CE MARKING OF *IN VITRO DIAGNOSTIC* MEDICAL DEVICES

LNE G MED

Edition 2014

LNE Guide - Table of Contents

1 - Introduction

LNE/G-MED is a highly-respected European Notified Body with much experience in European regulations. As a Notified Body, LNE/G-MED inspects and certifies a wide range of business and consumer products to be sold in Europe. While its expertise is vast and covers numerous Directives, LNE/G-MED wanted to focus its expertise on the medical device market to help manufacturers market their devices in Europe. The following guide is specific to the in vitro diagnostic medical devices (IVDs) for which LNE-G-MED has an extensive inhouse expertise and an experience as a Notified Body since the publication of the 98/79/EC directive.

This guide is for in vitro medical device manufacturers who may call on LNE/G-MED to receive the necessary certificates for CE Marking to put their products on the European market. This guide is no substitute for the regulations or the official guidance documents.

IVD manufacturers that need a fast time to market need a strategy to successfully navigate through the certification process framed by the 98/79/EC directive governing in vitro diagnostic medical devices.

With this Guide, LNE/G-MED will explain the requirements in the 98/79/EC directive, giving the manufacturer the ability to create a strategy adapted to their device that will help usher their device into Europe.

2. The regulatory framework

With the "Single Act" in December 1985, the Member States of the European Economic Community (EEC) created an area with no internal borders to allow the free movement of people, goods, and services. For medical devices these internal borders were especially onerous because each country maintained its own safety laws. However, the "New Approach" harmonized many technical barriers, allowing for freer medical device trade within the EEC.

Some major objectives and principles of the "New Approach" are:

- Freedom of movement for CE-marked devices throughout the European Economic Area;[1]
- CE marking is mandatory for marketing in vitro diagnostic medical devices (IVDs) in Europe, except for IVDs intended for performance evaluation;
- CE marked devices conform to all the "Essential Requirements" as defined in the relevant directives.
- Support of European Harmonized standards.
- If needed, a Notified Body certifies that a device conforms with the "Essential Requirements." A Notified Body is a third party that certifies a device so that it may be sold in all countries in the European Economic Area, regardless in which Member State the Notified Body has its headquarters.

2.1 To which products do the in vitro diagnostic medical devices directive apply?

The first step for any manufacturer is to determine if the device is covered by the IVD Directive. A manufacturer can look at the first article of the IVD Directive, which contain the definitions and exclusions.

The IVD Directive[2] defines medical device as:

...any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *Diagnosis, prevention, monitoring, treatment or alleviation of disease,*
- *Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
- *investigation, replacement or modification of the anatomy or of a physiological process,*

Control of conception,
and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.[3]

1 The European Economic Area (EEA) consists of the member states of the European Union, Norway, Iceland and Liechtenstein which are member states of the European Free Trade Association (EFTA).
2 98/79/EC
3 98/79/EC Art. 1(2)(a).

The IVD Directive defines in vitro diagnostic medical device as:

> ...any medical device, which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:
>
> • concerning a physiologic
> **Example: pregnancy test**
> • or pathological state, or
> **Example: HIV assay**
> • concerning a congenital abnormality, or
> **Example: evaluation of risk of trisomy 21**
> • to determine the safety and compatibility with potential recipients, or
> **Example: determination of blood group of the ABO system**
> • to monitor therapeutics measures.[4]
> **Example: digoxin assay**

Note 1: If no specimen is involved, or if the examination takes place in or on the human body (in vivo), the devices intended to be used for this examination are not IVDs.

Examples:
- A pulse oxymeter emitting light through the fingertip and absorbing infrared light, to measure the oxy/deoxyhemoglobin ratio is not an IVD,
- A continuous blood glucose monitoring system where the analytical function is carried out at the same time as the continuous specimen collection is not an IVD.

Note 2: If there is no medical purpose, then the device is NOT an IVD.

Example: tests for detecting drug abuse/alcohol that is intended to be used in law enforcement.

Specimen receptacles are IVDs. Specimen Receptacles are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of a specimen derived from the human body for the purpose of in vitro diagnostic examination.[5]

Examples: Blood collection tubes, urine sample containers

We should note that, for the most part, products that are for general laboratory use are not IVDs.

Examples: General centrifuges, general purpose pipettes, empty petri dishes, spectrophotometers

These products are IVDs when the products' manufacturer specifically intends them to be used for in vitro diagnostic examination purposes.

4 98/79/EC Art. 1(2)(b).
5 98/79/EC Art. 1(2)(b).

To be noted also is that invasive sampling devices or those which are directly applied to the human body for the purpose of obtaining a specimen are not considered to be accessories of IVD; they are medical devices within the meaning of Directive 93/42/EEC.

