Product Profile

Cellular Delivery of siRNA & ASO
In vivo Grade Oligo Production, Endotoxin Testing, and Lipid Modification Interference
siRNA, ASO, and Lipid-Conjugated Oligonucleotides
Research to Preclinical Transition
FDA Guidelines — ≤5 EU/mL Endotoxin Threshold
LAL Assay Interference, False-Positive and False-Negative Risks, and Mitigation Strategies

RNA Interference

EndoSmart™ *In vivo* Grade Oligos: Endotoxin/LPS Tested

Endotoxin/LPS Tested siRNA and Antisense Oligonucleotides
27-6490-XX   in vivo grade oligos endotoxin LPS tested

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Gene Link™

Endotoxin/LPS Tested siRNA and Antisense Oligonucleotides

for *In vivo* Preclinical Research Applications

Including Lipid-Modified Oligonucleotides: LAL Assay Interference, False-Positive/False-Negative Risks, and Mitigation Strategies

1. Introduction and Background

The use of synthetic oligonucleotides, including small interfering RNA (siRNA) and antisense oligonucleotides (ASO) *in vivo* biological research has expanded substantially over the past two decades. These modalities offer precise gene-silencing and transcript-modulation capabilities, making them valuable tools in both basic research and translational drug discovery. However, successful and reproducible *in vivo* experimentation with synthetic oligonucleotides depends critically on the purity and biological safety profile of the administered materials [1].

A primary and often overlooked concern in the preparation of oligos intended for *in vivo* use is contamination by bacterial endotoxins, specifically lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria. Endotoxin contamination at even sub-nanogram concentrations can trigger potent innate immune responses in mammals, confounding experimental results, inducing non-specific inflammatory signaling, and in some cases causing animal morbidity or mortality [2].

The analytical challenge is further compounded when oligonucleotides bear lipid conjugates or are formulated with lipid-based delivery systems. Lipid moieties, including cholesterol, fatty acid chains (C16 palmitoyl, C18 stearoyl, C18:1 oleyl), tocopherol, and components of lipid nanoparticles (LNPs) are inherently amphiphilic and can interact directly with the LAL enzyme cascade, thereby producing both false-positive and false-negative endotoxin test results. This report examines these analytical challenges and outlines practical considerations for valid endotoxin testing of lipid-modified oligonucleotide preparations.

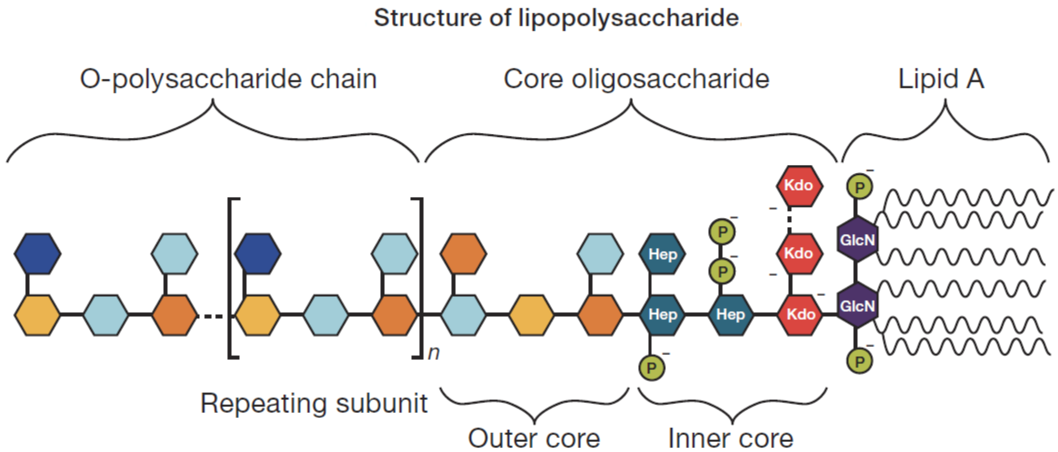
Gene Link's *in vivo* grade oligonucleotide production process is described as a reference model for research-grade materials intended for preclinical study preparation, including considerations specific to lipid-conjugated oligos.

2. Endotoxins and Their Relevance to Oligonucleotide Research

2.1 Biology and Source of Endotoxin

Lipopolysaccharide (LPS), commonly referred to as endotoxin, is a glycolipid present in the outer cell membrane of Gram-negative bacteria such as Escherichia coli, Salmonella, and Pseudomonas species. LPS is composed of three structural regions: lipid A (the bioactive, toxic component), core oligosaccharide, and O-antigen polysaccharide [5]. The lipid A moiety activates toll-like receptor 4 (TLR4) on innate immune cells, triggering release of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and interferons [2].

