CGMP MANUFACTURING FOR MOLECULAR DIAGNOSTICS
INTRODUCTION

cGMP manufacturing of Oligonucleotides for Molecular Diagnostics

With over 20 years experience in custom oligonucleotide synthesis, Eurogentec is a leading supplier of high quality reagents for genomic research to bench scientists around the globe.

With the recent expansion of our state-of-the-art GMP (Good Manufacturing Practice) facility and our ISO 13485 certification for production and sales of IVD oligonucleotides in Liège, Belgium, we have significantly increased our capacity for manufacturing cGMP components for DNA- and RNA-based Molecular Diagnostic assays.

Together with our manufacturing facilities in the United States and Japan we offer global redundancy and harmonization of experience, processes and facilities to ensure to our clients uninterrupted supply of high quality R&D and GMP-level assay components.

Why Partner with Eurogentec?

Experience: choosing a manufacturing partner early in the assay development process is an important first step toward successful assay validation and product commercialization. Eurogentec has extensive experience in all aspects of GMP manufacturing: from synthesis and purification to exhaustive FDA and CE quality compliance for fully customized filling, labelling and packaging. Our QA staff is very knowledgeable of European and U.S. regulatory guidelines and standards, ensuring strict adherence to the demands of regulatory oversight. Our facility and processes are fully compliant with European IVD directive 98/79 EEC and U.S. FDA regulations for GMP (FDA 21 CFR Part 820, 21 CFR 809.10, 809.30, 864.4020).

Flexibility: we collaborate with our partners to provide virtually unlimited flexibility to accommodate your product development and regulatory oversight teams unique requirements for customized processes and documentation. Together we develop customized and detailed manufacturing specifications that are ultimately converted into custom SOPs and protocols for manufacturing.

In addition, we are licensed to offer all major probe formats (single and double dye, Molecular Beacons, Scorpions, etc.) and a comprehensive inventory of standard and specialty DNA and RNA modifications. Our manufacturing chemists and QA & QC scientists can suggest cost-effective solutions for designing and optimizing customized purification and QC protocols that meet or exceed your most stringent specifications and budgetary constraints.

Reliability: whether you depend on a CMO for the manufacture of bulk qualified reagents or for complete fill and finish, a reliable supply stream is critical to the ultimate commercial success of your products. Eurogentec is able to provide you with exhaustive process checklists, detailed batch records, and regulatory-compliant labeling and packaging to your exact specifications.

From customized manufacturing specifications and custom documentation to challenging product labelling and packaging details, we work together to create customized processes and products that will satisfy your most demanding team members’ requirements.

Benefits of a Eurogentec Partnership

As an experienced and well-established B2B GMP manufacturing organization, Eurogentec is well aware of the critical role we play in our partner’s success. Complete confidence in our manufacturing processes is assured by:

> utilizing numerous redundant process control checklists to eliminate possible errors at all stages of manufacture;
> incorporating stringent SOPs and change control procedures to ensure rigorous lot-to-lot consistency;
> providing comprehensive and detailed batch record documentation substantiating strict adherence to our partners’ required quality specifications.

Every aspect of the manufacturing process is monitored and documented providing our partners a level of confidence in quality and regulatory compliance virtually unparalleled in the industry.

Eurogentec has a customer-proven track record of success in delivering our partner’s mission critical, GMP-assay components on time, every time—guaranteed!