Examples: Needles, lancets

The IVD Directive does not define "kit" but it is generally recognized that it is several components made available together and intended for use to perform an IVD examination. The whole combination that is placed on the market as one single product is treated as a kit and shall fulfill the requirements of the IVD Directive, including validating the combination.

A kit may contain IVDs which may be CE marked on their own, not CE marked, or a combination of both. A kit may also contain a combination of IVDs, medical devices (such as lancet, swabs) which must be CE marked according to 93/42/EEC, and other products like products for general laboratory use. The kit shall be CE marked, but shall not bear an additional CE marking on the outer packaging for the medical devices included in the kit.

Any doubt on whether a device falls into the IVD definition? Further guidance on what is, and is not, an IVD can be found in MEDDEV 2.14/1 Revision 2 January 2012.

Additionally, note that the scope covered by this legislation will be modified by the draft of the future IVD regulation.

2.2 Who is responsible for marketing in vitro diagnostic medical devices?

The manufacturer is responsible for putting their devices on the market. However, the IVD Directive takes into account the fact that many parties have their hand on a device before it actually goes to market. As a result, the IVD Directive defines what a manufacturer is, when a device is actually placed on the market, and put into service. The additional parties that have their hand on a device may also bear some responsibility for following the IVD Directive, depending on the parties' role.

Manufacturer

The IVD Directive defines a manufacturer 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.
>
> The obligations of this directive to be met by manufacturers also apply to the natural or legal person who assembles, packages, processes, fully refurbishes and/or labels one or more readymade products and/or assigns to them their intended purpose as devices with a view to their being placed on the market under his own name. This subparagraph does not apply to the person who, while not a manufacturer within the meaning of the first subparagraph, assembles or adapts devices already on the market to their intended purpose for an individual patient.[6]

6 98/79/EC Art. 1(2)(f).

In short, the IVD Directive defines the manufacturer as the party who has the responsibility for designing, manufacturing, packaging, and labeling a device under its own name. This is true even when a third party performs any of these tasks on behalf of the manufacturer. However, a manufacturer is not someone who adapts a device for a specific patient, even though the person may assemble that device.

If a manufacturer has no registered offices in Europe, it must appoint an authorized representative in one of the Member States. The manufacturer could then instruct the representative to take over some of the conformity assessment procedures. In this way, the authorized representative would seek the certification services of a Notified Body at the manufacturer's request.

Placing on the market

The IVD Directive defines when the device is actually placed on the market as:

> ...[T]he first making available in return for payment or free of charge of a device other than a device intended for performance evaluation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished.[7]

A device is placed on the market when it is first made available for sale, even to a distributor. This is true regardless if the device is brand-new or fully refurbished. It's important to note that each device of a given model is put on the market, and it is not that the model itself is put on the market. This definition doesn't apply to devices that aren't intended to be distributed or used on the community market.

Putting into service

The IVD Directive defines when a device is put into service as:

> *...[T]he stage at which a device has been made available to the final user as being ready for use on the community market for the first time for its intended purpose.*[8]

A device is put into service when it's available to the final user for its intended purpose.

Other Parties

Sometimes, in specific situations, other parties are also involved along with the manufacturer. These parties are:

Authorized Representative of the manufacturer is a legal person established in the EEC who acts as the face of the manufacturer to the Competent Authorities. More information about the Authorized Representative, its role, and its responsibilities can be found in MEDDEV 2.5/10.

Subcontractors or suppliers of the manufacturer who may be involved when establishing the conformity of the device. Information about the control of the suppliers and subcontractors may be found in the NBOG Best Practice Guide 2010-1.

7 98/79/EC Art. 1(2)(i)
8 98/79/EC Art. 1(2)(j)

Distributors can also be involved when:
- It is the European-based importer for a non-European manufacturer; and
- The distributor can be intermediary for transmitting post-market surveillance information

While it may seem confusing, LNE/G-MED is here to help discern which parties must be involved in a device's certification. To establish which parties must be involved in your device's certification, contact LNE/G-MED to speak with a project manager or one of our regulatory experts.

2.3 Role of Notified Bodies

As a third party officially nominated by their respective national authorities, notified bodies issue statutory certificates that manufacturers need to get their products on the market. As a result, notified bodies are key to performing the conformity assessments that the Directives establish.