In laboratory settings, endotoxin contamination arises from bacterial presence in water, glassware, reagents, and manufacturing environments. Synthetic oligonucleotide synthesis is conducted in organic solvents and controlled environments, but the final aqueous reconstitution and purification steps introduce risk of endotoxin contamination if endotoxin-free reagents and equipment are not employed throughout.



Endotoxins are complex lipopolysaccharides, which are biologically active structural components of the outer cell membrane of gram-negative bacteria. They consist of a core oligosaccharide chain, O-specific polysaccharide side chain (O-antigen), and a lipid component, lipid A, which is responsible for the toxic effects.

2.2 Biological Consequences of Endotoxin Contamination in Animal Studies

Endotoxin contamination in oligonucleotide preparations administered to animal models can have far-reaching biological consequences that obscure experimental interpretation:

- Activation of the innate immune system via TLR4 signaling, resulting in systemic inflammation independent of the oligo’s intended mechanism of action [2].
- Induction of interferon-stimulated genes (ISGs), potentially confounding gene expression studies or RNAi knockdown efficiency assessments [2].
- Hepatic and renal toxicity at higher endotoxin doses, complicating safety profiling of therapeutic candidates [6].
- Altered pharmacokinetics due to cytokine-mediated changes in liver enzyme activity and organ perfusion.
- Septic shock in sensitive animal strains or immunocompromised models at endotoxin concentrations as low as 1 EU/kg body weight [6].

2.3 FDA Endotoxin Limits and Regulatory Framework

The U.S. Food and Drug Administration (FDA) has established endotoxin limits for injectable products under 21 CFR and associated guidance documents [6]. For non-pyrogenic injectable formulations, the general limit is 5 EU/mL. For research-grade materials used in preclinical *in vivo* animal studies, the same threshold of ≤5 EU/mL is widely adopted. Gene Link's *in vivo* grade oligonucleotide production process is calibrated to this FDA-referenced standard, with a certification criterion of <5 EU/mL as measured by chromogenic LAL endotoxin assay at the final product stage [7].

3. Limulus Amebocyte Lysate (LAL) Testing: Principles and Methods

3.1 History and Mechanism of LAL Testing

The Limulus Amebocyte Lysate (LAL) assay is the gold standard method for endotoxin detection, derived from the blood cells (amebocytes) of the horseshoe crab (Limulus polyphemus) [5,8]. Upon contact with endotoxin, a serine protease cascade is activated within the LAL reagent, culminating in the cleavage of a chromogenic or turbidimetric substrate. This biological cascade provides exquisite sensitivity to LPS, with detection limits as low as 0.001 EU/mL in optimized kinetic formats [5].

3.2 Charles River Endosafe nexgen-PTS Platform

The Endosafe nexgen-PTS (Portable Test System) is an FDA-licensed, kinetic chromogenic LAL-based instrument developed by Charles River Laboratories for rapid, point-of-use endotoxin testing [9]. It integrates sample analysis, reagent dispensing, and result quantification into a single cartridge-based format with minimal hands-on time.

3.2.1 Instrument Design and Cartridge Technology

The nexgen-PTS utilizes single-use, pre-loaded test cartridges containing lyophilized LAL reagent and chromogenic substrate [9]. Each cartridge contains four channels: two for sample analysis and two for built-in spike controls, enabling concurrent sample quantification and spike recovery validation in a single test run. This design eliminates the need for separate standard curve preparation and reduces technician variability.

3.2.2 Kinetic Chromogenic Detection Principle

In the kinetic chromogenic format, endotoxin activates the LAL clotting cascade, which cleaves the synthetic chromogenic substrate pNA (para-nitroaniline) from Boc-Leu-Gly-Arg-pNA [9,5]. The release of yellow pNA is measured photometrically at 405 nm. The reaction is monitored kinetically, with the onset time of color development inversely correlated with endotoxin concentration.

3.2.3 Performance Characteristics

Parameter	Performance Specification
Detection Range	0.001 – 100 EU/mL (cartridge-dependent)
Test Time	~15–20 minutes per cartridge
Sample Volume	25 µL per channel
Spike Recovery Criteria	50–200% (standard acceptance)
Sensitivity (PTS20 cartridge)	0.005 EU/mL
Regulatory Status	FDA-licensed for lot release testing
Interference Check	Built-in spike control per cartridge
Data Output	EU/mL with pass/fail interpretation

3.2.4 Advantages Over Conventional LAL Methods

- Rapid turnaround: results within 15–20 minutes versus 60+ minutes for tube-based methods.
- Integrated spike controls: simultaneous endotoxin recovery validation.
- Small sample volume: 25 µL per channel, critical for low-yield oligonucleotide samples.
- Audit-ready data logging with time-stamped, operator-linked records.
- Minimal training requirement and reduced contamination risk.

