Scientific, we rise to this challenge by applying our breadth and depth of technologies and resources to support your efforts.

Partner with us to leverage our innovative technologies, high-quality products, technical expertise, and global support infrastructure. Our team works with you every step of the way, forming strategic alliances to help ensure your commercial success.

Raw material for mRNA therapeutics

We have a complete offering for all of your mRNA therapeutics needs, from *in vitro* transcription through *in vivo* delivery.

- Scalable systems support early-stage research through clinical development and commercialization
- Leading innovation driven by continual process optimization
- Comprehensive selection of Thermo Scientific™ TheraPure™ synthesis reagents
- Verified Invitrogen™ Dynabeads™ magnetic beads for superior analytical reproducibility
- Extensive library of proprietary delivery reagents
- Flexible licensing options



Customization

Building innovation into your mRNA platform for higher performance, market differentiation, or intellectual property positioning can be achieved with our array of custom capabilities.

- Formulations play an important role in the mRNA workflow. Use our proprietary formulations, or request your own developed formulation for enzymes, buffers, and nucleotides.
- Does your platform require raw materials with unique specifications? Our advanced analytical team specializes in the development and execution of methods to provide the level of control required for raw materials for therapeutics.
- Specialized reagents and modified nucleic acids can enhance mRNA stability, transcription efficiency, and yields. Our custom chemistry team works side by side with our customers to develop and manufacture complex nucleic acid-based molecules, including modified nucleotides and capping compounds.

World-class manufacturing

Reagents for mRNA therapeutics are manufactured in facilities certified to ISO 9001 or ISO 13485 standards. Our resources include bioprocessing facilities, a cleanroom, chemical synthesis laboratories, and QC testing sites to help ensure consistent product performance. For large-volume and custom services, we provide:

- Reagent formulation
- Nucleic acid synthesis, including modified nucleotides
- Bioprocessing
- Custom packaging and labeling



Quality assurance and regulatory compliance

Our controlled processes are designed for product quality and consistency, and we provide regulatory documentation and support.

Analytical testing methods

We manufacture each lot of product to high quality specifications using validated methods. Customizable quality specifications can be established for custom products, with the accompanying Certificates of Analysis. Our testing methods include:

- **Purity**—HPLC, LC-MS, and more
- **Consistency**—appearance, concentration, and pH
- **Functional activity**—enzyme activity and *in vitro* transcription assay

Regulatory documentation and support

In addition to standard Material Safety Data Sheets, we can provide documentation for custom products to help you meet your regulatory needs. Our logistics team is experienced in global distribution, and our quality assurance team can work directly with your regulatory staff to help manage change notifications and site audits.

mRNA therapeutics workflow



We offer a comprehensive range of custom and make-to-stock products for your mRNA workflow. Our products are highly optimized to work in concert, to help ensure superior performance and analytical reproducibility. And with our trusted Thermo Scientific™, Applied Biosystems™, and Invitrogen™ brands, you can expect and rely on quality, consistency, and convenience. If you can't find the right product for your workflow, or would like products built to your specifications, contact us and we will guide you.

“The relationship with Thermo Fisher Scientific secures our access to customized material essential for the manufacturing and commercialization of our RNA-based product candidates. In addition, as a life science services leader, Thermo Fisher can also deliver reagents at the scale needed to expand our manufacturing capacities.”

–CEO of biotechnology company

Synthesis

Accelerated development of mRNA-based therapeutics has necessitated the transformation of standard, research-grade *in vitro* transcription reagents into raw materials specifically designed and manufactured under advanced quality standards. TheraPure reagents for mRNA therapeutics provide our partners access to the most experienced development, analytical, and manufacturing teams in the industry.

The TheraPure name represents our highest level of purity for mRNA synthesis reagents, with products manufactured using high-definition analytics and tightly controlled purity standards. Our TheraPure portfolio offers a unique integrated solution for mRNA synthesis, including the following reagents.

Animal origin-free (AOF) and ampicillin-free (AF) enzymes

Our manufacturing process eliminates potential disease risks from prions (bovine spongiform encephalopathy and transmissible spongiform encephalopathy) and viruses. Components of animal origin are replaced with AOF components throughout the manufacturing process—from fermentation to enzyme formulation (Figure 1).