The main task of the notified body is to provide conformity assessment services according to the Directives, taking into account all of the guides, interpretive material, and standards. These activities include:
- Confirmation of the classification of medical device by the manufacturer taking into account the classification rules defined in the guidelines;

And depending on the class,
- The compliance of the medical device (testing, release of manufactured products, ...);
- The compliance of the manufacturer's quality system (on-site audit);
- Assessment of the technical documentation of the medical device, whether systematically, for the products most at risk, or on a sampling basis for medium-risk products; and
- Assessment of critical subcontractors.

The purpose of the quality system audits is to verify that the manufacturer defines, documents, and implements a coherent set of policies, procedures and practices to control and manage its business. The quality system must comply with applicable regulatory requirements. Examination of technical documentation and testing are intended to verify compliance of the medical device to all essential requirements.

A favorable assessment of the quality system and / or technical documentation allows the notified body to issue CE certificates. These certificates are necessary for the manufacturer to issue a declaration of conformity prior to placing the device on the market. This is the manufacturer's responsibility, that after verifying that all requirements are met and, where applicable, that all the notified body's necessary assessments lead to a CE certificate.

LNE / G-MED is actively involved in the European Commission-sponsored group of Notified Bodies, NB-MED. NB-MED meets twice each year in Brussels, Belgium, with European Commission and major professional European medical device manufacturers' organizations' representatives. During these meetings, practical issues that can lead to differences of interpretation or action are identified and openly discussed. These discussions result in consensus statements and recommendations that are written and prepared by task forces and overseen by the Group of Notified Bodies Recommendations (NBRG).

LNE / G-MED is also a member of the Professional Association Team NB.[9] As such, it was one of the five notified bodies responsible for drafting the Code of Conduct (CoC). The CoC intends to contribute to improving the implementation of the certification of medical devices under the CE marking by specifying criteria or jurisdictional elements relating to methods of assessment.

[9] http://www.team-nb.org/

3. What should a manufacturer do before contacting LNE/G-MED or another Notified Body?

The process outlined in the IVD Directive that allows a manufacturer to enter the European market in accordance with Directive 98/79/EC goes through several stages and involves some choices. Unsuitable choices can lead to extended delays or increased costs required to obtain certificates and possibly lead to deadlock.

Defining the best approach is of strategic importance.

The main steps are:

1. Identifying the "Manufacturer" and, where applicable, its agent, subcontractors and distributors;
2. Characterizing the products;
3. Determining applicable Directives;
4. Determining product classes for Directive 98/79/EC;
5. Selecting the most appropriate procedures to determine compliance - "Methods of proof"
6. Collecting necessary data for the chosen procedures or, in particular for meeting the demands of certain "horizontal" provisions (risk analysis, clinical evaluation, performance evaluation, etc.); and
7. Consulting LNE / G-MED once the appropriate procedure has been decided upon.

These milestones are the subject of the sub-chapters below.

3.1 Who is the "Manufacturer" of the Product?

The definition referenced earlier of this guide enables a company, on the basis of its activity and methods for marketing the product, to define whether it will be considered as the product manufacturer.

It should be noted that if an authorized representative is required, then the manufacturer may instruct his authorized representative established in the EEA, engaging some of the procedures laid down in Directives, including Annex III (EC Declaration of Conformity), V (EC type examination), VI (EC verification), VIII (Statement for devices intended for performance evaluation) of Directive 98/79/EC.

3.2 Characterizing the Product

Characterizing the product is fundamental because it establishes which European Directive should be used and which class is concerned if the product is an in vitro diagnostic medical device according to Directive 98/79/EC.

When the manufacturer establishes that the product meets the definition of an in vitro diagnostic medical device or an accessory, it should respond to certain specific and detailed questions, including:

- What is the manufacturer's intended use for the device in question, which will be included in the documents accompanying the device (sales literature, catalog, label, user guide, etc.)?
- Does the device depend on a source of energy other than that directly generated by the human body or gravity for its operation?
- Is a drug related to the use of the device? If so, how?
- Does the device incorporate products of animal origin?
- And any others.

3.3 Determining the Applicable Directives

By applying Article 1 of Directives 98/79/EC, 93/42/EEC, and 2000/79/EC, manufacturers can determine which Directives apply to which products. It is also necessary at this stage if another broader directive applies (EURATOM, EMC, machinery etc.). Difficulties may arise for some borderline products, like "protective equipment" (see Directive 89/686/EEC), cosmetics (Directive 76/768/EEC), and especially drugs (see Directive 2001/83/EC and further guidance).

The guide "MEDDEV 2.4 / 1 rev 9" (see § 2.3) and the manual "Borderline and Classification" (see § 3.4) provide guidelines for determining the boundary between medical devices and other products.

