CE MARKING OF MEDICAL DEVICES

Guide

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1. Introduction to the guide

This guide is aimed at manufacturers of medical devices/in vitro diagnostic medical devices who are thinking of going through LNE / G-MED to obtain the certificates needed for CE marking for the purpose of placing devices on the European market. It is also intended for people acting on their behalf.

It aims to give them the information that may help them make best use of the skills that LNE / G-MED can offer as a Notified Body for the application of the European directives regarding medical devices/IVD medical devices.

To comply with the provisions of these directives, manufacturers need to develop a strategy.

Indeed, these provisions place restrictions on them while, at the same time, offering them choices.

The manufacturer, who must take into account the interests and realities of his company, is thus confronted with a problem of optimization.

We hope that this guide will firstly help him to find the most appropriate solution for his needs, and secondly to take, in association with LNE / G-MED, the best possible approach to bringing his products onto the market.

To achieve this, this guide seeks to remind the main contents of the directives for each point covered and to indicate their links with the principal European standards.

In addition, and this is its main aim, the guide provides the necessary information on the way LNE / G-MED proceeds in its role and what it expects from the manufacturers it serves.

However, we would draw the reader’s attention to the fact that this guide is neither an official nor an exhaustive document.

Question with regard to the precise contents of directives, to their transposition into national law, to their interpretation for borderline issues – e.g. overlap with medicines, classification – can only be answered in relation to national or Community legislative texts and, where appropriate, to the “guidelines” published by the Commission of the European Communities.

However, LNE / G-MED is at the disposal of the manufacturers it serves to help them look at the problems posed by borderline or ambiguous cases and establish the strategy that will be most advantageous to them.
2. Regulation

2.1. The european directives regarding medical devices/IVD medical devices and their consequences for placing on the market in the european economic area

2.1.1. General

By the « Single Act », in december 1985, the Member States of the Economic European Community undertook to create an area without internal borders to allow the free movement of persons, goods and services. The completion of this « area » was planned for 1st January 1993 at the latest.

In practice, this involved the disappearance of the technical barriers to trade that were created by the significant differences in specific national laws from one country to another.

For medical devices, the characteristics of which are often critical in terms of safety of use, these technical barriers were especially numerous.

They could only be removed by replacing national laws with harmonized community legislation that guaranteed a "high level of health and safety protection for users and consumers".

The first attempts at harmonization by establishing « technical rules » for precise categories of devices by means of specific directives, rapidly proved to be too clumsy and somewhat ineffective.

That is why the « New Approach » was defined and put into practice to speed up the removal of technical barriers, in order to complete the « Single Market » within the planned period.

- In this context, 4 directives were provided for all medical devices, respectively in regard to:
  
  
  
  
  
  - breast implant (directive 2003 / 12 / EC, OJEC n° L28 of 4 February 2003),
  

It is important to take notice that the two last directives modify on other points the 93/42/EEC directive.
The directives are written in accordance with the « New Approach » model.

This is based on some major objectives and principles, notably:

- freedom of movement for CE marked devices throughout European Economic Area¹,

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).

- mandatory (after the end of the transitional periods laid down in each of the directives) CE marking for placing on the market. This obligation neither applies to devices intended for clinical investigations, nor to so-called "custom-made" devices (cf. precise definition of these two categories in directive 93/42/EEC), neither to in vitro diagnostic medical devices for performance evaluation,

- CE marking indicating that the devices so marked conforms to all the "Essential Requirements" as defined in the relevant directives, on the basis that compliance with european standards that qualify for "harmonized standard" status, involves the presumption of conformity with these essential requirements. (see paragraph 2.1.3.),

- precise definition of the procedures for establishing conformity with the "Essential Requirements" - , in each of the directives. These procedures provide, for certain classes of devices for appeals to third parties called "Notified Bodies". When appeal to such third parties is necessary, the certificates they provide are valid for placing on the market in all countries in the European Economic Area, whatever the Member State in which the Notified Body that delivered the certificates is based.

- After the directives are published in the Official Journal of the Economic Community (OJEC), the stages of their application are as follows:

  - Transposition into national law

European directives are aimed at Member States. The latter must therefore incorporate the provisions of directives into their laws and regulations without changing these provisions ; only the aspects that are covered neither by the Treaty of Rome, nor by the Single Act, in particular those that deal with sanctions, ethics or the control of public health funding remain within the jurisdiction of each country and may therefore differ from one to another.

However, the fact that a Member State has not carried out this transposition does not allow it to prevent a device carrying CE marking being placed on the market in its territory, once the starting date for application of the directive concerned has passed.


This law is completed by Conseil d’Etat decree n°95-292 of 16 March 1995 published in the JO of 17 March 1995.

Ordinance by President of French Republic N° 2001-198 of 1 March 2001 which transposes the directive 98/79/CE (in vitro diagnostic medical devices) is completed by implementation decrees.
• **Beginning of the transitional period of application**

A transitional period is laid down for the implementation of each directive. During this period, a manufacturer has the possibility of placing a device on the market of a given Member State by complying with:

- either the national legislation that existed in that State before the start of this period.

- or the directive concerned.

• The starting dates of the transitional periods are:

  - 7 June 2000 for directive 98/79/EC (in vitro diagnostic medical devices),

• **End of the transitional period**

After the end date of the transitional period, implementation of the provisions of the directive concerned becomes mandatory.

The provisions that resulted from national law prior to the directive cease to apply (once again, apart from those with regard to sanctions, ethics or the control of public health funding.