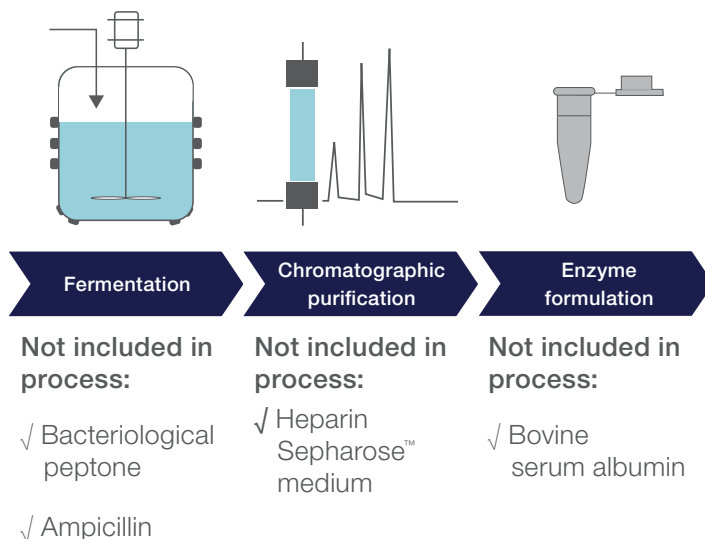


Figure 1. AOF and AF enzyme manufacturing process. Each step of our manufacturing process is carried out under stringent conditions. These enzymes are purified completely from cultures without animal-sourced components.

High-purity NTPs and modified nucleotides

Nucleotides are manufactured with greater than 99% triphosphate purity (as determined by quantitative HPLC) using a stringent purification process that eliminates cross-contamination from mono- and diphosphate forms and macromolecules such as DNases and proteases. Our nucleotides are available in various modifications to enhance specific properties, including increased nuclease resistance, increased translation, and decreased immunogenicity.

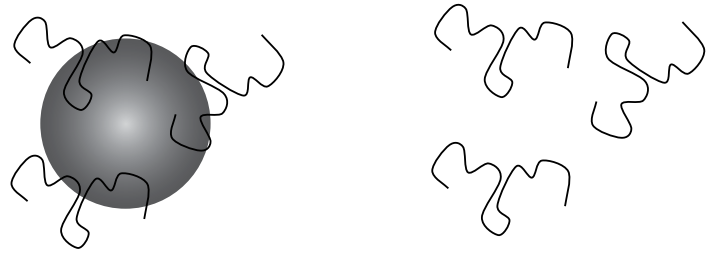
In vitro RNA synthesis product portfolio

<i>In vitro</i> transcription	Posttranscriptional modification	Template degradation
<ul style="list-style-type: none"> • TheraPure T7 RNA polymerase • TheraPure RNase inhibitor • TheraPure inorganic pyrophosphatase • TheraPure ATP, GTP, CTP, and UTP • TheraPure modified nucleotides • ARCA (cap analog) 	<p>Capping</p> <ul style="list-style-type: none"> • TheraPure capping enzymes • TheraPure 2'-O-methyltransferase <p>Poly(A) tailing</p> <ul style="list-style-type: none"> • TheraPure poly(A) polymerase 	<ul style="list-style-type: none"> • TheraPure DNase I

Purification

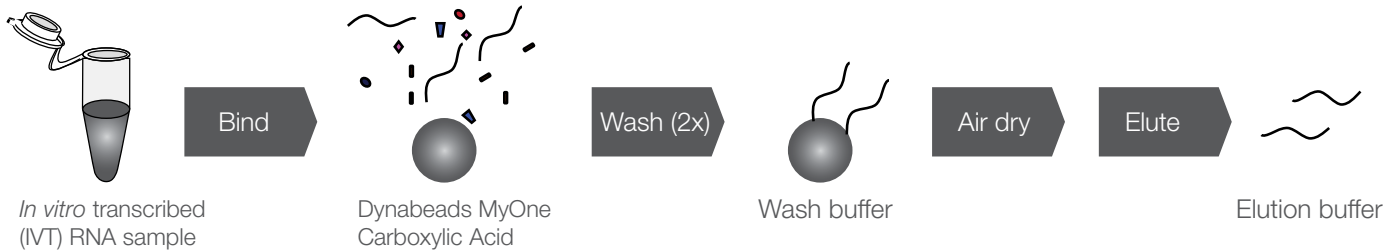
Purification by generic capture

- Invitrogen™ Dynabeads™ MyOne™ Carboxylic Acid for generic capture of mRNA
- In-process purification
- Optimized buffers available under confidential disclosure agreement (CDA)
- Increased mRNA concentration