3.4 What is the Class of the Medical Device?

Although we are not talking about class, in vitro diagnostic medical devices are divided into 2 groups: IVDs that fall within Lists A (safety) and B (diagnosis) of Annex II and those that are not on these lists. The guides MEDDEV 2.1 / 3 rev 3 (see § 2.3), MEDDEV 2.1 / 6, MEDDEV 2.17 / 1 rev 2 and the manual Borderline and Classification (see § 2.3) provide guidelines for determining the class of medical devices.

3.5 Choice of the Conformity Evaluation Procedures

The conformity evaluation procedures are designed to evaluate compliance with the essential requirements of the directives. They are the main obligations of the manufacturer to place medical devices on the market in the EEA. Once a device gains compliance according to the procedures, the manufacturer may affix the CE marking on the device in question and put it on the market.

The choice of the procedure, which is the manufacturer's, must be performed as described in Article 9 of Directive 98/79/EC regarding medical devices for in vitro diagnosis according to reagent grade (or related item) to see why, Annex II of the Directive.

Choosing the procedure best suited to the manufacturer's needs can be guided by the following criteria:

- The operation of the business for the organization to ensure the required quality (quality system); and
- How to design and manufacture of medical device taking into account the share of outsourced processes.

The Directive states which procedures are possible with each type of IVD. Flow charts showing the procedures are included below. Essentially, the conformity assessments have two aspects:

- Evaluating the design of the medical device to determine if it meets the requirements of the Directives; and
- Assessing the ability of the manufacturer to mass produce conforming devices and to fulfill its regulatory obligations.

The manufacturer has the obligation to respect the regulatory process it chose prior to placing the device on the market and it must be able to demonstrate its approach. Also, depending on the type of IVD it may also be required to verify compliance of this process by a third party: the notified body.

Depending on the type of IVD, the choice of different possible procedures (methods of proof) consists in the association of various modules. These procedures are shown in figures below.

The only procedure that doesn't require a Notified body is the "CE Declaration of Conformity." This procedure can only be used for some IVDs.

3.6 Demonstrating the Conformity to the European Regulatory Scheme: Some Key Principles

Essential Requirements

All the directives refer to the "Essential Requirements" as the technical conditions to which medical devices must comply in order to be put on the market. Annex I of these directives describe the Essential Requirements. Article three of Directive 93/42/EEC states, for instance, "The devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned."

Part I of Annex I describes the general requirements applicable to any medical device, including the risk management and clinical evaluation. Part II of this annex sets out the essential requirements, which are grouped according to the following themes:

- Chemical, physical, and biological properties;
- Infection and microbial contamination;
- Construction and environmental properties;
- Devices with a measuring function;
- Protection against radiation;
- Requirements for medical devices connected to or equipped with an energy source;
- Information supplied by the manufacturer; and
- Requirements for self-testing devices.

Risk Management

The concept that a manufacturer should eliminate or reduce risks as far as possible while designing and manufacturing the device is included in the Essential Requirements. Manufacturers catalog these risks as well as the actions they take to eliminate and minimize these risks in a Risk Management File, which is part of the technical documentation for the device. The EN ISO 14971 standard is the European Harmonized Standard for risk management.

European Harmonized Standards

Because of the general nature of the essential requirements, as they apply to all medical devices, and the difficulty of guaranteeing a common approach from all manufacturers and Notified Bodies, the "New Approach" attributes a particular role and significance to standards. Where the European essential requirements provide goals for proving a medical device's safe and effective performance, the harmonized standards provide methods for reaching those goals. Their application is not mandatory for placing on the market in the EEA. However the compliance with all European Harmonized Standards is a presumption of conformity with the essential requirements.

The bodies responsible for developing and ratifying these standards at the European level are CEN and CENELEC. Their national equivalents for France are AFNOR and UTE.

Common Technical Specifications

Specifically, Directive 98/79/EC introduces (exclusively) for the most critical devices – those mentioned in Annex II List A and, if necessary, List B – the concept of "Common Technical Specifications." These specifications establish appropriate performance evaluation and re-evaluation criteria, batch release criteria, reference methods, and reference materials.

Experts of Member States Authorities set up these Common Technical Specifications, which were officially adopted and published in the OJEU of 3 February 2009.

Manufacturers are, usually, required to comply with the CTS. If, for a duly justified reason they don't comply with those specifications, they must adopt solutions of an equivalent level.

Performance evaluation

A critical piece of the technical documentation that demonstrates the IVD's compliance with the Essential Requirements is the performance evaluation of the device. The performance evaluation demonstrates that the device's performance meets the manufacturer's specified claims and intended use taking into account the generally acknowledged state of the art. The type of performance evaluation is directly linked to:

- The nature of the IVD (qualitative or quantitative determination);
- The intended purpose (diagnosis, screening, monitoring, predisposition, prognosis, prediction, etc.);
- The specimen type;
- The target population tested;
- The intended user and intended environment;
- The expected analytical and clinical performance characteristics; and
- The technology involved.