The ending dates of the transitional periods are:

  - 31st December 1994 for directive 90/385/EEC,
  - 14 June 1998 for directive 93/42/EEC,
  - 7 December 2003 for directive 98/79/EC,
  - 13 December 2005 for directive 2000/70/EC.

However, for clinical mercury-in-glass, maximum reading thermometers, the end date for the transitional period is postponed to 30th June 2004. For France, see decree n°95-292 of 16 March 1995, published in JO of 17 March 1995.
2.1.2. Scope of the directives

- Directive 93/42/EEC applies to medical devices and their accessories that fit the following definitions:

**Medical devices**

Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software 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, prevention, monitoring, treatment or 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.

**Accessory**

Any article which, whilst not a device is intended specifically by its manufacturer to be used with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device.

- The directive does not apply to:

  - "in-vitro diagnostic devices,
  - active implantable devices covered by directive 90/385/EEC,
  - medicinal products covered by the directive 65/65/EEC,
  - cosmetic products covered by directive 76/768/EEC,
  - human blood, human blood products, human plasma or blood cells of human origin or to devices which incorporate at the time of placing on the market such blood products, plasma or cells,
  - transplants or tissues or cells of human origin nor to products incorporating or derived from tissues or cells of human origin,
  - transplants or tissues or cells of animal origin, unless a device is manufactured using animal tissues which is rendered non-viable or non-viable products derived from animal tissues."

**Note:**

The directives do not give a definition of the word "animal" and of the expression "nonviable". In March 1995 a working group of the CEN Technical Committee 316 proposed the following definitions:

- Animal: all vertebrates, including fish, amphibians, reptiles, birds and mammals, excluding humans (homo sapiens).
- Nonviable tissue: tissue that cannot sustain metabolism or multiplication at the time of final use.
**Directive 90/385/EEC applies to “active implantable” medical devices, i.e. those which fit the following definition:**

**Active implantable medical device**

Any medical device whose operation depends on an electrical energy source or any source of energy other than that generated directly by the human body or gravity, which is designed to be implemented in full or in part, by surgical or medical operation, into the human body or, by medical operation, into a natural office, and which is intended to remain in place after the operation.

**Directive 90/385/EEC also applies:**

- to non-active implanted parts which are necessary to the operation of the active implanted device itself, for example the electrode probes of internal cardiac pacemakers,
- to non-implantable accessories, whether active or inactive, which are specifically intended by the manufacturer to be used to ensure the proper operation of the active implanted device itself (e.g. filler kit for implantable injectors).

**Directive 98/79/EC applies to in vitro diagnostic medical devices and to their accessories that fit the following definitions:**

**In vitro diagnostic medical device**

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 physiological or pathological state,
  or
- concerning a congenital abnormality,
  or
- to determine the safety and compatibility with potential recipients,
  or
- to monitor therapeutic measures.

Specimen receptacles are considered to be in vitro diagnostic medical devices. “Specimen receptacles” are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination.

Products for general laboratory use are not in vitro diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination.
Accessory

Any article which, whilst not being an in vitro diagnostic medical device, is intended specifically by its manufacturer to be used together with a device to enable that device to be used in accordance with its intended purpose. For the purposes of this definition, invasive sampling devices or those which are directly applied to the human body for the purpose of obtaining a specimen within the meaning of directive 93/42/EEC, shall not be considered to be accessories to in vitro diagnostic medical devices.

- Directive 2000/70 applies to medical devices incorporating stable derivates of human blood or human plasma:

The objectives of these directive is to modify the directive 93/42/EEC not only by extending the scope to the mentioned devices but also to precise particular dispositions which are specific to them.

Note: The directives apply to “finished” products, i.e. those ready for putting on the market for medical application, whether these products are designed to function on their own or in combination with other devices. Spare parts intended for the repair of medical devices, together with intermediate products necessary for the manufacture of a medical device and not utilized by the final user, - such as a raw materials or components - , are not covered by these directives.

These directives apply to medical devices which are put on the market by their manufacturer.

It is essential to take into account the following definitions:

Manufacturer

The natural or legal person with responsibility for the design, manufacture, packaging and labelling 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 ready-made 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.

Placing on the market

The 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.

Putting into service

The 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.
2.1.3. Essential requirements

All the directives refer to the “essential requirements” as the technical conditions to which medical devices must mandatorily comply for being put on the market. Annexes I of these directives describe these essential requirements.

Article 3 of directive 93/42/EEC stipulates:

« 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 II of this annex sets out these 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,
  - establishment of clinical data.

- In addition, and in view of the impossibility of drawing up an exhaustive list in this domain, part I of the annex is expressed in general terms, stipulating in particular:

« The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patient, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a level of protection of health and safety.

The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one of the functions referred to in article 1st, paragraph 2 point a), as specified by the manufacturer,

Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended. »

(extracts from text)
2.1.4. The importance of standards and their use

These regulatory reference base with which medical devices must comply, consists of the essential requirements alone.

In view of their general nature, - 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.

Their application is not mandatory for placing on the market in the EEA.

On the other hand, as specified in article 5 of directive 93/42/EEC,

« ...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 adopted pursuant to the harmonized standards the references of which have been published in the Official Journal of the European Communities ; Member States shall publish the references of such national standards.