Bind → Wash → Elute

Capture workflow



Binding capacity

- Up to 1.6 mg mRNA per mg of Dynabeads MyOne Carboxylic Acid
- Flexible and scalable protocol with a high recovery rate (Figure 2)

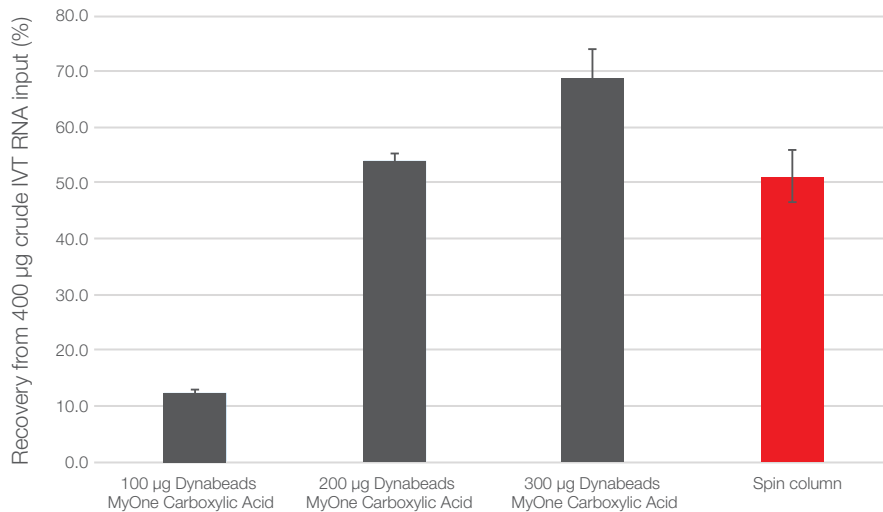


Figure 2. High mRNA recovery, as determined using the Invitrogen™ Qubit™ 4 Fluorometer.

For more information on applications using Dynabeads magnetic beads, contact us at oemdynal@thermofisher.com or visit thermofisher.com/dynabeads

Formulation and delivery

Optimized proprietary delivery

We utilize a combinatorial method to identify compounds and optimize formulations specific for different RNA payloads through proven design of experiments (DoE) and extensive proprietary know-how in the field of transfection (Figure 3).

- Extensive screening of potential candidates to select the optimal lipid nanoparticle (LNP) formulations
- DoE to optimize LNP formulation process parameters

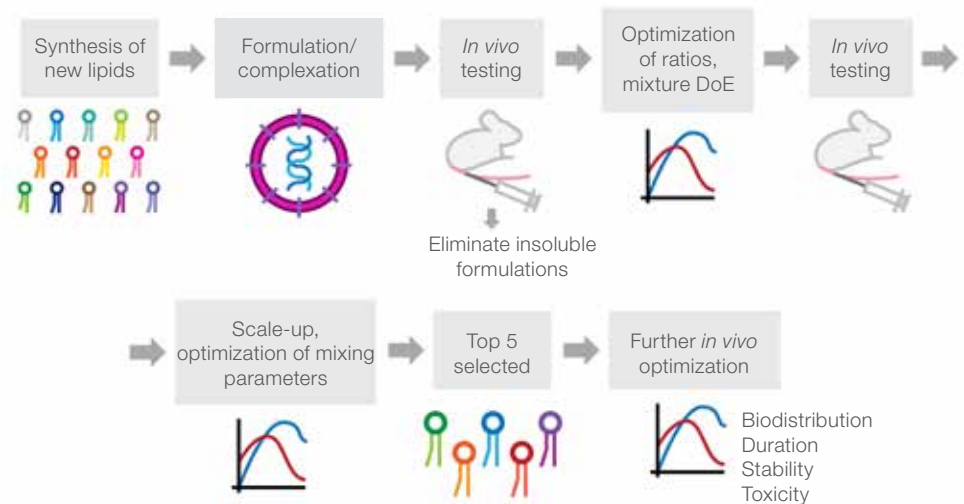


Figure 3. Schematic of DoE and formulation screening.

High-efficiency mRNA delivery

Invitrogen™ Invivofectamine™ Rx Reagent provides a method for *in vivo* mRNA delivery (Figure 4), allowing our partners to accelerate their research and development of new technologies.