3.7 Demonstrating Conformity of the Quality System

The European directives require the manufacturer to implement a quality management system for some types of IVDs. The objectives and structure of the QMS are described below.

EN ISO 13485 (Medical devices - Quality management systems - Requirements for regulatory purposes) is the European Harmonized standard on this matter. Specific attention should be paid to the European foreword of this standard. Indeed, Annexes ZA, ZB and ZC of EN ISO 13485:2012 show the comparison between the chapters of the standard and the requirements of the annexes of the Directives.

More information about what a QMS is expected to be may be found in the following guidance documents: NBOG BPG 2010-1 and NBOG BPG 2010-2 (http://nbog.eu/2.html).

4. What will LNE/G-MED do ?

When a manufacturer chooses LNE/G-MED to be its Notified Body to help usher its device to market, it also choses efficiency and expertise.

4.1 General practices

It is important to know the nature of the conformity assessment procedures for IVDs according to the Essential Requirements of the IVD Directive. These procedures are the main parts of the manufacturer's obligations for marketing medical devices in Europe. When the device complies with the Essential Requirements through the assessment procedures, the manufacturer can then put the CE marking on the device and market the device.

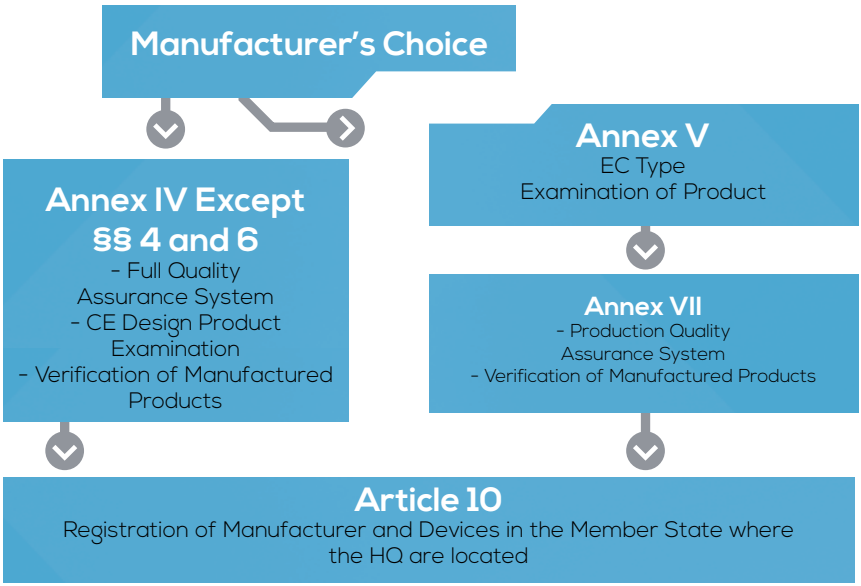
The manufacturer chooses the conformity assessment procedure, although the manufacturer can't choose any procedure for any device. Manufacturers can find the conformity assessment procedures for IVDs in Article 9 of the IVD Directive.

In choosing the conformity procedure, the manufacturer should keep in mind its own quality system and how it fits in with the rest of the business organization, and the manufacturing process including any outsourced processes. The choice of conformity procedure also affects the certification time and cost for both current and future devices.

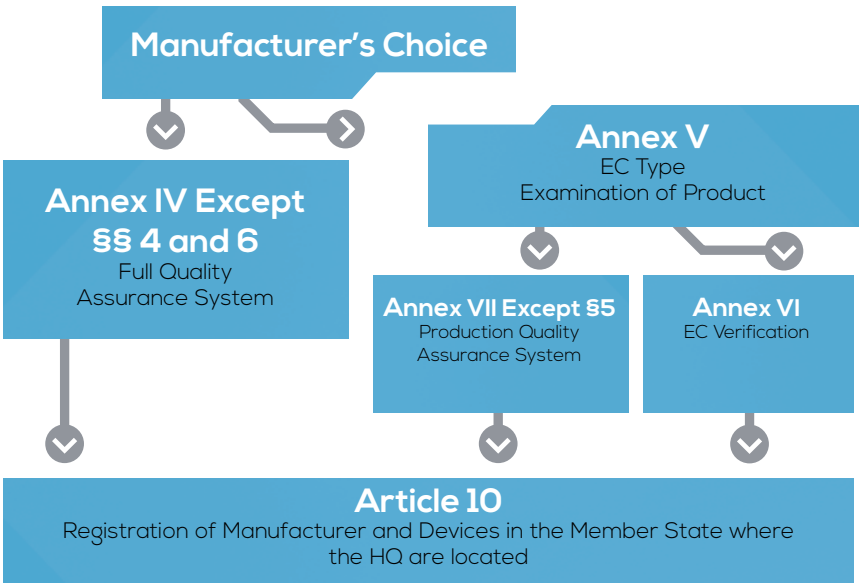
4.2 Description of evaluation procedures in the IVD Directive

