ASR OLIGONUCLEOTIDES AS CRITICAL GMP COMPONENTS OF LAB DEVELOPED TESTS

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This white paper provides an overview of the use of GMP Analyte Specific Reagent (ASR) oligonucleotides in Lab Developed Tests (LDTs), the regulatory requirements for GMP-compliant manufacturing of ASRs and suggestions of how to select an ASR manufacturer that is compliant with the cGMP statutes.

Information used in this white paper was obtained from a variety of documents in the public domain including regulatory guidelines and industry standards (1-2) as well as our own direct experience and expertise in this field. Due to the complexity of the subject matter, this document is not intended to address every detail on the subject of ASRs. Instead, it aims to advance understanding of the key requirements for compliance that manufacturers must meet to provide the highest level of ASR quality. Compliance ensures that clinical laboratories utilizing cGMP-manufactured ASR oligonucleotides as critical components in LDTs will provide diagnostic test results that are reproducible, safe and effective for their clients and, ultimately, their patients.

What are the regulations for ASRs?

The regulatory framework for medical devices has specific regulations for ASRs which can be found in the U.S. Code of Federal Regulations (CFR) [21 CFR 864.4020(a)]. ASRs are defined as

"Antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens."

ASRs are used by clinical laboratories in LDTs and are the "active ingredients" of these tests. A single forward/reverse oligonucleotide primer pair, an individual forward or reverse primer or a nucleic acid probe (whether untagged or tagged) intended to bind a single complementary amplified or unamplified nucleic acid sequence are classified as ASRs. ASR manufacturers must follow cGMP guidelines [as set forth in the Quality System Regulation (QSR) defined in 21 CFR Part 820] to ensure the quality of these critical component reagents. The guidelines also state that ASRs must be labeled specifically with *"Analyte Specific Reagent. Analytical and performance characteristics are not established."* [21 CFR 809.10(e)]. The laboratory that designs and develops the LDT, in which the ASR is used, must provide all necessary verification and validation and has to comply with the Clinical Laboratory Improvement Amendments (CLIA). (42 U.S.C. 263a 62 FR 62252). For more information regarding ASRs, we recommend the FDA guidance document: *"Guidance for Industry and FDA Staff, Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions" issued on, September 14, 2007.*

How will the FDA's increased regulation of LDTs impact you?

Historically, the FDA has maintained a policy of "enforcement discretion" over laboratories and LDTs. However, the FDA is now revising this approach and instead adopting a new, more vigorous approach to the regulation of LDTs. During the week of July 23, 2010, the FDA sent letters to 14 companies advising them that they may be marketing unapproved genetic tests requiring 510(k) approval.

The changing FDA approach will directly affect an organization that utilizes oligonucleotides in LDTs (such as CLIA labs) and highlights the urgent need for CLIA labs to begin sourcing critical assay components such as ASRs from cGMP-compliant suppliers. If your organization is currently sourcing these oligonucleotides from vendors who provide them as Research Use Only (RUO) components, we advise you to mitigate that risk by selecting a vendor who is able to provide fully GMP QSR-compliant ASR oligos.

How do you know whether a supplier is fully GMP-compliant and qualified to supply ASR oligos?

Several oligo manufacturers claim GMP-compliance. However, as there is no independent certification body to verify compliance to the FDA QSRs, full compliance cannot be checked. In reality, many oligo suppliers claim to be GMP-compliant, but in fact do not have a quality management system in place that is fully compliant to the FDA's GMP QSRs.

A practical way for a CLIA lab to check whether an oligo supplier is in full GMP-compliance, and therefore is able to produce ASRs, is to assure that the supplier has a quality system in place certified against the medical device ISO 13485:2003 quality standard. This standard is similar in many aspects to the FDA's QSRs. As a result, a quality system, preferably certified by an independent organization against ISO 13485, is an appropriate

means to assess full GMP-compliance. Further credibility is added to the GMP-compliance claim if the notified body is licensed to certify and accredited by FDA to perform audits on the FDA's behalf.

Is the quality of ASR oligos higher than that of research-grade oligos?

Absolutely yes! ASR oligos can be manufactured using customized, more stringent specifications, such as % purity. As ASR oligos are produced using a GMP-compliant quality management system that controls the entire manufacturing process from order entry to shipping, it assures more consistent quality and less lot-to-lot variation when compared with research-grade oligos. An ISO 13485 certified ASR manufacturer would have implemented a comprehensive risk management system to control and minimize manufacturing risks. This provides an even higher level of Quality Assurance. If, in addition, ASR manufacturing takes place in a controlled cleanroom environment, microbial contaminants and cross-contamination of your oligos with oligos manufactured for other laboratories are effectively avoided.

How much more expensive are ASR oligos than research-grade oligos?

ASR oligos are more expensive due to a number of reasons. Compliance with cGMP requirements demands implementation of a detailed and comprehensive quality system. This governs every aspect of ASR manufacture from raw material supplier validation to final product release and shipment, on-going risk analysis, methods documentation and validation and on-going training of staff dedicated to ASR production. In addition, ASR manufacturing according to cGMP requires (1) strict adherence to validated SOPs and quality measures, (2) maintenance of detailed checklists documenting every step of the manufacturing process, (3) assembly of comprehensive batch records, (4) careful review and official signed release of final product and batch record, (5) archival storage of batch records for several years and (6) archival storage of retention samples for future reference, if needed.

These processes are unique to the ASR manufacturing process and consequently add an additional cost burden to ASR manufacturing. Final price is also dependent on the synthesis scale, the type of oligo, number and types of modifications, percent purity and final yield of purified material required, and whether the oligo is ordered as part of a group of oligos. Oligos ordered as part of a larger group of oligos for manufacture at the same time are priced less than if ordered individually as the numerous synthesis set-up costs can be amortized over the entire group rather than burdened onto a single oligo. Likewise, similar cost savings can be achieved when larger synthesis scales of a single oligo are ordered.

ASR/GMP oligonucleotides from Eurogentec

Eurogentec is registered with the FDA as a Class I manufacturer of custom ASR oligonucleotides, defined by the FDA as being intended for use in in vitro diagnostic (IVD) applications. ASR oligos are manufactured at our ISO 13485-certified facilities in accordance with cGMP guidelines and in compliance with FDA's QSRs [21CFR Part 820, 21CFR Part 864.020 and FDA 21 CFR 809.10(e)]. An internationally renowned certification body in the medical field, LNE/G-MED, has certified our production process to ISO 13485. LNE/G-MED is also accredited by the FDA as a third party body or AP (Accredited Person) to perform such inspections.

For over 6 years, Eurogentec has served many diagnostic companies in the North American market. They have audited our facilities and concluded that we are fully compliant to FDA's GMP/QSRs. All of our ASR oligo manufacturing takes place in classified Class 100,000 and 10,000 cleanrooms (learn more by viewing our virtual tour on the Eurogentec website, www.eurogentec.com), mitigating environmental and cross contamination risks.

Find out how Eurogentec can support you in making your LDTs compliant with the FDA guidelines. We can send a technical specifications guide that compares the differences between ASR- and RUO-grade oligos. Please request one from us by e-mailing ivd.na@eurogentec.com.

Disclaimer

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References

1. "The value of GMP-compliance Part 2: The U.S. perspective," IVD Technology, July 2008, p. 18-20.
2. "Guidance for Industry and FDA Staff, Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions," U.S. Food and Drug Administration, September 2007.

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