4. Gene Link *In vivo* Grade Oligonucleotide Production Process

Gene Link, Inc. provides research-grade oligonucleotides specifically manufactured and quality-controlled for *in vivo* biological applications. Gene Link recommends *in vivo* grade oligos for antisense oligonucleotides (ASO) or siRNA testing at a research level before entering preclinical studies. The production pipeline integrates endotoxin control at every stage of synthesis, processing, purification, QC analysis, normalization to final shipping.

4.1 Endotoxin Testing and Certification

All stages of the *in vivo* oligo production process are subjected to endotoxin testing and certified either to be below the limit of detection or to fall within FDA guideline thresholds, with a final concentration specification of <5 EU/mL as determined by a chromogenic LAL assay. All *in vivo* oligos are shipped dried (lyophilized) and, upon request, may be supplied at a normalized reconstituted concentration in endotoxin-free water or TE buffer. *In vivo* oligonucleotides are not certified as sterile.

4.2 Quality Grade Levels and Purification Methods

Quality Grade	Purification Method	Final Filtration	Recommended Use
Desalted	Gel filtration / size-exclusion chromatography	0.22 µm prior to lyophilization	Short oligos, basic *in vivo* knockdown studies
Reverse Phase Purified (RPC)	Reverse phase chromatography (C18)	0.22 µm prior to lyophilization	Higher purity siRNA duplexes
PAGE Purified	Polyacrylamide gel electrophoresis & desalting	0.22 µm prior to lyophilization	Full-length enriched; critical preclinical work

4.2.1 Desalted Grade

All desalted grade *in vivo* oligos are desalted to remove residual salts by gel filtration/size-exclusion chromatography. The final step is filtration using a 0.22 µm filter prior to lyophilization.

4.2.2 Reverse Phase Purified (RPC) Grade

All RPC grade *in vivo* oligos, after RPC purification, are filtered using a 0.22 µm filter prior to lyophilization. RPC effectively removes truncated failure sequences, free nucleotides, and hydrophilic synthesis byproducts.

4.2.3 PAGE Purified Grade

All PAGE purified grade *in vivo* oligos, after gel purification and desalting, are filtered using a 0.22 µm filter prior to lyophilization. PAGE purification provides the highest resolution for full-length sequence enrichment and is recommended for IND-enabling preclinical stages.

6. Testing Protocol: Endosafe nexgen-PTS for Oligonucleotide Samples

6.1 Sample Preparation Considerations

Oligonucleotide samples present specific analytical challenges for LAL-based endotoxin testing that must be addressed to ensure valid results. High-concentration nucleic acid solutions can exhibit inhibitory or enhancing effects on the LAL cascade, and the pH and ionic strength of the sample must be compatible with the assay reagents. The following preparative steps are recommended:

- Reconstitute lyophilized samples in LAL Reagent Water (LRW, ≤0.005 EU/mL) at a defined concentration.
- Adjust sample pH to 6.0–8.0 if outside this range.
- For lipid-modified samples: apply relevant pre-treatment (see Section 5.4) prior to dilution.
- Prepare dilution series (minimum 1:10 and 1:100) to identify the MVD yielding spike recoveries within 50–200% [5,3].
- Gene Link tests *in vivo* grade oligo samples in duplicate with the integrated spike controls on the nexgen-PTS cartridge.

6.2 Acceptance Criteria and Result Interpretation

Parameter	Acceptance Criterion	Action If Failed
Endotoxin Concentration	<5 EU/mL (final product)	Reject lot; investigate source
Spike Recovery	50–200%	Repeat at higher dilution or investigate matrix interference
Duplicate CV%	≤25%	Repeat test; review cartridge handling
Negative Control (LRW)	<0.05 EU/mL	Investigate LRW and environmental contamination
Lipid-modified samples: rFC orthogonal	Consistent with LAL result (±2-fold)	Investigate discordance; report both values; apply conservative result
Cartridge Lot Validity	Within expiry; stored 2–8°C	Replace cartridge lot