The evaluation procedure is a combination of the different modules, taking into account the device's class. The IVD Directive states which procedures are possible for each class. Flow charts showing the procedures, list A and list B:

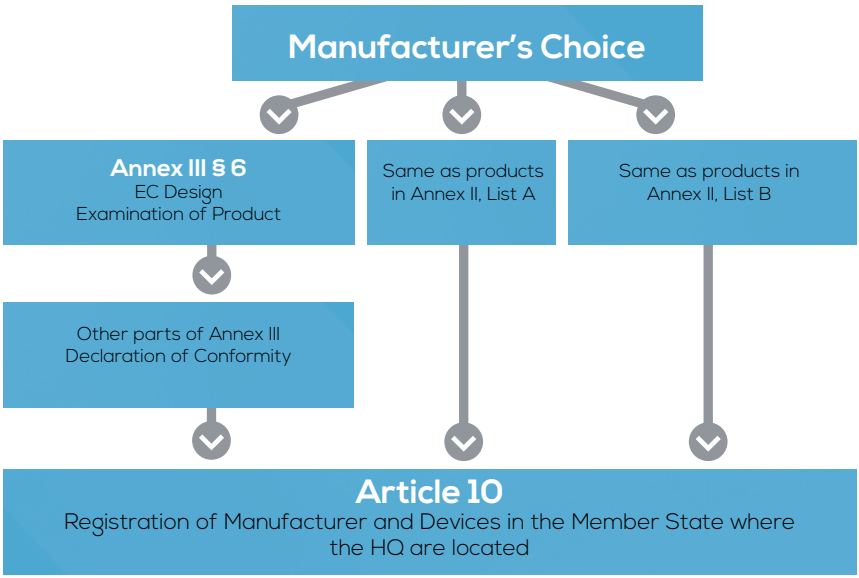
Devices referred to annex II, list A



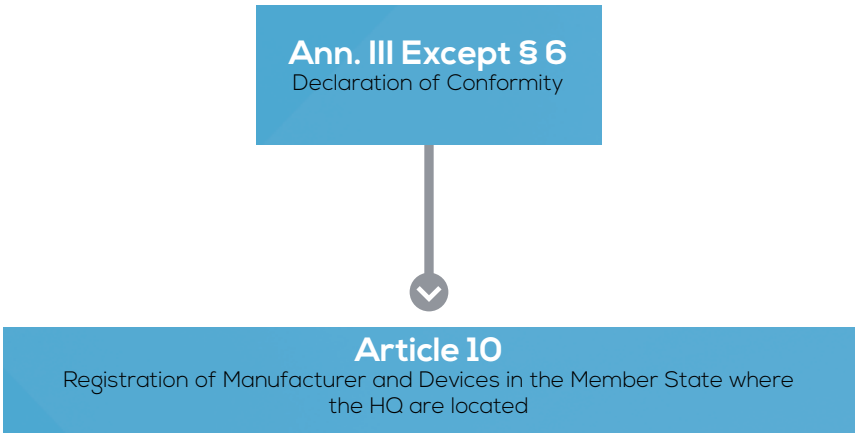
Devices referred to annex II, list B



Self-Testing Devices (except in Annex II)



General IVDs



Essentially, the conformity assessments have two aspects:

- Evaluating the design of the IVD to determine if it meets the requirements of the IVD Directive; and
- Assessing the ability of the manufacturer to mass produce conforming devices and to fulfill its regulatory obligations.

The only procedure that doesn't require a Notified body is the "CE Declaration of Conformity." This procedure can only be used for general IVDs that are not listed in Annex II, list A or B or those that are not for self-testing.

Evaluating the in vitro Medical Device's Design

The design evaluation is either:

- The responsibility of the manufacturer as part of the Declaration of Conformity (Annex III to the IVDD); or
- Performed by the Notified Body according to the Product Design Examination (Annex IV.4 to the IVDD) or the Type Examination (Annex V to the IVDD).

