IVD TECHNOLOGY
FOR IN VITRO DIAGNOSTICS DEVELOPMENT & MANUFACTURING

Regulatory Requirements for Diagnostic Oligo Manufacturing:

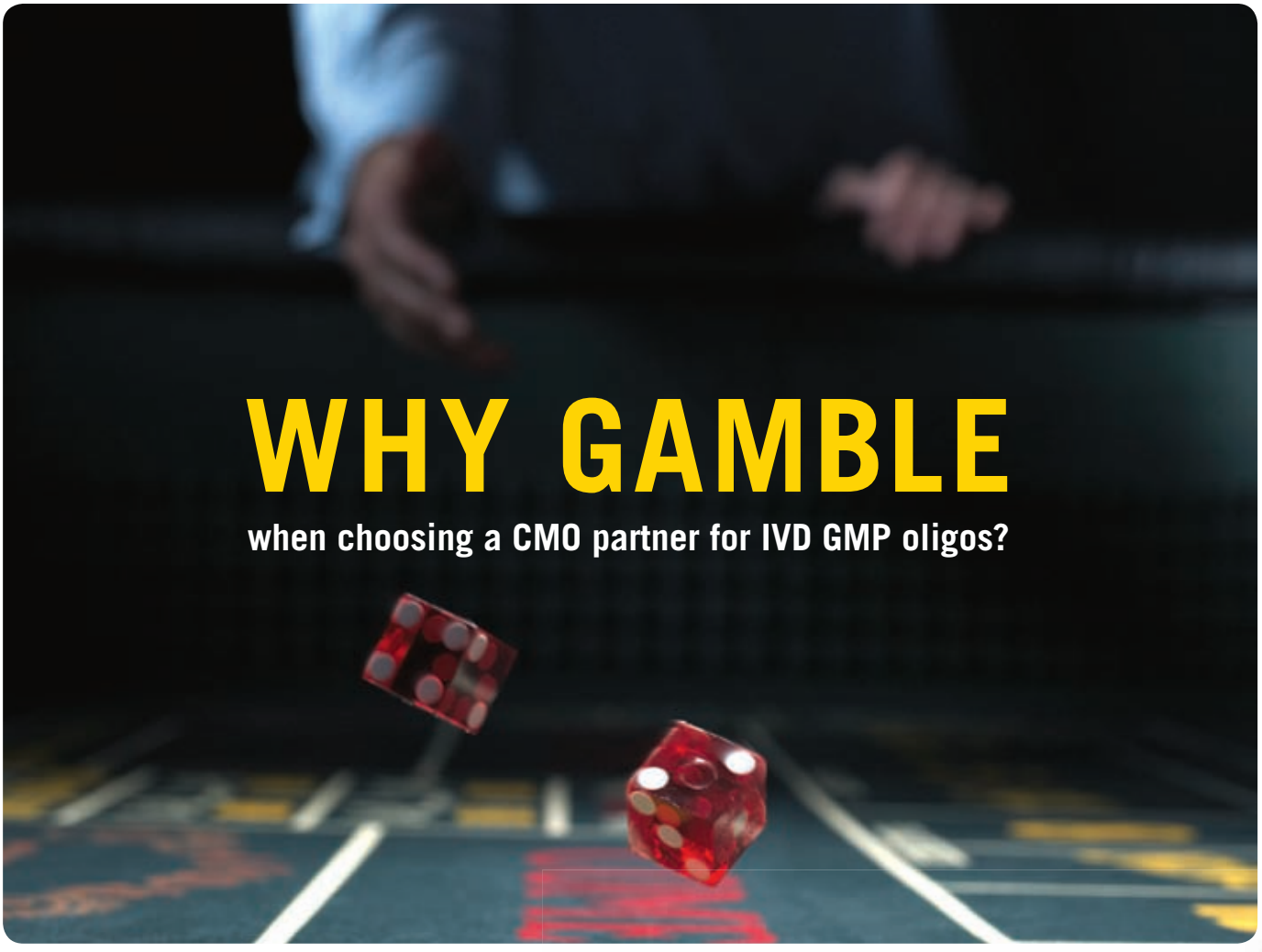
The Value of GMP Compliance

Part 1

The EU Perspective

Part 2

The US Perspective



WHY GAMBLE

when choosing a CMO partner for IVD GMP oligos?