For the purpose of this directive, reference to harmonized standards also includes the monographs of the European Pharmacopoeia notably on surgical sutures and on interaction between medicinal products and materials used in devices containing such medicinal products the references of which have been published in the Official Journal of the European Communities... »

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.

For acquisition of the published standards and getting information about standards on work, you have to apply to the here above standard organizations.

The present guide is not intended to provide a list of these standards.

However, the main “horizontal” standards (dealing with characteristics common to numerous device categories) which have the status of “harmonized european standards” are sometimes quoted in some of these chapters.

In addition to, annex A of the present guide refers to the website where the lists of european harmonized standards are quoted.

Particular case of Common Technical Specifications

Specifically, the directive 98/79/EC introduces for (and exclusively for) the most critical devices – those mentioned in annex II list A and, if necessary list B – the concept of “common technical specifications” (CTS).
These specifications establish appropriate performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials.
They have been set up by experts of Member States Authorities and officially adopted and published in OJEC of 16 May 2002 (volume L 131/17).
Manufacturers are, as a general rule, obliged to be required to comply with CTS; if, for duly justified reasons they don’t comply with those specifications, they must adopt solutions of a level at least equivalent thereto.

2.1.5. Problems of interpretation

Despite the precautions taken during the drafting of the directives, some articles and even some concepts need additional clarification and details in order to be properly understood and applied in the same way by the different players.

To do this, the Commission of the European Communities is developing guides or interpretation texts.

These are researched and drafted by groups of experts from the different Member States and from the different interested groups: governments, users, industrialists, …

They do not have the status of regulatory texts. For this reason, the basis for decision or action remains the directives themselves together with the bills that transpose them into the national laws of Member States.

However, they can be used to provide significant help in the interpretation and application of the directives, and to avoid mistakes which might sometimes prove very damaging to manufacturers.

Actually, these guides are:

* Scope, field of application, definitions:
  - Definitions of “medical devices”, “accessory” and “manufacturer” MEDDEV 2.1/1 dated 04/1994
  - Field of application of directive “active implantable medical devices” MEDDEV 2.1/2 Rev 2 dated 04/1994
  - Treatment of computers used to program implantable pulse generators MEDDEV 2.1/2.1 dated 02/1998
  - Interface with other directives – Medical devices/medicinal products MEDDEV 2.1/3 Rev 2 dated 07/2001
  - Interface with other directives – Medical devices/directive 89/336/EEC relating to electromagnetic compatibility and directive 89/686/EEC relating to personal protective equipment MEDDEV 2.1/4 dated 03/1994
  - Medical devices with a measuring function MEDDEV 2.1/5 dated 06/1998

* Essential requirements:
  - EMC requirements MEDDEV 2.2/1 Rev 1 dated 02/1998
  - “Use by” – date MEDDEV 2.2/3 Rev 3 dated 06/1998

* Classification:
  - Classification of medical devices: part 1 and part 2 MEDDEV 2.4/1 Rev 8 dated 07/2001
* Conformity assessment procedure :
- Content of mandatory certificates
  MEDDEV 2.05/1
- Quality assurance. Regulatory auditing of quality systems of medical device manufacturers
  MEDDEV 2.05/2 Rev 3 dated 06/1999
- Subcontracting quality systems related
  MEDDEV 2.05/3 Rev 2 dated 06/1998
- Reporting of design changes and of changes of the quality system
  MEDDEV 2.05/5 Rev 3 dated 02/1998
- Homogenous batches (verification of manufacturers products)
  MEDDEV 2.05/6 Rev 1 dated 02/1998
- Conformity assessment of breast implants
  MEDDEV 2.05/7 Rev 1 dated 07/1998
- Evaluation of medical devices incorporating products of animal origin
  MEDDEV 2.05/8 dated 02/1999
- Evaluation of medical devices incorporating products containing natural rubber latex
  MEDDEV 2.05/9 Rev 1 dated 02/2004

* Clinical evaluation :
- Guide
  MEDDEV 2.7.1 dated 04/2003
- post market follow up
  MEDDEV 2.12/2 dated 05/2004

* Notified Bodies :
- Designation and monitoring of Notified Bodies within the framework of EC Directives on Medical devices
  MEDDEV 2.10/2 Rev 1 dated 04/2001

* Products using materials of biological origin :
  MEDDEV 2.11/1 Rev 1 dated 04/2005

* Market surveillance :
- Medical devices vigilance system
  MEDDEV 2.12/1 Rev 4 dated 04/2001
- Appendix
  MEDDEV 2.12/1 Rev 4 dated 11/2001

* Transitional period :
- OJ C242 of August 8, 1998
  MEDDEV 2.13 Rev 1 dated 08/1998

• Other guidances :
- IVD
  MEDDEV 2.14/1 & 2 Rev 1 dated 01 & 02/2004
- Committees, working parties relevant for medical devices
  MEDDEV 2.15 Rev 2 dated 07/2001

To avoid unexpected difficulties and emerging security problems, the European Commission has adopted positions contained in the following documents :

* Communication of the Commission concerning transitory dispositions for implementing directive 93/42/EEC on medical devices published on 1.8.98 OJEC vol. C/242/5

* Communication of the Commission “on essential safety requirements and conformity assessment schemes of directive 93/42/EEC on medical devices in relation to Breast implants” dated 15 November 2001
In addition, the Commission has prepared a guide intended to explain the concepts of the “New Approach”. This guide deals with the placing on the European market of CE marked products and is not restricted to medical devices. It is called “Guide to the implementation of directives based on the New Approach and the Global Approach”.