Design Examination

LNE/G-MED reviews the device's design from a technical file that the manufacturer provides. Additionally, LNE/G-MED will approve the manufacturer's complete QMS. The manufacturer will receive a Certificate of Design Examination, valid for five years according to the Directive.[10] LNE/G-MED will also provide a design review report. The manufacturer must inform LNE/G-MED of any plan for substantial changes of the products covered by the certificate.

EC Type Examination

LNE/G-MED will certify that a representative sample of the device's production meets the Essential Requirements. To do so, LNE/G-MED will examine and evaluate the design, manufacturing, and product performance documentation. It will also conduct inspections and necessary tests to ensure that the device complies with the Essential Requirements. The Directives allow LNE/G-MED to issue an EC Type Examination certificate for 5 years, and LNE/G-MED will provide an EC Type Examination report. The manufacturer must inform LNE/G-MED of any plan for any substantial changes to the products covered by the certificate.

Evaluating the Manufacturer's Quality Management System

The manufacturer also chooses the conformity assessment route that the Notified Body uses to assess its manufacturing quality system and regulatory compliance:

- Under the manufacturer's direct responsibility as part of the Declaration of Conformity (Annex III in the IVDD);
- As part of the Full Quality Assurance System or Production Quality Assurance System assessments; or
- As part of the EC Verification, done on a unitary or sampling basis.

10 98/79/EC Annex IV Art. 9(10)

Full Quality Assurance System

In the Full Quality Assurance System assessment, LNE/G-MED evaluates the manufacturer's quality system for the products that the certificate will cover, and it will ensure the manufacturer consistently applies the quality system. LNE/G-MED performs all the audits, and the manufacturer must inform LNE/G-MED of any substantial changes to the approved system or the covered products. Depending on the device, Annex IV.4 "design review" may not apply.

Production Quality Assurance

LNE/G-MED will monitor and approve the manufacturer's QMS for the manufacture and final inspection of the product. To do so, LNE/G-MED will evaluate the manufacturer's QMS for the products and ensure the manufacturer consistently applies the system. LNE/G-MED will also perform any necessary audit. The manufacturer must inform LNE/G-MED of any substantial changes to the approved system or the product covered.

EC Verification

LNE/G-MED will examine and test the device by checking every product or statistical control of a homogenous sample of each batch (batch sampling) to ensure the device complies with the Essential Requirements. LNE/G-MED will then issue an EC Certificate.

EC Declaration of Conformity

The manufacturer ensures and declares that the products comply with the Essential Requirements. To do this, the manufacturer must submit the technical documentation for a conformity assessment. Notified Bodies are not involved in this module.

Verification of Manufactured Products

Verification of the manufactured products (batch control procedure) concerns in-vitro diagnostic medical devices covered in Annex II list A of Directive 98/79/CE. Companies manufacturing such products are subjected to the requirements of Annexes IV point 6 and VII point 5 of 98/79/CE.

The NB-MED guidance document 2.5.4/Rev. 2 outlines three batch control procedures. LNE/G-MED uses two of them, depending on the device:

- **Procedure 1:** LNE/G-MED controls samples of the batch of product to be verified LNE/G-MED makes realise the verification of the products by a subcontracting laboratory
- **Procedure 2:** The Company controls a panel obtained from suppliers that LNE/G-MED chooses, according to an approved procedure. This procedure is applicable when the panels are available from the suppliers appointed by LNE/G-MED. Characteristics of the panel shall be in conformity with the technical requirements specified by LNE/G-MED;

CE Marking

IVDs, other than laboratory-developed tests and those intended for performance evaluation, which meet the applicable Essential Requirements must have EC conformity marking when they are placed on the market.

The manufacturer must affix the CE marking so it is visible, legible, and indelible on the device or its packaging, as well as in the instructions for use.

CE marking must be accompanied by the identification number of the notified body responsible for the implementation of the procedures covered in annexes III, IV, V, VI and VII of the IVD Directive when the class of the devices requires a Notified Body's involvement.

LNE / G-MED's identification number is 0459.

The CE conformity marking has the following form.[11]

Proportions must be respected and vertical dimension shall not be less than 5 mm.

Devices for Performance Evaluation

> *...[M]eans any device intended by the manufacturer to be subject to one or more performance evaluation studies in laboratories for medical analyses or in other appropriate environment outside how own premises.*[12]

In such a case, the manufacturer shall follow the procedure described in the Annex VIII of the IVD Directive. It shall draw up a Statement of Conformity of the device to the requirements if the IVD directive, apart from the aspects covered by the evaluation and those itemized in the statement. The Statement of Conformity indicates that every precaution has been taken to protect the health and safety of the patient, user, and other persons.