7. *In vivo* Study Design Considerations

7.1 Route of Administration and Endotoxin Sensitivity

The route of administration of oligonucleotides in animal models significantly influences the tolerable endotoxin threshold. Intravenous (IV) and intrathecal (IT) routes carry the greatest endotoxin sensitivity [6]. Intraperitoneal (IP) and subcutaneous (SC) routes are generally more tolerant, though endotoxin-mediated inflammation can still confound results. The <5 EU/mL standard is a conservative threshold appropriate for the most sensitive routes encountered in preclinical research [7]. For cholesterol- or lipid-conjugated siRNA administered IV, the practical endotoxin sensitivity may be further elevated due to the lipid's own inflammatory potential via TLR4 (cholesterol oxidation products are known TLR4 ligands) [2], reinforcing the importance of rigorous endotoxin control.

7.2 Selection of Oligonucleotide Grade for Study Type

Study Type	Recommended Grade	Purification	Rationale
Target validation (in vitro to *in vivo*)	Desalted *in vivo* grade	Size-exclusion + 0.22 µm	Cost-effective; adequate for initial feasibility
Dose-response and efficacy studies	RPC *in vivo* grade	RPC + 0.22 µm	Higher consistency; reduced truncation products
Toxicology and IND-enabling preclinical	PAGE *in vivo* grade	PAGE + desalt + 0.22 µm	Highest purity; full-length enriched
Cholesterol- or lipid-conjugated siRNA *in vivo*	RPC or PAGE *in vivo* grade	RPC or PAGE + 0.22 µm	Lipid conjugate QC requires validated interference-mitigation testing protocol

Study Type	Recommended Grade	Purification	Rationale
LNP-formulated siRNA	PAGE *in vivo* grade (pre-formulation)	PAGE + desalt + 0.22 µm	Test at siRNA drug substance level; separate excipient QC required
ASO CNS (IT/ICV)	PAGE *in vivo* grade	PAGE + desalt + 0.22 µm	CNS routes: highest endotoxin sensitivity

7.3 Handling and Reconstitution of *In vivo* Grade Oligos

- Reconstitute only in certified endotoxin-free water (LRW, ≤0.005 EU/mL) or endotoxin-free TE buffer.
- For lipid-conjugated oligos: use endotoxin-free PBS or other physiological buffer appropriate for the lipid modification; avoid aqueous solutions with organic co-solvents that may not have been endotoxin-tested.
- Use sterile, single-use, endotoxin-free plasticware for all reconstitution, dilution, and dosing steps.
- For cholesterol-siRNA or C18-siRNA, gentle sonication or heating (37°C, 5–10 min) may be required to achieve homogeneous reconstitution; perform in endotoxin-free tubes.
- Re-test reconstituted lipid-modified samples by nexgen-PTS (with validated interference-mitigation protocol) if there is any doubt about endotoxin status.

8. Quality Documentation and Regulatory Compliance

8.1 Certificate of Analysis (CoA) Requirements

In vivo grade oligonucleotides from Gene Link are accompanied by a Certificate of Analysis documenting the endotoxin test result (EU/mL), the method (chromogenic LAL), the acceptance threshold (<5 EU/mL), the purification grade, and mass/OD yield data. For lipid-modified oligos, the CoA may additionally specify the validated testing dilution, any pre-treatment applied (e.g., Tween-80 disaggregation).

8.2 Alignment with GLP Principles

Although Gene Link's *in vivo* grade oligos are manufactured for research use and are not GMP certified, the production process incorporates key GLP-aligned elements, including instrument calibration and qualification records for the chromogenic LAL testing system, use of certified reference standard endotoxin (RSE or CSE) for standard-curve generation, traceability of test records to specific production lots, and defined acceptance criteria with explicit pass/fail thresholds. For lipid-modified oligos, method-validation records, including spike recovery across dilution series and documentation of interference-mitigation strategies should also be included in the batch record.

8.3 Endotoxin Testing Within a Broader QC Framework

Endotoxin testing is a critical but not exclusive quality parameter. A complete QC framework for *in vivo* grade oligonucleotide release should additionally include mass spectrometry or HPLC-based purity and identity confirmation, OD_{260} quantification, analytical HPLC or PAGE for truncation product assessment, and stability assessment. For lipid-modified oligos, lipid conjugation efficiency should be confirmed by analytical methods (e.g., HPLC, mass spectrometry) to ensure the lipid modification is present and uniform before commencing *in vivo* studies.