2.1.6. Coordination of Notified Bodies

As third parties officially designated by their administrative national authorities, Notified Bodies deliver regulatory certificates needed by manufacturers for putting their products on the market; the Notified Bodies are then the main responsible for the functioning of conformity assessment procedures as indicated by the directives.

In spite of the details given by the directives, guides and standards large interpretation ways exist. In the context of the European Union Single Market, it is essential that the directives provisions be used in the practice with rigorous and constraining levels to assure an uniform implementation by the Notified Bodies requested by the manufacturers. Therefore, a coordination of Notified Bodies has been set up by the European Commission. This coordination takes place by organizing meetings in which Notified Bodies have to send their representatives (plenary meeting). Two such meetings are called each year in Brussels with the participation of representatives from the European Commission and from European professional organizations of medical devices manufacturers. During these meetings, practical questions are identified where interpretation or action is showing differences allowing the corresponding debate to be held. These discussions ends by consensual declarations or by “recommendations” written by “task forces” and supervised by the “Notified Bodies Recommendations Group” (NBRG).

The list of available recommendations is given in annex B of the present guide.

These recommendations constitute a good basis for dialogue between manufacturers and Notified Bodies and favour an homogeneous and uniform approach by them.

LNE / G-MED shares largely the elaboration of these recommendations by taking part regularly to the different working groups. LNE / G-MED takes largely into account the content of these recommendations in its relationship with the manufacturers of medical devices and consequently in the execution of its tasks.
2.2. Others directives to be taken into consideration where applicable

| WARNING | some medical devices also come under the jurisdiction of other “new approach” or “old approach” directives which concerns aspects not specific to the medical domain. |

When this occurs, the devices in question must, in order to be placed on the market, comply with all the directives that apply to them.

However, given that directives concerning medical devices are so-called specific to products covered, their essential requirements encompass, in principle, the applicable requirements of the more general directives.

However, these more general directives develop and precise these requirements so that the manufacturer needs to have a look on it when their products are concerned and have to assure that the provisions which are applicable to these products are fulfilled.

**CE marking then reflects this general conformity.**

A difficulty appears where several directives leave the choice of which system to apply to the manufacturer for a transitional period

In this case, **CE marking shows that the devices only meet the provisions of the directives applied by the manufacturer. The references of the directives applied, as published in the *Official Journal of European Community*, must then be indicated on the documents, notices or instructions that come with the device.**

More precisions are given in the European Commission guide already mentioned “Guide to the implementation of directives based on the New Approach and the Global Approach”.

- The following non-exhaustive list gives the references of the directives that may be relevant.
  - Directive 84/466/EURATOM of the Council of 3 September 1984, relating to the radiological protection of persons subject to medical examinations and treatments.
3. With LNE / G-MED, how do you obtain the certificates required for CE marking?

The procedure which enables a manufacturer to access the European market in accordance with directives 90/385/EEC, 93/42/EEC et 98/79/EC (see paragraph 2.1.), involves several stages and requires certain choices. Making the wrong choices can prolong the time taken or increase the costs involved in obtaining the certificates, or even lead to deadlock.

- **Identifying the best approach is therefore of strategic importance.**

The main stages are as follows:

- identifying the entity "Manufacturer" and, where applicable, his authorized representative, his subcontractors and his distributors,
- characterizing the products concerned,
- deciding which directive(s) applies (apply),
- deciding the classes in the sense of directives 93/42/EEC and 98/79/EC, to which the products belong,
- choosing the most appropriate procedures – modes of proof - for establishing conformity,
- collecting the data necessary to the chosen procedure or procedures, notably to fulfill the needs resulting from certain "horizontal" provisions (risks analysis, clinical evaluation,…),
- the actual LNE / G-MED consultation procedure itself (= regulatory evaluation).

These main stages are covered in the following subsections.
3.1. Identifying the manufacturer and other parties where applicable

In terms of the directives (93/42/EEC article 1.2.f and 98/79/EC article 1.2.f), a manufacturer is:

« the natural or legal person with responsibility for the design, manufacture, packaging and labelling 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 ready-made products and/or attributes to them their intended purpose as a device 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. »

The "intended purpose" is, (see 93/42/EEC article 1.2.g and 98/79/EC article 1.2.h) :

« the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials. »

"Placing on the market" is, (see 93/42/EEC article 1.2.h and 98/79/EC article 1.2.i) :

« the first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the community market, regardless of whether it is new or fully refurbished. »

It is important to note that each exemplar ("each device") of a given model, and not the model or type self, has its own putting on the market ; this definition don’t apply to devices which are not destined to distribution chain and/or to utilisation on the community market (customs transit, …).

The manufacturer defined in this way may appoint an authorized representative in one of the Member States of the European Economic Area ; this option becomes an obligation for a manufacturer whose registered office is not in the EEA if he wants to place class I or custom-made devices on the market.

The manufacturer may then instruct his EEA-based representative to undertake some of the procedures laid down by the directives ; notably annexes III (EC type examination), IV (EC verification), VII (EC declaration of conformity) and VIII (Devices for special purposes) of the directive 93/42/EEC or annexes III (EC declaration of conformity), V (EC type examination), VI (EC verification), VIII (Declaration for devices intended for performance evaluation) of directive 98/79/EC.
Other parties

Subcontractors or suppliers of the manufacturer constitute parties who may be involved when the conformity of devices is being established, notably in the following two cases:

- the manufacturer chooses to have his quality assurance system ("full" or "production") approved. The manufacturer’s control over subcontracting must then be established by the Notified Body which may then, in duly justified cases, carry out an audit on one subcontractor or another,
- the manufacturer places products on the market in a sterile condition. If sterilization is contracted out, the need to approve the part of the quality system which results in sterility makes it necessary for the subcontractor to be audited (or for the results of a previous audit to be formally acknowledged).

