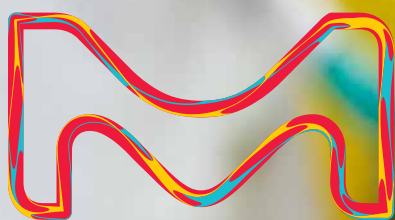


Custom Oligos for Commercial Use

- Life Science Research Tools
- Molecular Diagnostics
- Laboratory Developed Tests



The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Sigma-Aldrich®
Lab & Production Materials

Quality Assurance

At the foundation of our manufacturing processes is a robust Quality Management System (QMS), which drives compliance to our following Quality Registrations:

- ISO 9001 for manufacturing research-grade oligonucleotides
- ISO 13485 for manufacturing diagnostic-grade oligonucleotides
- ISO 14001 for effective environmental management

This quality culture is integrated into all aspects of our business. Key components of our QMS include:

Certificates of Analysis

Our certificates of analysis (CoA) come with relevant information, such as molecular weight and melting temperature. We can also include mass spectral and analytical HPLC traces. In addition, we can work with you to develop the content and format for your CoA to meet your incoming release criteria and streamline your acceptance process.

Document Control

Good documentation practices are critical to our QMS including detailed batch records for ISO 13485 manufacturing. Staff are continuously trained to stay current on document and underlying process changes.

Change Notification

Customers who are included in our Change Control Notification program are linked with our Quality Assurance Change Management process for transparency and risk mitigation.

Vendor Management

We produce the highest quality chemicals and reagents providing unmatched strength in supply chain management. For externally sourced materials, our supplier qualification program ensures materials meet our exacting standards. Our enterprise resource planning systems and meticulous record keeping provide complete material traceability throughout manufacturing.

Business Agreements

Establishment of confidential disclosure agreements and supply agreements are key to a successful partnership. Our agreements clearly communicate expectations and responsibilities to ensure confidentiality, product requirements, and continuity of supply.

Corrective and Preventive Actions

We continually strive to improve the effectiveness of our QMS by eliminating and preventing nonconformances in addition to validating actions taken along with their effectiveness.



Project Expertise

From early-stage research through commercial launch, we provide project expertise to ensure your success.

Project Management

We believe that accountability, predictability, responsiveness, and flexibility are the keys to project success and customer satisfaction. A project management professional will work with you from the start of the project through order fulfillment.

Product Development Support

When your project requires innovative approaches to novel oligonucleotide constructs or formulations, our scientists are available for collaboration in developing:

- Conjugates and complex dye labeling
- Customized purification and analytical methods
- Optimized ready-mixes and customized PCR/amplification enzyme formulations
- Product and process optimization to maximize manufacturability
- Component or kit packaging design and private labeling