PARTNER WITH A PROVEN CMO WINNER

After years of effort and significant capital invested in developing and validating your company's IVD assays, you're finally ready to go to market. From ISO 13485:2003 to US 21 CFR 820 and EU IVD Directive 98/79 EEC compliance, Eurogentec has the global facilities, trained personnel, experience and quality management systems to comply with the most demanding GMP manufacturing requirements for IVD oligos.

PARTNER WITH EUROGENTEC!

For a free brochure outlining our extensive GMP manufacturing capabilities for IVD oligos, please email IVDT@eurogentec.com or visit our website at www.eurogentec.com/IVDT.

Eurogentec
Experience true partnership

Eurogentec North America, Inc. / 3347 Industrial Ct, Suite A / San Diego, CA 92121 / USA
Email: ivdt@eurogentec.com / Web: www.eurogentec.com/ivdt / Tel. 1 (858) 793-2661 / Toll free (US/Canada): 1 (877) 387-6436

Eurogentec S.A. / LIEGE Science Park / Rue du Bois Saint Jean 5 / 4102 Seraing / Belgium
Email: ivdt@eurogentec.com / Tel.: +32 4 372 74 00 / Fax: +32 4 372 75 00

The value of GMP compliance Part 1: The EU perspective

Critical components from GMP-compliant CMOs provide important advantages for molecular diagnostic assay manufacturers.

BY PETER HAIMA, ANNE-FRANÇOISE EMONTSPOHL, AND MARC KLINKHAMER

Primers and probes are critical components of IVD molecular diagnostic assays. Performance parameters like detection limit and specificity will vary significantly with variations in oligonucleotide quality. Despite the critical importance of oligonucleotide quality, many IVD start-ups seem to struggle with the quality and regulatory needs for oligonucleotides that are produced following good manufacturing practices (GMP). They are subsequently tempted to source less-expensive non-GMP oligonucleotides, which are verified for functional performance through an incoming quality control (QC) procedure.

A need for written guidance on how to determine the quality and regulatory needs for GMP oligos has become clear from several communications between IVD manufacturers and the authors. Eurogentec SA (Liège, Belgium), a contract manufacturing organization (CMO) for IVD GMP oligos and compliance, and Xendo Pharma Services BV (Leiden, The Netherlands), a consultant agency for the health care industry, developed a series of articles that address whether IVD manufacturers need to source critical components from GMP-compliant CMOs from regulatory, legal, quality, risk management, and financial perspectives.

Information included in the articles was obtained from legal documents, guidelines, and standards, as well as from discussions held with auditors from notified bodies who are involved in the daily regulation of IVDs and the application and enforcement of the legal requirements. Part 1 of this two-part series covers the necessity to provide guidance on maintaining GMP oligonucleotides standards from a European perspective.

Background

IVD products marketed in Europe must comply with the legal requirements set in the IVD Directive 98/79/EC, a document that has been transposed into national laws and approved by all member states of the European Union (EU).[1] When an IVD product complies with all IVD Directive requirements, the product receives a CE mark that allows the manufacturer to freely market the product throughout the EU. High-risk IVDs also require the involvement of a notified body to complete this process.

In the IVD Directive, the manufacturer is defined as "the natural or legal person with responsibility for the design, manufacture, packaging, and labeling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party." Oligonucleotides and DNA polymerase are critical components that may affect the performance of an IVD and its compliance with the essential requirements of the IVD Directive. Any deviation from the specifications and manufacturing process of these critical components carries the risk of affecting the performance characteristics of the IVD. However, the IVD manufacturer is responsible for determining which components of the IVD product are deemed critical.

GMP is often used in reference to ISO 13485, a document that explains the quality management systems of medical devices and their requirements for regulatory purposes.[2] Additionally, GMP is specifically named and detailed in the quality system regulation (QSR) issued by FDA.[3] In the case of high-risk IVDs, a regulatory inspection by a notified body serves as the only certification process for the IVD Directive.

For low-risk IVDs, there is no requirement for an inspection, and the IVD manufacturer can claim compliance to the requirements of the IVD Directive based on their own judgment. For those manufacturers, ISO 13485 certification of the quality system by an accredited certification organization can provide independent evidence for GMP compliance. In this situation, the certification organization can be other than a notified body.

IVD Directive Regulation

The IVD Directive, Annex 3, paragraph 4 states:

> The manufacturer shall take necessary measures to ensure that the manufacturing process follows the principles of quality assurance (QA) as appropriate for the products manufactured.