- Multicomponent, proprietary lipid nanoparticles
- Uniformly sized (90 nm)
- >90% encapsulation efficiency
- Potency demonstrated by *in vivo* luminescence (1×10^{10} photons/sec) at 1 mg mRNA dose per kilogram of body weight (Figure 4)
- Specificity shown in liver, spleen, lung, and muscle
- Scalable process

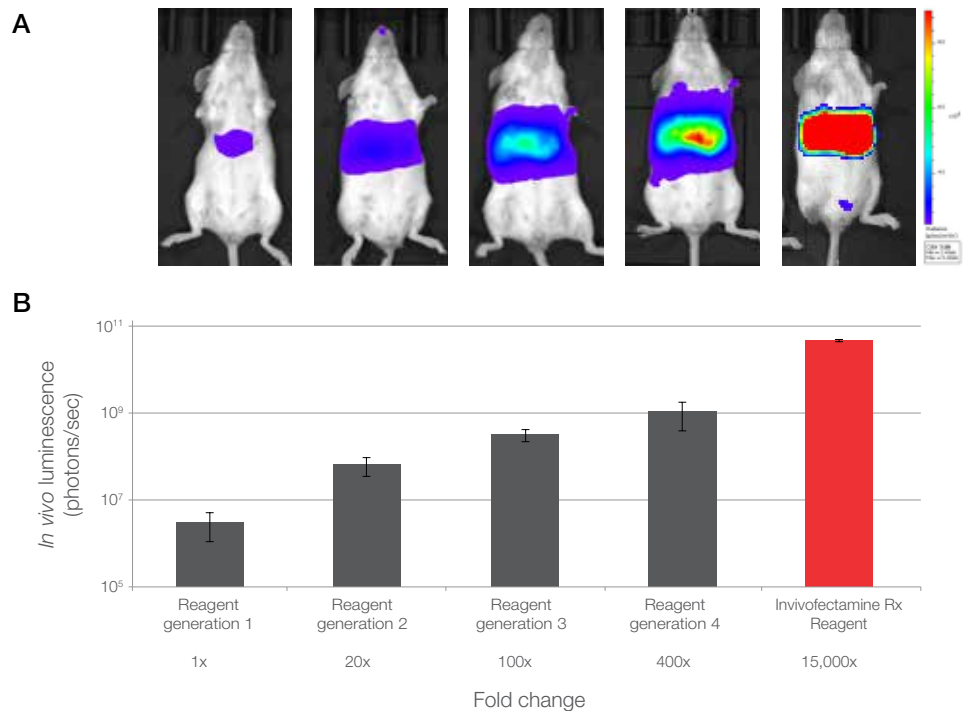


Figure 4. Sequential improvement in performance of reagents through DoE. Invivofectamine Rx Reagent shows progressive improvement in *in vivo* delivery of firefly luciferase mRNA, based on (A) visual and (B) quantitative assessment of luciferase expression 4 hours after intravenous injection into mice.

Ordering information

The following are representative products offered by our Commercial Supply team. Additional sizes are available. We can also provide custom formulations and other packaging configurations to meet your needs. If you're interested in a product that isn't shown, contact us and we'll work with you to meet your requirements.

Ordering information

Product	Quantity	Cat. No.
Synthesis		
TheraPure T7 RNA Polymerase	300 units	
TheraPure Inorganic Pyrophosphatase	10 units	
TheraPure RNase Inhibitor	2,500 units	
TheraPure Poly(A) Polymerase	80 units	
TheraPure Capping Enzyme	1,000 units	
TheraPure 2'-O-Methyltransferase	5,000 units	
TheraPure DNase I	1,000 units	Inquire at NATxOEM@thermofisher.com
TheraPure ATP	0.25 mL	
TheraPure GTP	0.25 mL	
TheraPure CTP	0.25 mL	
TheraPure UTP	0.25 mL	
Cap Analog (m ⁷ G(5')pppG)	100 units	
ARCA (Anti-Reverse Cap Analog)	10 units	
Purification		
Dynabeads M-270 Carboxylic Acid	10 mL	Inquire at oemdynal@thermofisher.com
Dynabeads MyOne Carboxylic Acid	10 mL	
Delivery		
Invivofectamine Rx Reagent	10 reactions	Inquire at outlicensing@thermofisher.com

Find out more at [thermofisher.com/mrnatx](https://www.thermofisher.com/mrnatx)

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