Distributors may, where applicable, be concerned in the following cases:

- the distributor is the EEA-based importer for an outside-based manufacturer. The device’s labelling (or its outer packaging or instructions) must then carry, in addition to the manufacturer’s details, those of the person responsible for placing on the European market or those of the representative or those of the importer (see 93/42/EEC, annex I, section 13.3.a and 98/79/EC, annex I.B.8.4),
- the distributor(s) may constitute – de facto – an intermediary for the transmission of information regarding actual or potential incidents or accidents. As the manufacturer undertakes to set up appropriate methods of applying the necessary corrective measures and of informing the Competent Authorities, the distributor(s) also has (have) responsibility.

To establish all the parties directly or indirectly concerned in CE certification, you can consult LNE / G-MED.

3.2. Characterization of the products concerned

Paragraph 2.2, of this guide lists certain directives which may, depending on the characteristics of the products concerned, also apply in very specific cases.

Paragraph 2.1, defines the scope of directives 93/42/EEC, 2000/70/EC, 90/385/EEC and 98/79/EC, respectively with regard to medical devices and to active implantable medical devices.

The characterization of the products is of fundamental importance, as it determines which European directives are to be complied with, together with the classes to which the devices belong when they come under the jurisdiction of directive 93/42/EEC.

When it is known that the product in question corresponds to the definition of an active implantable (see 90/385/EEC), or of a medical device (see 93/42/EEC), or of an in vitro diagnostic medical device (see 98/79/EC), or else a medical device accessory, precise and relevant replies must be given to certain questions, notably:
• what is the **use for which the manufacturer intends the device in question**, and which will appear in the documents that come with the device (sales documents, catalogue, labels, instructions,…)?

• is the **principal** effect of the device obtained by pharmacological (or immunological or metabolic) means?

• does the device require a source of energy other than that directly generated by the human body or gravity in order to operate?

• is the device used in combination with a medicinal product? If so, how?

3.3. **Establishing which directive(s) applies**

On the basis of the answers to the questions above, the definitions given in article 1 of directives 90/385/EEC, 93/42/EEC, 2000/70/EC et 98/79/EC, can be applied to decide whether one of these directives applies, and if so, which one.

At this stage, it is also necessary to check whether, if applicable, another broader directive, i.e. one that is not specific to the medical sector, is also applicable. This occurs infrequently; in this context, it may be useful to look at the list indicated in chapter 2.2.

Difficulties may arise for certain products, notably those that lie on the borderline with "personal protection equipment" (see directive 89/686), cosmetics (directive 76/768), and above all medicinal products (see directive 65/65 and additional directives).

The Commission’s guide "MEDDEV 2.1/3 rev 2" provides valuable advice for identifying the border between medical devices and medicinal products.

3.4. **Establishing the class of the device (Case of directive 93/42/EEC)**

- **Case of directive 93/42/EEC**

The devices which come under the jurisdiction of directive 93/42/EEC, are divided into four classes: I, IIa, IIb, III.

Classification is done in accordance with the rules laid down in annex IX of that directive.

It is essential to go through all the rules in Part III of annex IX, as it is common for several of these rules to be applicable to one product. When this happens, the highest class is the right one.

- **These rules are based on the following criteria:**
  - period of use,
  - invasive character or not, and type of invasiveness,
  - possibility of reuse or not,
  - therapeutic or diagnostic purpose,
  - dependence on an energy source or not,
  - part of the body in contact with the device.
In addition, the following considerations must be kept in mind:

- several rules may be applicable to some devices; so one should go through them ALL when looking into a particular device. When this occurs, the highest class is the right one,
- the most critical part of the body should be taken into account,
- accessories are classified independently of the devices they combine with,
- the software acting of a device belongs to the same class as the device,
- the software which constitute in itself a device are to be classed as a device.

The rules of classification fall into five major groups:

**Rule 1 to 4:** non-invasive devices
It should, however, be noted that these rules may cover devices in contact with wounds or biological fluids

**Rule 5:** devices that are invasive via a body orifice
The definition of a "body orifice" includes permanent artificial openings (notably stomies).

**Rules 6 to 8:** devices that are invasive via surgery
The period of action and the part of the body concerned are fundamental criteria here.

**Rules 9 to 12:** additional rules for active devices
These distinguish therapeutic purpose from diagnostic purpose; they take account, in particular, of the level of danger caused by the administration of a substance or an energy.

**Rules 13 to 18:** special rules intended for special categories of device.

To be noted the following important definition:

**Active medical device:**
Active medical device operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices.

**3.5. Choice of procedures for assessment of conformity**

The purpose of these procedures is to evaluate conformity to the essential requirements of the directives. They constitute the main part of the manufacturer’s obligations for placing medical devices on the market in the EEA.

Once conformity is achieved in line with one of these procedures, the manufacturer may put CE marking on the device in question and then put the device on the market.
The choice of the procedure is a matter for the manufacturer.