The IVD Directive does not have a specific protocol for establishing a quality system (QS) for the IVD manufacturing process, which includes control and evaluation of suppliers. Manufacturers have the option of setting up a QS that is compliant to ISO 13485, but other approaches are acceptable as well. Unfortunately, a manufacturer will not know if the chosen system is appropriate until after judgment by a notified body or a competent authority. However,

IVD Directive, article 5, paragraph 1 offers IVD suppliers a helping hand:

> Member States shall presume compliance with the essential requirements referred to in Article 3 in respect of devices, which are in conformity with the relevant national standards transposing the harmonized standards, the reference numbers of which have been published in the *Official Journal of the European Communities*.

Essentially, a manufacturer that has followed the IVD Directive requirements and can demonstrate compliance with a harmonized standard for setting up a QS will be presumed appropriate. ISO 13485 is a harmonized standard for QS, and, in practice, it is the standard guidance for the majority of European IVD manufacturers.

Legal Authority

In the field of IVDs, the authorities are responsible for the issuance of national laws, which must be based on the IVD Directive. If a major health and safety problem occurs with a specific product or similar products from other manufacturers, the authorities will contact the IVD manufacturer directly. In such a case, the authority of the member state where the problem occurred will follow a vigilance procedure and perform an assessment with the manufacturer.

The assessment largely consists of a root cause analysis of the problem in relation to the IVD product. The better the QA system performs during the analysis, the more favorable the assessment and the measures taken by the authority after the analysis is complete. For example, if the IVD manufacturer has exerted inappropriate control over a supplier of a critical component and this particular component is the cause of the problem, then the IVD manufacturer could receive the most severe consequence of an unfavorable assessment: exclusion from the European market.

Contrary to the responsibility of law issuance and vigilance duties, the EU authorities have delegated the process of IVD conformity assessment for high-risk IVDs (CE marking) to the notified bodies. Therefore, a notified body can also be regarded as an authority. Specifically, when an IVD is listed in Annex II, list A or list B of the IVD Directive (the high-risk IVDs), the product conformity assessment must be performed together with a notified body, which will issue a CE certificate if the product is found to be in compliance with the IVD Directive. The CE certificate must be issued before the manufacturer can affix the CE mark to the IVD.

Paragraph 3.3 of Annexes 4 and 7 of the IVD Directive stipulates that the notified body must audit the manufacturer's QS for the assessment process, and "the assessment procedure must include an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors." Whether or not an inspection of a supplier is substantiated is further outlined in the notified bodies consensus document of February 2000.[4] An inspection of a supplier of critical components may be necessary, but the notified body will base this necessity on various factors, such as the certification status of the supplier (e.g., the ISO 13485 standard).

Aspects of Quality

The ISO 13485 standard becomes an obvious choice when it comes to ensuring product quality. Section 7.4.1 of ISO 13485 states:

> The type and extent of control applied to the supplier and the purchased product shall be dependent upon the effect of the purchased product on subsequent product realization or the final product.

In the case of critical components, it is clear that the extent of control should be maximized because of its potential effect on the IVD performance. Therefore, requiring a QS process during the manufacturing of critical components would be logical.

If a critical-component supplier is ISO 13485 certified by an independent organization, the IVD manufacturer could consider using this certificate as sufficient proof of supplier evaluation, thereby minimizing costly supplier audits. Alternatively, a highly similar quality system, such as the U.S. QSR, can be used. However, a QS based on ISO 9001 could be seen as too minimal or broad.[5] For example, ISO 9001 lacks a requirement for traceability, but it is mandatory in the ISO 13485 standard. On top of the supplier's QS, the manufacturer will have to further control the supplier and supplier components by use of its supplier monitoring system. Other IVD requirements are clearly mentioned in ISO 13485, which is reflected in the increased number of required documented procedures (6 versus 20).

Risk Management Process

The newly revised ISO 14971:2007 standard is a widely accepted tool for medical device risk management.[6] IVDs undergo a product risk analysis that examines the IVD's function in normal and fault condition modes. Annex H of the ISO 14971 standard lists hazards associated with IVDs in fault condition modes, which could result in the product failing to meet the performance characteristics required for medical use (e.g., trueness, precision, specificity). The listed hazards could result in within-batch inhomogeneity, batch-to-batch inconsistency, nonspecificity, sample or reagent carryover (contamination), and stability failures.