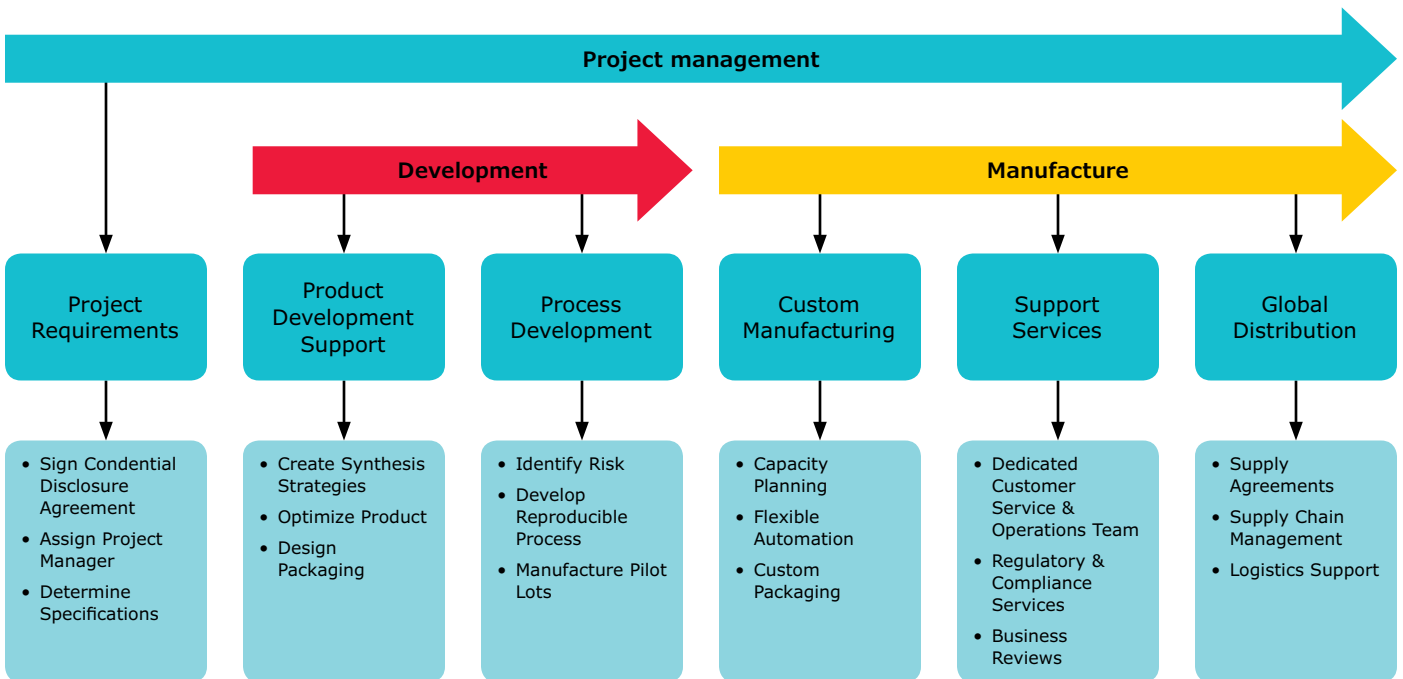
Process Development

Process development is a critical step in creating a robust and economical manufacturing process. To set process specifications, we:

- Identify critical control parameters and risks
- Develop consistent and reproducible processes
- Create specifications and manufacturing documents
- Provide small lots for stability testing, design verification, and design validation
- Manufacture the necessary pilot batches to achieve production scale

We can develop unique methods or adopt your existing protocols to meet your specifications. Our expertise in methods transfer ensures your proven analytical procedures are integrated into our quality systems. Our multi-million dollar investment in state-of-the-art instrumentation and our experienced team of scientists are the foundation for our development and qualification process.

Manufacturing Overview



Reliable Manufacturing

We have the personnel, infrastructure, equipment, and facilities to handle all of your manufacturing requirements.

Flexible Manufacturing

Our robust manufacturing processes are designed with our customers in mind. Our flexibility in manufacturing results from our technical expertise and core manufacturing capabilities, including:

- Flexible automation
- Range of production scales
- Stringent quality control
- Laboratory Information Management System (LIMS)

We understand that consistency is critical to manufacturing success. Our engineers design and maintain proprietary synthesis platforms, processing equipment and facilities. Instruments are qualified and an extensive preventive and predictive maintenance program ensures optimal performance. Utilizing our in-process controls and LIMS to capture information, process adjustments can be made in real time.

Our manufacturing expertise makes us the partner of choice for designing and creating solutions for all your production needs.

Custom Formulations & Packaging

We can formulate the most complex components with precision and accuracy. We have the ability to:

- Formulate liquids and dry powders on a small to large scale
- Accommodate a variety of packaging configurations including microtiter plates, tubes and bottles
- Package a single component or an entire kit to your specifications
- Private label your product

Support Services

Our commitment to our partners is evident in all aspects of our business. We routinely tailor programs to meet customer requirements including:

- Functional testing of your product
- Regulatory compliance consulting
- Audits of any of our facilities
- Forecasting and capacity planning
- Quarterly business reviews
- Key performance indicators (KPIs)
- Inventory management services
- Global warehousing and distribution



**Customer care
and reliability
are in our DNA**

Accelerate your success,
from concept to market,
with our custom
oligonucleotide expertise
and collaborative
service approach.

Basic Commercial Capabilities

Whereas our research offering comes with breadth and speed (SigmaAldrich.com/standardoligos), our commercial capabilities come with depth and consistency (SigmaAldrich.com/compliantoligos). Both product portfolios deliver high-quality oligonucleotides.

Custom DNA Oligos

Basic PCR primers, SYBR® Green Primers, isothermal amplification primers, sequencing primers, and more.

Specifications	
Synthesis scales	0.2, 1.0, 10.0 & 15.0 µmol
Purifications	Desalt & HPLC
Sequence Lengths	10–70 bases (inquire for longer sequences)
Modifications	5' Phosphate (inquire for others)
Formats	Supplied dry or in solution in tubes

Custom qPCR Probes

Dual-Labeled Probes for the 5' nuclease assay.

Specifications	
Amounts	1, 3, 5 & 10 OD
Purifications	HPLC
Sequence Lengths	15–40 bases
Modifications	Reporters [6-FAM™, HEX™, JOE™, TAMRA™, ROX™ & Cyanine 5] Quenchers [TAMRA™ & Onyx Quencher™] Internal [Locked Nucleic Acid® (LNA®)]
Format	Supplied dry in tubes

Onyx Quencher™ dark quencher

Onyx Quencher™ (OQ™) is our proprietary quencher for Dual-Labeled Probes. Similar to other dark quenchers, OQ™ emits heat instead of light and therefore offers an improved signal-to-noise ratio compared to traditional fluorescent quenchers, such as TAMRA™. It is license- and royalty-free.