MAIN FEATURES AND BENEFITS OF OUR SERVICES

<table>
<thead>
<tr>
<th>Features</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedicated Key Account Follower to oversee the entire process from order entry through release and shipment</td>
<td>Optimal communication between the customer and production</td>
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<tr>
<td>Dedicated clean rooms, equipment, purification columns and raw materials</td>
<td>Minimize risk of contamination</td>
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<tr>
<td>Synthesis, purification, assay fabrication and packaging following strictly controlled SOPs</td>
<td>The quality you demand, all the time, every time</td>
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<tr>
<td>Stringent QC combined with rigorous analytical method validation</td>
<td>Consistent lot-to-lot reproducibility</td>
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<tr>
<td>Quality management system certified with ISO13485:2003 and compliant with FDA 21 CFR part 820 QSR</td>
<td>Products compliant with EU &amp; US regulatory requirements</td>
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<tr>
<td>Comprehensive batch records and redundant process checklists</td>
<td>Step-by-step traceability from start to finish</td>
</tr>
<tr>
<td>Flexible solutions for each phase of product development and product commercialization</td>
<td>Cost-effective, you get exactly what you need, when you need it.</td>
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<tr>
<td>Wide range of synthesis scales (10 mmol up to 4 mmol) and long oligomer lengths (up to 200-mers for DNA and 80-mers for RNA)</td>
<td>Flexibility to meet your yield specifications during every phase of development and commercialization</td>
</tr>
<tr>
<td>Comprehensive inventory of modifications</td>
<td>Flexibility in designing assay components customized for your assays</td>
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Flexibility and Partnership are key

Eurogentec understands the complex and oftentimes ambiguous EU and US statutes regulating the manufacture of assays and assay components destined for IVD applications. Additionally, Eurogentec has the practical knowledge and hands-on experience required to implement the numerous manufacturing & administrative systems needed for compliance.

Of course, our B2B Partners may have additional requirements that exceed our standard regulatory compliance systems. These may include requests for custom analytical, purification or QC protocols, expanded batch record documentation, custom-designed labelling and packaging and even plans identifying alternative manufacturing sites to guard against interruption of product supply stream. Based on input gained through regular partner consultations with our manufacturing management teams, we are able to provide our partners with custom-tailored plans that accommodate their unique compliance requirements.

> Our management teams and production staff have the practical knowledge and expertise to customize most manufacturing processes to our partner’s specifications.
> Our main cGMP production site in Belgium is complemented with redundant production facilities in the U.S. and Japan.
> Our technical methods and processes are harmonized at each of our facilities ensuring each site’s adherence to Eurogentec’s technical, QC and Quality Management Systems.

One Partner from R&D through Commercialization

Eurogentec recognizes that documentation requirements differ as IVD products progress from R&D and prototype phase to validation and eventual commercialization. Incurring no compromise in oligonucleotides quality, we offer our partners the flexibility of choosing from three increasingly detailed levels of documentation appropriate for each phase of product development:

1. RESEARCH Oligos
   This is the most cost effective option. It is available for the early phases of assay development. Standard documentation provided.

2. Pre-DIAGNOSTIC Oligos
   Attractively priced between Research and Diagnostic Oligos and tailored to the early phases of assay development. Provides oligonucleotides with the diagnostic process (diagnostic optimized and validated methods, qualified equipment) in a classified clean room facility. Controlled facility. Documentation is minimized to keep the cost down.

3. DIAGNOSTIC Oligos
   Tailored for middle and late phases of product development and commercialization. Production and documentation are optimized for diagnostic purpose and can be fully customized according to our partner’s needs. Detailed checklists are used for all steps in the manufacturing process ensuring complete process control monitoring and traceability. This process is ISO13485-certified and fully GMP compliant (FDA 21 CFR part 820 QSR)
QUALITY

Our Quality Management System (Belgian site) is fully certified to the ISO13485:2003 Quality Standard and compliant with FDA’s Quality System Regulations (21 CFR 820). The GMP facility incorporates a card-key system for access to the manufacturing floor and permits full segregation of synthesis, cleavage/deprotection, purification and fill & finish processes. Access of the various clean rooms of different classes (class 100,000 and 10,000 with class 100 working zones) requires airlock pass-through and gowning policy.

Quality Systems

We have built a strong and comprehensive cGMP quality system over the past 15+ years:

> cGMP manufacturing authorization since 1993 for our recombinant protein and vaccine production. Over 70 products prepared for phase I and phase II clinical trials
> Current ISO 9001:2000 certification
> Quality Management System certified to ISO 13485:2003 and compliant with 21 CFR Part 820 standards
> Rapidly growing portfolio of diagnostic and service laboratory partners in Europe and North America