Critical components, largely identified in a production process risk analysis, can be involved in many of the listed hazards as well. Depending on the fault condition's impact on the patient, risk reduction measures would be required to warrant an acceptable IVD. The risk reduction and control focus on, but are not limited to, the critical components of the IVD. An appropriate QS (ISO 13485 or similar) for the production of the critical components, including a proof of the quality system's efficacy (such as ISO 13485 certification), is an effective and acceptable risk reduction measure. The absence of an appropriate QS may result in an increased risk level, possibly to a level that cannot be acceptably justified by the IVD manufacturer.

It should be noted that the classifications listed in the IVD Directive Annex 2 (list A or B) do not play a significant role in performing IVD risk management. The essential requirements and others, as defined in the IVD Directive, are similar for Annex 2 and nonannex 2 IVDs. If an IVD manu-

facturer decides to outsource the manufacturing activities, the IVD company should make sure that the outsourcing partner adheres to the essential requirements of the IVD Directive, such as supplier control.

Financial Consideration

GMP manufacturing of critical components for IVDs requires significant investments in GMP facilities (mainly class 100,000 clean rooms) and the set up and maintenance of an ISO 13485–based QS. Additionally, the extensive quality procedures and documentation for traceability add fixed costs to the overall process. The scope of the QS spans the manufacturing chain for the entire GMP oligonucleotides manufacturing process (see Figure 1).

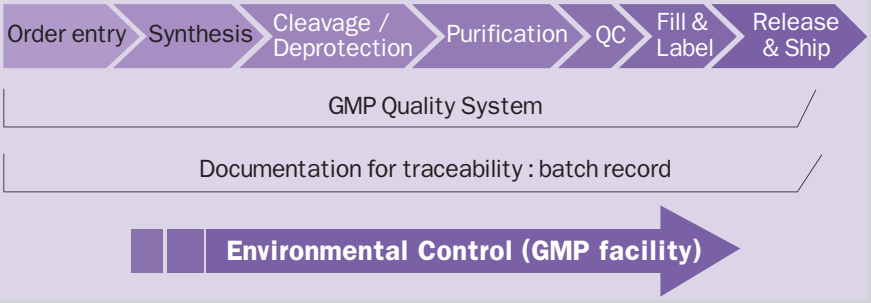


Figure 1. GMP oligonucleotide manufacturing: quality system, documentation, and environmental control.

The financial impact, however, is largely dependent on the scale and final yield of the critical components. Figure 2 shows how the cost of producing a FAM-labeled molecular beacon is affected when a manufacturer has the freedom to upscale the production. Costs are shown as percentages of the GMP oligonucleotide at the lowest yield delivered (5 nmol). At higher yields, the price curves approach each other at levels far below the initial prices for the smallest yield. The prices for GMP and non-GMP oligonucleotides clearly demonstrate the economy-of-scale effect.

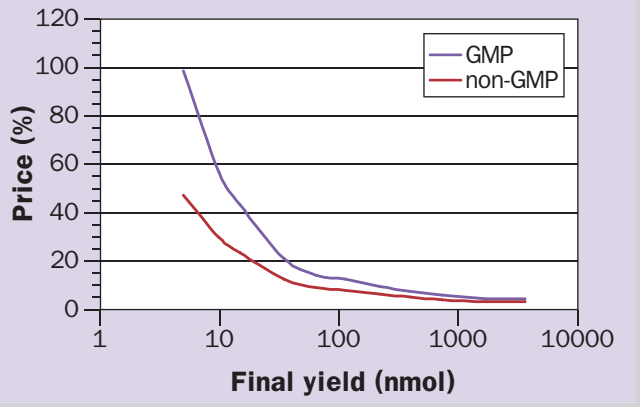


Figure 2. Relationship between price (per nmol) and purchased amount for a GMP and non-GMP oligonucleotide (40-mer FAM labelled molecular beacon).

Conclusion

As a leading principle, the IVD manufacturer is responsible for its CE-marked molecular diagnostic assays and the quality of critical components supplied. The IVD Directive and corresponding laws require the manufacturer to implement a quality system for molecular diagnostic assay production, including control of suppliers and supplied components. The ISO 13485 standard is not required, but it is generally accepted to set up an effective QS.

Any interaction between the IVD manufacturer and the authorities (both national authorities and notified bodies) will benefit from the ISO 13845 certification process with all critical component suppliers. The vigilance and conformity assessment procedures will pose fewer hurdles to the manufacturer than without an ISO 13845–based system.