The technical documentation associated with this statement shall be made available to the authorities.

Devices for performance evaluation do not have a CE marking and there is no involvement of Notify Body in this procedure.

11 98/79/EC Annex X.

12 98/79/EC Art. 1 (e)

New Devices

A device is new[13] if:

> *(a) There has been no such device continuously available on the community market during the previous three years for the relevant analyte or other parameter;*
> *(b) The procedure involves analytical technology not continuously used in connection with a given analyte or other parameter on the community market during the previous three years.*

When registering devices, the fact that the device is "new" shall be indicated in the notification to the competent authority.

4.3 Vigilance and Post-Market Surveillance

Vigilance and post-market surveillance are processes that are implemented with various purposes by a competent authorities and manufacturers in order to get information about the product as soon as it is on the market and during its lifetime and to react if necessary in case of incident or potential incident.

A manufacturer must include a post-market surveillance system in its QMS and provide for ways to collect and act on information about the safety and efficacy of its devices. The system tracks events that the manufacturer analyzes to determine the reasons behind the potentially adverse events.

Any incident which, directly or indirectly, might lead or might have led to the death of a patient, user or other person or to a serious deterioration of their state of health must be reported.

While manufacturers collect information about their device through post-market surveillance, Competent Authorities collect information about devices according to the vigilance procedure laid out in Article 11. Competent Authorities are able to take actions, like recalls, to protect the public health according to the manufacturer's post-market surveillance actions and their own vigilance actions.

4.4 What can a manufacturer do when the regulations don't answer his or her questions?

Despite best intentions, the reality of regulations and legislations is that sometimes they need clarification to be understood and applied in a consistent manner. To help manufacturers and other regulatory professionals, the European Commission develops guides and interpretive texts for the directives, although it should be noted that they aren't legally binding. But these guides provide significant help in interpreting, applying, and avoiding mistakes when interpreting the directives. These guides can be found on the European Commission's website.[14]

LNE/G-MED, as a well-respected Notified Body, enjoys the ability of guiding a device to market through CE Marking certification process. Part of this ability comes from its large pool of regulatory and technical experts, specialists in all of medical device directives, including the IVD Directive.

13 98/79/EC Art. 10(4)
14 http://ec.europa.eu/health/medical-devices/regulatory-framework/index_en.htm.

4.5 Where does the CE marking fit in with the global regulatory frameworks?

The positioning of IVDs

Regulations for IVDs have grown over the years, refl ecting the market growth and the increased importance of IVDs in the global healthcare management. Many regulatory systems function around common principles:

- A device classification system;
- A pre-market evaluation;
- A QMS requirement (frequently based on EN ISO13485);
- A post-market surveillance system including vigilance; and
- A device monitoring centered around the risk management (frequently based on EN ISO14971).

The Global Harmonization Task Force (GHTF) was created to promote worldwide harmonization of medical device regulatory practices. The working groups' documents that the GHTF issues are widely regarded with great value and were the basis for developing new regulatory systems in several countries. These are great tools for manufacturers that intend to globally market their device.

Even though there are differences among the different countries' regulations, the concepts behind the regulatory schemes are similar and implementation is a necessary first step to access the regulated markets.
The IVDD directive is an example of regulatory framework implementing those concepts. The draft revision of the European regulation, published in fall 2012, will further implement these concepts by changing the classification system to a risk-based classification system.

Our services

TESTING & CALIBRATION

- Electrical safety and EMC testing
- Climate-mechanical test (accelerated aging, transportation simulations...)
- Physicochemical testing
- On-site or in-laboratory measurements

CERTIFICATION

Voluntary or Regulatory Certification
- LNE/G-MED, Notified Body CE 0459
- Management and issuing of NF Marks in the medical field
- Access to international markets: Canada, Brazil, Japan, Taiwan, Australia, New Zealand

RESEARCH & TRANSFER

Serving the Safety and Health Industry
- Reference standard development
- Development of new methods
- Stakeholder in the normative field

TRAINING & INFORMATION

- On-site or intra-company training courses (regulatory requirements, CE marking, risk management)
- Technical seminars (MD Forum, IVD Seminar, MRI compatibility seminar)

TECHNICAL ASSISTANCE

- Technical/regulatory assistance
- Prototype Specification Drafting
- Benchmark Development
- Performance Validation

Contact

United States

LNE/G-MED North America

Washington (DC office)
3930 Knowles Ave. Suite 306
Kensington, Maryland 20895
Tel : (301) 495-0477

Rocklin (California office)
5701 Lonetree Blvd, Suite 318
Rocklin, CA 95765, USA

gmedna@lne-gmed.com
www.lne-america.com