Quality System Management

> High level of education and training
> Strict process segregation and employee gowning policy
> Supplier qualification and evaluation
> Comprehensive Batch records with full traceability
> IQ/OQ/PQ maintenance and calibration standards
> Dedicated equipment
> Stringent document change control procedures
> Deviation management
> Process control
> Exhaustive analytical method validation
> Critical analysis & documentation rationale
> Independent QC department for assuring exact specifications prior to release
> Routine internal audits
> Customer quality audits
> Sample retention to facilitate troubleshooting
> Quality Agreements and/or Supply Agreements as extension of the manufacturing contracts to clearly define our responsibilities to our partners

Highly Controlled Upstream Process Control

> Each supplier is carefully screened and approved
> All reagents undergo rigorous Quality Control testing to guarantee exceptional quality and reproducibility of the finished product

Customized QC Release Methods

In partnership with our customers, we develop a QC Release Methods Repertoire customized for their specific requirements. We offer exceptional flexibility by providing a large selection of standard and customized QC release methods any of which can be incorporated into their customized repertoire.

Typical QC Release Methods

✓ Final mass determination (release by O.D., μmols, weight)
✓ Physical inspection of product
✓ MALDI-TOF or ESI Mass Spectrometry
✓ HPLC anion exchange
✓ HPLC reverse phase
✓ Capillary Gel Electrophoresis
✓ Direct sequencing using enzymatic cleavage and MALDI-TOF
✓ Enzymatic tests for DNA-enzyme conjugates
✓ Probe/dye activity: fluorescence, signal to noise ratio, melting profile for Molecular Beacons
✓ Heavy metals
✓ Residual solvents
✓ pH
✓ Water content (Karl Fisher)
✓ Endotoxins
✓ Bioburden
SYNTHESIS, PURIFICATION & DELIVERY PROCESSES

Synthesis

- Synthesis scales from 10 nmol to 4 mmol.
- Dedicated equipment and reagents.
- The widest range of modifications (>100) in the industry, including dyes, spacers, linkers, and unique amidites only available through Eurogentec.
- Development and production of customized modifications.
- Automated or manual mixing of different backbones for wobble synthesis, creating degenerate sites within an oligonucleotide sequence.
- Specific amidite mixes according to your requests.
- Large selection of chemistries such as LNA®, Phosphorothioate, RNA, 2′OMe RNA, customized mixtures of backbones and chimeric oligonucleotides. Please inquire for the availability of additional modifications.

Purification

Applications and regulations in Molecular Diagnostic assays call for oligonucleotides that are of exceptional purity. Eurogentec offers several preparative purification options to fulfill and meet our customers’ specific requirements:

- Anion exchange HPLC
- PAGE
- Reverse phase HPLC
- Disposable solid phase cartridge
- Dedicated HPLC columns
- Ultrafiltration (large scale only)
- Multiple purification steps

Product delivery

- Customized mixtures of individual oligonucleotide
- Conjugated oligonucleotides (HRP, AP, synthetic peptides, proteins)
- Final product formulation (lyophilized or in solution with customized buffers) and labelling according to customer specifications
- Fill and finish in dedicated room with HEPA air filter
- Customized packaging and labelling

Certificate of Analysis

Our products are provided with a certificate of analysis, a document detailing the release based on the batch record and signed by the QC authorized person.

Stability Testing

In addition Eurogentec offers stability testing of oligonucleotides following our standard or customized procedures.
CUSTOMER CARE

First and foremost, the Eurogentec diagnostic team believes that knowing its customer needs and expectations is essential to the success of any collaboration. Long-term relationships with our customers are built on trust and mutual respect. In dealing with you as customer we operate from following values:

Quality
We provide the highest quality services and continuously work on maintaining and further improving our quality level.

Respect
We respect you as a customer and operate from the principle that we are partners. We are honest, open and flexible.

Innovation
We expand our services continuously with advanced and innovative technologies.

Service
We are in service to your business and provide timely and adequate answers to all of your questions. We are proactive and responsible in our approach.

A dedicated Key Account Follower acts as your “eyes and ears” in the production plant. Your assigned “Eurogentec in-house advocate” monitors the complete production process and is able to provide you with frequent real-time updates during each production run.