From a quality and risk management perspective, sourcing critical components from a GMP-compliant supplier using an ISO 13485–based or similar QS is required. GMP components like oligonucleotides are not necessarily more expensive than non-GMP components if ordered at higher yields.

Although the above conclusions are based on European standards, they largely apply to U.S. standards as well. At several meetings, FDA officials have expressed the opinion that IVD manufacturers and IVD service providers should source their critical assay components from GMP-compliant suppliers. The next article in this two-part series will address the same topics from an FDA perspective.

References

1. "Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on In Vitro Diagnostic Medical Devices," *Official Journal of the European Communities* L 331/1 (1998).
2. ISO 13485:2003, "Medical Devices: Quality Management Systems Requirements for Regulatory Purposes" (Geneva: International Organization for Standardization, 2003).
3. *Code of Federal Regulations*, 21 *CFR* 820.
4. "The Manufacturer's Responsibility for the Quality of the Subcontractor's Performance of Quality of Their Products" (European Association of Notified Bodies for Medical Devices, 2000) NB-MED/2.5.2/Rec1; available from Internet: www.team-nb.org/documents/cat_view-139.html.
5. ISO 9001:2000, "Quality Management Systems: Requirements" (Geneva: International Organization for Standardization, 2000).
6. ISO 14971:2007, "Medical Devices: Application of Risk Management to Medical Devices" (Geneva: International Organization for Standardization, 2007).

The value of GMP compliance Part 2: The U.S. perspective

U.S. regulatory agencies encourage diagnostic manufacturers to seek GMP-compliant suppliers as sources for critical components.

BY PETER HAIMA, PETER SCOTT, AND MARC KLINKHAMER

The first part of this two-part series (*IVD Technology*, June 2008) focused on the European regulatory, quality, and risk management aspects of sourcing critical components for molecular diagnostic assays. This second article will focus on the regulatory situation in the United States and the FDA perspective where it specifically differs from the European perspective as described in Part 1.

Some IVD manufacturers believe functional quality control (QC) testing on incoming critical components is an adequate replacement for good manufacturing practices (GMP) of those components. The *Federal Register* addresses this issue with the following statement:

> The intent of §820.50 is to ensure that device manufacturers select only those suppliers, contractors, and consultants who have the capability to provide product and services. The quality of a product or service is established during the design of that product or service, and achieved through proper control of the manufacture of that product or the performance of that service. Section 820.50 thus mandates that products be manufactured and services be performed under appropriate [quality assurance] QA procedures. Finished device manufacturers are required under §820.50 to establish the requirements for, and document the capability of, suppliers, contractors, and consultants to provide quality products and services.[1]

The following quote from the World Health Organization (WHO) supports the above statement:

> Good quality must be built in during the manufacturing process. GMP prevents errors that cannot be eliminated through quality control of the finished product.[2]

As a consequence, incoming quality control (IQC) is not an adequate replacement for GMP manufacturing of critical components. Quality cannot be completely inspected or tested in products after implementation. For example, IQC is unable to detect or is likely to miss low-level cross-contamination, documentation errors, variations in impurities, and sequence errors (e.g. ACGT instead of AGCT). These variations could result in failing to meet the IVD performance characteristics required for use in certain patient samples (e.g., precision, specificity, and detection limit). GMP manufacturing in a GMP facility, including a proof of effectiveness of the quality system (QS) such as ISO 13485 certification, reduces the risks associated with such errors.

FDA Regulations

The regulatory framework for medical devices in the United States is different from the IVD products regulation in Europe. While the European Union has three separate directives (IVD Directive, Medical Devices Directive, and Active Implantable Medical Devices), the United States has one set of regulations applicable to medical devices which include IVD devices, such as molecular diagnostics.[3-5] The U.S. regulation system has no provisions concerning directives that need to be transposed into national laws, notified bodies, or different competent authorities. The regulations are clearly described in the *Code of Federal Regulations* (*CFR*). For example, 21 *CFR* 820 defines the GMP requirements, often referred to as the quality system regulation (QSR), which apply to medical devices. These regulations are similar to ISO 13485; however, they offer much more detail in the specific IVD device requirements. FDA is appointed to the task of enforcing the requirements.

The law is clear regarding the requirement for molecular diagnostic manufacturers to source critical components from GMP-compliant contract manufacturing organizations (CMOs). According to of 21 *CFR* 820:

> The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance.