It should be made according to the methods described in:

- article 9 of directive 90/385/EEC modified by article 21.3.2 of directive 93/42/EEC, for active implantable medical devices (AIMD),
- article 11 of directive 93/42/EEC for other medical devices (MD), depending on the class to which the device in question belongs, the class being previously determined as indicated in paragraph 3.4. of the present guide,
- article 9 of directive 98/79/EC for in vitro diagnostic medical devices depending from the category of reagent (or associated element) ; see annexe II of 98/79/EC directive.

The manufacturer should consider the choice of the procedure best suited to his needs as an element of his strategy, -as indicated in paragraph 1. of this guide-, as on this choice depend:

- firstly, the delays and costs involved in obtaining the necessary certificates for existing and future devices ; a wrong choice may delay the obtaining of a certificate (for example, in the case of a class IIa or IIb device, if annex II – (directives 93/42/EEC and 90/385/EEC) –full quality assurance system– is chosen, where the system set up is unable to meet all the requirements of this annex but would be completely in line with annex VI – product quality assurance – or annex V –production quality assurance-).
- secondly, the actual operation of the manufacturer in terms of organization in order to ensure the required quality (quality systems).

3.5.1. Assessment procedures for directives 90/385/EEC (active implantable medical devices) and 93/42/EEC (medical devices)

For greater clarity in the rest of this chapter, "active implantable medical devices" are classified alongside class III medical devices. The substantial differences between these two categories in fact lie only in the application dates of the corresponding directives and the content of the essential requirements.

For more precise information on AIMD, you should directly refer to directive 90/385/EEC itself (modified by article 21 of directive 93/42/EEC and by article 9 of directive 93/68).

Depending on the class of the device, the choice of the different possible procedures involves combining different modules ; they are indicated in figures A, B, C, and D below.

Each of the different procedures from which the manufacturer can choose for a device of a given class is enough to establish conformity.
The modules are the following:

- **Annex II**: EC declaration of conformity "full quality assurance system", with or without "examination of the design of the product" (directives 90/385/EEC modified and 93/42/EEC),
- **Annex III**: EC type examination (directives 90/385/EEC modified and 93/42/EEC),
- **Annex IV**: EC verification (directives 90/385/EEC and 93/42/EEC),
- **Annex V**: EC declaration of conformity "production quality assurance" (directives 90/385/EEC and 93/42/EEC),
- **Annex VI**: EC declaration of conformity "product quality assurance" (directive 93/42/EEC),
- **Annex VII**: EC declaration of conformity (directive 93/42/EEC).

The choice of annexes II, III, IV, V or VI requires the involvement of a Notified Body.

The application of annex VII does not require such involvement, unless the device in question is placed on the market in a sterile condition or if it has one or more "measuring" functions; in this case, the involvement of the Notified Body has equivalent scope to annex V, except that it is restricted solely to the aspects of the manufacture which cover the securing and maintaining of sterility or, depending on the case, the metrological aspects alone.

- **Broadly speaking**, there are two sides to the assessment of conformity:
  - assessment of the design of the product in question,
  - assessment of manufacturing quality.

- **Assessment of the design** may, depending on the manufacturer’s decision:
  - be done by the Notified Body as in section 4 of annex II ("examination of the design of the product"),
  - be done by the Notified Body as in annex III ("type examination"),
  - be under the manufacturer’s direct responsibility as in annex II excluding section 4 (control of design) or as in annex VII (simple "declaration of conformity").

- **The assessment of manufacturing quality** may, depending on the manufacturer’s decision:
  - be done by the Notified Body as in annex II (full quality assurance), or as in annex V (production quality assurance) or as in annex VI (product quality assurance),
  - be under the manufacturer’s direct responsibility as in annex VII (single declaration of conformity).

Finally, the **product can be "directly" assessed by the Notified Body** as in annex IV ("EC verification"), whether the said verification is done on a “unit” basis or by statistical sampling.
Class III and A.I.M.D.

Manufacturer’s choice

Full Q.A. system with examination CE of the design (Annex II)

EC type examination (Annex III)

Manufacturer’s choice

EC verification (Annex IV)

Production Q.A. (Annex V)

CE Marking

Figure A
Class II b

Manufacturer’s choice

Full Q.A. system without examination of the design (Annex II excluding section 4)

EC type examination (Annex III)

Manufacturer’s choice


CE Marking

Figure B
Class II a

Manufacturer’s choice

Full Q.A. system without examination of the design (Annex II excluding section 4)

EC declaration of conformity (Annex VII)

Manufacturer’s choice

EC verification (Annex IV)

Production Q.A. (Annex V)

Product Q.A. (Annex VI)

CE Marking

*Figure C*
Figure D
Below is a brief description of LNE / G-MED’s role in the work required by the different assessment procedures.

3.5.1.1. Examination of the design (Annex II section 4)

This module can be chosen for class III devices and active implantable devices; where it accompanies approval of the full quality assurance system (annex II).

LNE / G-MED approaches examination of the design from a dossier supplied by the manufacturer.

Note: more detailed information on the contents of the different dossiers can be obtained from LNE / G-MED project managers.

This modules leads to the granting of a design examination certificate which, under the directive, is valid for a maximum period of 5 years. In addition, LNE / G-MED supplies a design examination certificate.

For devices placed on the market before the relevant directive came into force, their prior presence on the market is taken into account so that the manufacturer is not penalized. Existing “proofs” are allowed for so as make it easier to establish conformity.