Custom iScale Oligos™ DNA

Milligram and gram quantities of material.

Specifications	
Amounts	10, 25, 50, 100, 250 & 500 mg 1–5 g
Purifications	Desalt (≤5 g) HPLC (≤1 g max)
Sequence Lengths	10–50 bases (inquire for longer sequences)
Modifications	Biotin, Biotin TEG, Biotin dT, phosphate, Amino-Modifier (C3, C6, C6 dT, C7, C12), TET™, HEX™, 5-Me-dC, Spacer (12, 18, C3), dSpacer, Thiol-Modifier-C3 S-S, 2'-OMe & phosphorothioate Inquire for other modifications
Format	Supplied dry in tubes
Services	If the oligonucleotide is to be used <i>in vivo</i> , <i>in vivo</i> -grade purification and all the following services are recommended: salt exchange, endotoxin testing and filtration

Custom Next-Gen Sequencing Oligos

Custom NGS adapters.

Specifications			
Options:	NGSO-Bronze	NGSO-Silver	NGSO-Gold
Cross Contamination	<2%	<1%	<0.25%
Scales & Minimum Yields	0.05 µmol (1–3 OD) 0.2 µmol (3–8 OD) 1.0 µmol (9–13 OD) Inquire for larger scales	0.2 µmol (10 nmol or 2–6 OD depending on sequence length) Inquire for larger scales	0.2 µmol (3– 8 OD) 1.0 µmol (9–13 OD) 5.0 µmol (Quote) Inquire for larger scales
Purities	70–85%	65–80%	85–95%
Sequence Lengths	10–80 bases	10–80 bases	10–80 bases
Modifications	5'-Phosphate Phosphorothioate 5-Me-dC	5'-Phosphate Phosphorothioate 5-Me-dC	5'-Phosphate Phosphorothioate 5-Me-dC
Formats	Supplied dry in tubes	Supplied in solution in tubes or 96-well plates Standard: 100 µM in water, TE (10 mM Tris, pH 7.5-8.0, 1 mM EDTA) or Tris (10 mM Tris-HCl, pH 8.0) Inquire: 30-150 µM in water or 30-130 µM in TE/Tris buffer Mixing available: Yes Duplexing available: No	Supplied dry in tubes
Platform Compatibility	Illumina, Thermo Fisher (Ion Torrent™), & PacBio™	Thermo Fisher (Ion Torrent™)	Illumina, Thermo Fisher (Ion Torrent™), & PacBio™
Typical Applications	Targeted sequencing of select genes or panels	SNP genotyping & variant detection	Manufacturing of commercial kits

Quality Control

Our ability to guarantee performance is directly related to our comprehensive understanding of oligonucleotide chemistry and synthesis platforms, our analytical systems, and our experience in methods development.

Starting Materials & Chemistry

Critical raw materials are sourced from within and include: phosphoramidites, solid-phase synthesis supports, reagents and solvents. Upon receipt of critical raw materials, incoming quality control is performed and may include water content analysis, phosphoramidite identification, solid support verification and acceptance based upon a Certificate of Analysis. Additionally, a rigorous supplier qualification program is part of our quality management system, which allows us to manage supplier relations and performance.

Instrumentation & Synthesis

Our in-house engineering team includes mechanical, electrical and software professionals who design and qualify our proprietary synthesis and processing equipment. Instruments are qualified through an established design review process, as well as Installation Qualification, Operational Qualification and Process Qualification (IQ/OQ/PQ) programs. An extensive preventive and prognostic maintenance program for instruments provides optimal performance, ensuring consistency and reliability. Our LIMS continuously monitors the progress of each oligonucleotide in real-time and nonconforming products are flagged for quarantine.

Sequence Identity Verification by Mass Spectrometry

Mass Spectrometry (MS) is the technology of choice for analyzing oligonucleotides. Coupled with synthesis process qualification, it ensures that the correct sequence has been synthesized. Every oligonucleotide is thoroughly characterized by MS to ensure that by-products are below an acceptable ceiling as they can negatively affect performance, even if the correct sequence was synthesized.

Purity Verification by Analytical HPLC

MS can provide qualitative assessments of purity, while quantitative assessments are provided by RP-HPLC (reverse-phase high-performance liquid chromatography), IE-HPLC (ion-exchange high-performance liquid chromatography) and UPLC (ultra performance liquid chromatography).

Quantification by UV Spectroscopy

An absorbance reading at 260 nm is taken of every oligonucleotide. For accuracy, multiple measurements are taken using an automated spectrophotometer equipped with path-length correction.

Final Inspection

All products are subjected to a final visual inspection prior to packaging.

To learn more, visit
[SigmaAldrich.com/compliantoligos](https://www.sigmaaldrich.com/compliantoligos)

Sigma-Aldrich®

Lab & Production Materials

Merck KGaA
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SigmaAldrich.com/compliantoligos

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