PROFESSIONAL SUPPORT FOR MANUFACTURERS OF DIAGNOSTIC ASSAYS

> All projects are handled with complete confidentiality. A confidential disclosure agreement (CDA) is standard and is executed during the initial stages of communication.
> Project-specific details (synthesis scales, chemistry, QC specifications, sequences, regulatory requirements, time frame, patent situation, etc.) are discussed and documented.
> Quality Agreements and/or Supply Agreements are extensions of the manufacturing contract clearly defining Eurogentec’s and or partner’s respective obligations.
> Upon request, a pilot run program may be initiated prior to making a final offer.
> Eurogentec is registered in the USA as an ASR manufacturer with the FDA under Medical Device Manufacturer registration number 3003830126.
## COMPARISON OF RESEARCH, Pre-DIAGNOSTIC AND DIAGNOSTIC OLIGONUCLEOTIDES.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>RESEARCH</th>
<th>Pre-DIAGNOSTIC</th>
<th>DIAGNOSTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Order entry</td>
<td>Automated entry of oligo sequence into manufacturing system</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Additional sign off procedure to ensure correct entry in manufacturing system</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Using our proprietary Oligoflex synthesizers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Quality control</td>
<td>Customized methods and specifications</td>
<td>Option</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Purification</td>
<td>Customized methods and specifications</td>
<td>Option</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Quantification</td>
<td>Triplicate measurements</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fill &amp; finish</td>
<td>Monitors entire manufacturing process and communicates with customer</td>
<td>Some</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional customer requirements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Customer specifications</td>
<td>Custom-defined for above processes</td>
<td>Some</td>
<td>Option</td>
<td>Option</td>
</tr>
<tr>
<td>Dedicated lot of raw materials</td>
<td>Specific lots can be reserved on request</td>
<td>Option</td>
<td>Option</td>
<td>Option</td>
</tr>
<tr>
<td>Dedicated purification columns</td>
<td>Specific equipment will be purchased and reserved upon request</td>
<td>No</td>
<td>Option</td>
<td>Option</td>
</tr>
<tr>
<td>Quality Management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMP compliance</td>
<td>ISO 9001-2000</td>
<td>Certified</td>
<td>Certified</td>
<td>Certified</td>
</tr>
<tr>
<td></td>
<td>ISO 13485-2003</td>
<td>No</td>
<td>Compliant except for documentation</td>
<td>Certified</td>
</tr>
<tr>
<td>Environmental control</td>
<td>Card-key system for restricted access</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>GMP governed/entry procedure, airlock pass-through</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Clean rooms class 100,000</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Clean rooms class 10,000</td>
<td>No</td>
<td>Option</td>
<td>Option</td>
</tr>
<tr>
<td>Quality Control validation</td>
<td>QC equipment qualification</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>QC method validation</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Raw materials</td>
<td>Supplier Qualification and Evaluation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Incoming Quality Control</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Customer audit</td>
<td>Customer visits and audits of Eurogentec facilities, onsite documentation review</td>
<td>Option</td>
<td>Advised</td>
<td>Advised</td>
</tr>
<tr>
<td>Process control/Traceability/Batch records</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process control</td>
<td>Every aspect of manufacturing is monitored and documented (batch record, archived for 5 years)</td>
<td>No</td>
<td>Minimal Documentation</td>
<td>Detailed Documentation, full batch record</td>
</tr>
<tr>
<td>Certificate of Analysis (CoA)</td>
<td>Document detailing the product release following the batch record, signed by QC department, relevant analytical data is attached (e.g. HPLC &amp; MS profiles, ...)</td>
<td>No, only a Technical Data Sheet</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Release procedure</td>
<td>Released by QC-authorized person based on the detailed review of the batch record and CoA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Traceability</td>
<td>- Facility/clean room - Equipment - Technician/operator - Raw material - Process steps (Checklists)</td>
<td>No</td>
<td>Only for Facility, Operator &amp; Equipment</td>
<td>Yes</td>
</tr>
<tr>
<td>Sample retention</td>
<td>Kept 3 years for troubleshooting and traceability</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
Eurogentec, Your manufacturing partner of choice

For inquiries, please contact the Eurogentec Diagnostic Oligonucleotides team:

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