However, in the absence of the formal technical documents laid down by the directive, which are normally established at the device design stage, LNE / G-MED requires that the technical dossier should contain the technical data it needs, notably certain input and output data for design (including clinical data) and the technical performances assigned.

3.5.1.2. EC type examination (Annex III)

This module can be chosen for class III devices, class IIb devices and active implantable devices.

- LNE / G-MED has to establish and certify that a representative sample of the production covered fulfills the essential requirements.

It examines and assesses the documentation which allows an understanding of the design, manufacture and performances, containing amongst other things:

- the description of the product,
- the results of risk analysis, of tests…, the list of standards applied, clinical data,
- the intended labelling, instructions for use…

LNE / G-MED sends the manufacturer a questionnaire in which the latter states the resources he has put in place to meet the essential requirements.

It carries out or arranges for the carrying out of the inspections and tests necessary for the verification of conformity with the essential requirements.

Conformity with the essential requirements allows LNE / G-MED to deliver a EC type examination certificate that is valid for a maximum of 5 years. In addition, it provides a EC type examination report.
3.5.1.3. **Full quality assurance system (Annex II)**

This module can be chosen by the manufacturer for active implantable devices, class III, class IIb and class IIa devices. For the latter two classes, the part described in point 4 of annex II "Examination of the design", does not apply.

**This proof mode takes the form of approval and monitoring, by a Notified Body, of the quality assurance system for the design, manufacture and final inspection of the products in question.**

For this, LNE / G-MED carries out an evaluation of the manufacturer’s quality assurance system **for the products concerned**, and must ensure that this system is applied permanently.

The necessary audits are performed by LNE / G-MED.

LNE / G-MED takes account of reports of audits performed for voluntary certification of quality systems when they are performed by bodies that it recognizes and when they show that the systems comply with the corresponding ISO/CEN standards (ISO 9001 and EN 13485). This taking account means that the requirements of annex II of the directive which have their equivalent in the said certificates are presumed to be fulfilled and are not verified during additional audits intended to evaluate conformity with the other requirements.

- The manufacturer must keep up-to-date documentation in the form of written policies and procedures on quality (programmes, plans, manuals, records...), which include, amongst other things :
  - product description,
  - the monitoring and checking procedures for the design of the medical devices (results of risk analysis, standards applied, clinical data...),
  - inspection and Q.A. techniques for manufacturing,
  - examinations and tests before, during and after manufacture,
  - intentions for labelling, instructions for use...,
  - the procedures for the corrective actions and the manufacturer’s undertaking to notify the Competent Authorities of the serious adverse incidents.

The manufacturer must inform LNE / G-MED of any significant plans for change to the approved system or the range of products covered.

**For active implantable devices and class III devices, LNE / G-MED must also carry out the examination of the design dossier for each product (cf above).**

3.5.1.4. **EC verification (Annex IV)**

This module can be chosen by the manufacturer for active implantable devices and for classes III, IIb and IIa devices.
LNE / G-MED conducts examinations and tests:

- of each product or,
- of a statistical sample for each homogeneous batch, to check conformity with the essential requirements and the EC type examination certificate or, for class IIa medical devices, with the technical documentation referred to in annex VII,

and provides a certificate.

For medical devices placed on the market in a sterile condition, LNE / G-MED carries out an audit of the production quality assurance system and monitors it as described in annex V, only in respect of manufacturing aspects relating to the securing and maintaining of sterility.

### 3.5.1.5. Production quality assurance (Annex V)

This module can be chosen by the manufacturer for active implantable devices and for classes III, IIb and IIa devices.

This module involves the approval and surveillance, by LNE / G-MED, of the quality assurance system for the manufacture and final inspection of the products concerned.

The application of the system must guarantee the conformity of products to the type described in the EC type-examination certificate or, for class IIa medical devices, to the technical documentation referred to in annex VII.

For this, LNE / G-MED carries out an evaluation of the manufacturer’s quality assurance system for the products in question, and must ensure that this system applied permanently.

The necessary audits are performed by LNE / G-MED.

LNE / G-MED takes account of reports of audits performed for voluntary certification of quality systems when they are performed by bodies that it recognizes and when they show that the system comply with the corresponding ISO/CEN standards (ISO 9001 and EN 13485). This taking account means that the requirements of annex V of the directive which have their equivalent in the said certificates are presumed to be fulfilled and are not verified during additional audits intended to evaluate conformity with the other requirements.

Note: Standard EN 13485 is applicable with the exclusion clauses as indicated in § application.

The manufacturer must keep-up-to-date documentation in the form of written policies and procedures on quality (programmes, plans, manuals, records…) which include, amongst other things:

- inspection and quality assurance techniques for manufacturing,
- examination and tests before, during and after manufacture,…,
- procedures associated with the corrective action, together with the undertaking to inform the Competent Authorities of incidents as defined in annex V of the applicable directive.

The manufacturer must inform LNE / G-MED of any significant plans for change to the approved system or the range of products covered.
3.5.1.6. **Product quality assurance** *(Annex VI)*

This module can be chosen by the manufacturer for classes IIb and IIa devices.

**This module involves the approval and surveillance, by LNE / G-MED, of the quality assurance system for the final inspection and tests of the products concerned** (examinations and tests of each product or representative sample).

The application of the system must guarantee the conformity of products to the type described in the CE type-examination certificate or, for class IIa medical devices, to the technical documentation referred to in annex VII.

For this, LNE / G-MED carries out an evaluation of the manufacturer’s quality assurance system for the products concerned, and must ensure that this system is applied permanently.