With this law in consideration, manufacturers of molecular diagnostics do not have any legal recourse to impose GMP on their critical-component suppliers. However, experience with other FDA guidances implies that although FDA guidance documents are voluntary, implementation is highly recommended in order to facilitate a smooth product clearance and site inspection. Additionally, 21 *CFR* 820 requires manufacturers of molecular diagnostics to "establish and maintain the requirements, including quality requirements, which must be met by suppliers." A practical way for a manufacturer to meet this requirement is to assure that a

supplier has a QS in place that is either certified against the ISO 13485 standard or compliant with the QSR, or both. A QS based only on ISO 9001 could be regarded as insufficient because traceability requirements are lacking, and IVD requirements, such as documented procedures, are minimal (6 in ISO 9001 versus 20 in ISO 13485).

FDA Investigations

The depth and breadth of an FDA investigation depend on the rationale for the facility visit. Most FDA inspections are prompted by one of three situations: a routine inspection, a for-cause inspection, or a premarket approval (PMA) inspection. One of the requirements for FDA approval of a PMA device is an FDA facility inspection if an investigation has not recently occurred for a similar product.

A routine facility investigation will include a review of the corrective and preventive action (CAPA) system and several other major subsystems. In the absence of any concerns discovered during the review that would lead the investigator to request a closer evaluation of the incoming area (i.e., control over suppliers), the potential for a detailed review of the area is minimal. However, if the inspection is for cause and due to a reported field corrective action that directly relates to the product not meeting the package insert claims (i.e., the instructions for use), the investigator will evaluate the incoming area. During a PMA inspection, all areas of the production process, from incoming materials inspection and control to final product release, will be thoroughly evaluated.

As with most audits and investigations of an IVD manufacturer, the investigator will want to survey the entire facility. If an area appears disorderly or out of control, it will be noted and evaluated further by the investigator. Regardless of the rationale for the inspection, it is clear that the incoming area and supplier control will be either directly or indirectly evaluated during every FDA investigation.

FDA's general approach is to determine if the manufacturer has made every reasonable attempt to prevent the use of incorrect or suboptimal raw materials in an IVD product. FDA will hold the manufacturer responsible for the product that they produce and release on the market, regardless of the supplier, its data, or its certification. However, in some cases, the supplier may also be investigated should FDA believe it is warranted.

As previously indicated, FDA regulations state that the manufacturer shall "establish and maintain the requirements, including quality requirements, which must be met by suppliers." In order to satisfy the FDA guidelines regarding establishing and maintaining quality requirements, especially by suppliers, manufacturers typically set up programs that may include and combine any of the following: supplier audits, supplier ISO 13485 (or equivalent) certification, contract laboratory analysis of the raw material, in-house evaluation of the material, certificates of analysis, and certificates of conformance.

During a routine FDA investigation, many facility issues could result in a detailed review of the incoming inspection area, such as stability problems, complaints, or nonconforming-material reports relating to raw materials. The investigator's review may evaluate the raw-material inspection procedures, quarantine, and holding areas.

At several meetings, FDA officials have expressed the opinion that IVD manufacturers and IVD service providers should preferably source their critical assay components from GMP-compliant suppliers. During an investigation, FDA will determine whether the raw materials provided by a supplier are adequately controlled by the manufacturer. Therefore, it is important to develop a detailed incoming-material inspection process. An ISO 13485 (or equivalent) certification of the supplier's QS of critical components could be an essential part of the process.

Analyte Specific Reagents

In the United States, FDA has established a separate set of regulations for analyte specific reagents (ASRs) which are defined as the following:

> 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.[6]

Critical components, such as primers and probes as defined in the first part of this article, directly delivered to a clinical diagnostic laboratory, can be considered ASRs. The laboratory will use an ASR for inclusion in an in-house–developed diagnostic test (i.e., laboratory-developed test (LDT)) and must comply with the Clinical Laboratory Improvement Amendments (CLIA).[7] With respect to the supplier, if an ASR is not involved in any high-risk blood banking test or high-risk infectious-disease test (e.g., human immunodeficiency virus or tuberculosis), it can be considered a Class I medical device.