9. Summary and Conclusions

The use of endotoxin-controlled, *in vivo* grade siRNA and ASO oligonucleotides is an essential prerequisite for reliable and interpretable *in vivo* preclinical research. Bacterial endotoxin contamination in oligonucleotide preparations can trigger potent non-specific immune responses, introduce confounding variables, and cause direct animal toxicity. The Charles River Endosafe nexgen-PTS provides a rapid, sensitive, FDA-licensed platform for endotoxin quantification using the kinetic chromogenic LAL principle.

The incorporation of lipid modifications — including cholesterol, C16 palmitoyl, C18 stearoyl, C18:1 oleyl, tocopherol, and multi-component LNP systems — significantly complicates endotoxin testing. These modifications can cause false-negative results through competitive binding to Factor C, micelle-mediated enzyme denaturation, and LPS sequestration, or false-positive results through optical interference (LNPs) or sub-CMC cascade activation. Standard LAL testing without interference validation is insufficient for lipid-modified oligonucleotide preparations.

A validated, modification-specific testing strategy is required for each lipid-conjugated oligo, including empirical determination of the minimum valid dilution, pre-treatment with appropriate non-ionic detergents where needed, and orthogonal confirmation by recombinant Factor C (rFC) assay for high-risk modifications such as cholesterol, tocopherol, and LNP-formulated siRNA.

Gene Link's in vivo grade production process certifying <5 EU/mL at the drug substance level by chromogenic LAL, with three purification grades (Desalted, RPC, and PAGE) and universal 0.22 µm final filtration—provides a well-documented and technically appropriate starting point for both unmodified and lipid-conjugated siRNA and ASO oligonucleotides intended for preclinical in vivo research.

References and Resources

Primary References and Technical Resources

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Regulatory Guidance Documents

- ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products (Chemical Substances).
- FDA 21 CFR Part 610.13: Sterility and Pyrogenicity Standards for Biological Products.
- USP <85>: Bacterial Endotoxins Test — including Inhibition/Enhancement Testing requirements.
- FDA Guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials (endotoxin dose calculations).
- EMA Reflection Paper on the Use of Recombinant Factor C in Place of LAL Assay for Batch Release Testing of Medicinal Products (EMA/CHMP/BWP/245500/2020).

This technical report is prepared for informational and research planning purposes. Gene Link in vivo grade oligonucleotides are intended for research use only and are not sterile certified. Researchers should consult their institutional IACUC, regulatory affairs, and quality assurance teams when designing formal preclinical studies. Endotoxin testing method validation for lipid-modified oligonucleotides is the responsibility of the end user and must be performed independently for each unique lipid conjugate and formulation.

Non-Silencing/NTC Control SmartBase™ siRNA Duplexes			
	Catalog #	**Qty**	**Product**
			NTC Control SmartBase™ siRNA for human, mouse and rat **No cellular delivery ligand**
❑	27-6740-05	5 nmols	SmartBase™ siRNA NTC PAGE Purified 5 nmols
❑	27-6740-10	10 nmols	SmartBase™ siRNA NTC PAGE Purified 10 nmols
❑	27-6740-20	20 nmols	SmartBase™ siRNA NTC PAGE Purified 20 nmols
			NTC Control SmartBase™ siRNA for human, mouse and rat **Trivalent GalNAc delivery ligand**
❑	27-6741-05	5 nmols	SmartBase™ siRNA NTC with Trivalent GalNAc PAGE Purified 5 nmols
❑	27-6741-10	10 nmols	SmartBase™ siRNA NTC with Trivalent GalNAc PAGE Purified 10 nmols
❑	27-6741-20	20 nmols	SmartBase™ siRNA NTC with Trivalent GalNAc PAGE Purified 20 nmols
			NTC Control SmartBase™ siRNA for human, mouse and rat **Cholesterol-TEG delivery ligand**
❑	27-6742-05	5 nmols	SmartBase™ siRNA NTC with Cholesterol-TEG PAGE Purified 5 nmols
❑	27-6742-10	10 nmols	SmartBase™ siRNA NTC with Cholesterol-TEG PAGE Purified 10 nmols
❑	27-6742-20	20 nmols	SmartBase™ siRNA NTC with Cholesterol-TEG PAGE Purified 20 nmols
			NTC Control SmartBase™ siRNA for human, mouse and rat **α-tocopherol delivery ligand**
❑	27-6743-05	5 nmols	SmartBase™ siRNA NTC with α-tocopherol PAGE Purified 5 nmols
❑	27-6743-10	10 nmols	SmartBase™ siRNA NTC with α-tocopherol PAGE Purified 10 nmols
❑	27-6743-20	20 nmols	SmartBase™ siRNA NTC with α-tocopherol PAGE Purified 20 nmols

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