For some suppliers, the Class I classification is appealing because such devices are exempt from premarket notification. However, it is noteworthy that Class I device manufacturers are required to follow GMP. GMP are identified in the QSR and defined in 21 *CFR* 820. Contrary to the critical-component supplier for an IVD manufacturer, who is encouraged but not required to follow the GMP, the supplier of an ASR is obliged to follow such regulations.[8]

From the laboratory perspective, CLIA regulations are enforced by the Centers for Medicare & Medicaid Services (CMS). Therefore, certain diagnostic tests conducted in a U.S. clinical laboratory on a patient's sample can be performed using two different types of molecular diagnostic assay: one that originates from an IVD manufacturer that is cleared or approved by FDA, or an LDT from a laboratory that is regulated by CMS.

Some primers and probes are sold in the United States as products for research use only (RUO). FDA requires such products to be labeled "For research use only, not for use in diagnostic procedures."[9] The required text makes it clear that the diagnostic aspect is not applicable for RUO products, and consequently, FDA does not require RUO products to

be manufactured in compliance with GMP. RUOs are not regulated by CMS, because CMS only regulates lab testing performed on humans in the United States not intended for research testing purposes.

If a lab orders an RUO product, it cannot be used in any in-house–developed test or diagnostic assay. According to the label text, the laboratory may only utilize the material for research purposes, and even the most stringent IQC will not alter the status of the RUO.

Conclusion

Quality cannot be inspected in critical components that have been produced. A QS, preferably certified by an independent organization against an international standard such as ISO 13485, is an appropriate means to assess the quality of a supplier's system and the component. With respect to FDA, there is no strict requirement for critical-component suppliers to comply with GMP; however, the agency encourages suppliers to embrace GMP.

FDA facility inspections routinely will not review the QC over suppliers in detail. However, if the inspection is related to a PMA filing, for cause (e.g., a field corrective action related to the product not meeting its claims), or a general production concern, this area will receive intensive attention from FDA.

Critical components, such as primers and probes supplied to a clinical laboratory, need to comply with specific regulations for ASRs and have to be manufactured under GMP. On the other hand, there are no specific regulations requiring a QS for RUO products in the United States. Manufacturers should use labeling according to the intent of the RUO product.

The regulations in Europe and the United States are complex and differ in several ways. However, it is clear that high-quality molecular diagnostic assays require high-quality inputs. Therefore, from a quality and risk management perspective, sourcing of critical components from a GMP-compliant supplier is a logical step, to be followed preferably by compliance with a widely accepted standard (e.g., ISO 13485) with independent certification.

References

1. "Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation (Subpart E—Purchasing Controls)," 21 *Code of Federal Regulations*, part 820.50, in *Federal Register* 61(195):52625, October 7, 1996.
2. "GMP Questions and Answers," the WHO Web site, (Geneva; 2007 [cited 14 September 2007]); available from Internet: www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en.
3. "Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on In Vitro Diagnostic Medical Devices," *Official Journal of the European Communities* L 331/1 (1998).
4. "Directive 93/42/EEC of the European Parliament and of the Council of 14 June 1993 on Medical Devices," *Official Journal of the European Communities* L169/1 (1993).
5. "Directive 90/385/EEC of the European Parliament and of the Council of 20 June 1990 on the Approximation of the Laws of the Member States Relating to Active Implantable Medical Devices," *Official Journal of the European Communities* L189/17 (1990).
6. "Analyte Specific Reagents," *Code of Federal Regulations*, 21 *CFR* 864.
7. "Laboratory Requirements," *Code of Federal Regulations*, 42 *CFR* 493.
8. "Draft Guidance for Industry and FDA Staff: Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions," Center for Devices and Radiological Health Web site (Rockville, MD [cited 14 September 2007]); available from Internet: www.fda.gov/cdrh/oivd/guidance/1590.pdf.
9. *Code of Federal Regulations*, 21 *CFR* 809.10(c)(2)(i)

Peter Haima, PhD, is IVD services manager at Eurogentec SA (Liège, Belgium). He can be reached at p.haima@eurogentec.com.

Anne-Françoise Emontspohl, PhD, is quality system manager at Eurogentec SA (Liège, Belgium). She can be reached at a.fr.emontspohl@eurogentec.com.

Marc Klinkhamer, PhD, is a senior consultant at Xendo Pharma Services BV (Leiden, The Netherlands). He can be reached at marc.klinkhamer@xendo.com.

Peter Scott is a regulatory and quality consultant with 20 years senior management experience with medical devices based in the United States. He can be reached at psfs71@hotmail.com.