The necessary audits are performed by LNE / G-MED.

LNE / G-MED takes account of reports of audits performed for voluntary certification or quality systems when they are delivered by bodies that it recognizes and when they show that the systems comply with the corresponding ISO/CEN standards (EN 46003). This taking account means that the requirements of annex VI of the directive which have their equivalent in the said certificates are presumed to be fulfilled and are not verified during additional audits intended to evaluate conformity with the other requirements.

The manufacturer must keep **up-to-date documentation** in the form of written policies and procedures on quality, including, among other things, the description of post-manufacture examinations and tests, procedures associated with the corrective action, together with the undertaking to inform the Competent Authorities of incidents as defined in annex VI of the applicable directive.

The manufacturer must inform LNE / G-MED of any significant plans for change to the approved system or the range of products covered.

For devices placed on the market in a sterile state, LNE / G-MED carries out an audit of the production quality assurance system and monitors it as described in annex V, but only for the aspects of manufacture regarding the obtaining and maintaining of sterility.

3.5.1.7. **EC declaration of conformity** *(Annex VII)*

This module can be chosen by the manufacturer for classes IIa and I devices.

The manufacturers ensures and declares that the products conform with the essential requirements, and must prepare technical documentation which allows conformity to be assessed, containing, amongst other things:

- the product description,
- the design drawings and manufacturing methods,
- the results of the design calculations and of the inspections carried out,
- the results of the risks analysis, the list of standards referred to,
- the clinical data,
- the intended labelling, instructions for use…
For **medical devices placed on the market in a sterile condition and class I medical devices which have a measuring function**, LNE / G-MED audits the production quality assurance system and monitors it as described in annex V, but only for the aspects of manufacture concerned respectively with the **securing and the maintaining of sterility**, or with **metrological requirements**.

**Note:**
It should be recalled that, for class I devices, the manufacturer is obliged to observe the national laws that transpose the provisions described in article 14 of the directive 93/42/EEC (Registration of persons responsible for putting on the market).

### 3.5.1.8. Particular case of software

Where it falls within the definition of medical device, a software have to be assessed and certified as any other medical device with help of an adequate combination of modules as previously described. However, taken into account the abstract character of a software, particularities which are related to design verification ability, to production or repeatability verification, to make use of modules combination (see figures A, B, C, D) have to be adapted. More information on these point is available in NB-MED/2.2/Rec 4 recommendation elaborated by the coordination of European Notified Bodies.

### 3.5.2. Assessment procedures for directive 98/79/EC (In vitro diagnostic medical devices)

For in vitro diagnostic medical devices, directive 98/79/EC don’t define classes for the devices covered.

The intervention of a Notified Body is only mandatory for products intended for self-testing, that is to say used by the patient self or an other non-professional, and for products referred to the two lists (A and B) of annex II of the directive.

The principle of these intervention and the delivery of certificates are the same as for other medical devices (see paragraph 3.5.1.).

LNE / G-MED, being notified for a big range of products and conformity assessment procedures may :

- **issue certificates related to** :
  - products design examination,
  - EC type examination (of products),
  - approval and surveillance of full quality assurance system,
  - approval and surveillance of production quality assurance,

- **perform verification of manufactured products for devices referred to in annex II, list A (batch release) as indicated in annex IV point 6 of directive 98/79/EC.**

The possible combinations of these different procedures for establishing conformity, according to categories of product, are the following :
Devices referred to annex II, list A

Manufacturer’s choice

- full Annex IV
  - Full quality assurance system
  - CE design product examination
  - Verification of manufactured products

- Annex V
  - EC type examination of product
  - Annex VII
    - Production quality assurance system
    - Verification of manufactured products

Article 10

Registration of manufacturer and devices (in the Member State where headquarters are located)

Figure E
Devices referred to annex II, list B

- Manufacturer’s choice
  - Annex IV except sections 4 and 6
  - Full quality assurance system
  - Annex V
    - EC type examination of product
    - Manufacturer’s choice
      - Annex VII except section 5
      - Annex VI
        - Production quality assurance system
        - EC verification
  - Article 10
    - Registration of manufacturer and devices (in the Member State where headquarters are located)

*Figure F*
Devices referred to self-testing (except list in Annex II)

Manufacturer’s choice

Annex III section 6

EC design examination of product

Other parts of Annex III

Conformity declaration

Same as products Annex II, list A

Same as products Annex II, list B

Article 10

Registration of manufacturer and devices (in the Member State where headquarters are located)

Figure G
**Particular cases**

- **Device for performance evaluation**

  **Annex VIII**

  Particular declaration:

  Technical documentation make available to the Authorities

- **“New» products**

  (no availability during the previous three years, analytical technology not continuously used during the previous three years)

  **Article 10 section 4**

  Additional obligation:

  Mention the« new » product for registration

  **Figure H**
In all other cases

Annex III except section 6

<table>
<thead>
<tr>
<th>Conformity declaration</th>
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<tbody>
<tr>
<td>Technical documentation</td>
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<tr>
<td>(content see annex III)</td>
</tr>
<tr>
<td>Principle of quality assurance</td>
</tr>
<tr>
<td>must be followed</td>
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<tr>
<td>Systematic procedure</td>
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<tr>
<td>to review experience</td>
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<tr>
<td>gained from devices in the post-production</td>
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*Figure I*
3.5.2.1. Design examination (Annex IV section 4)

The intervention of LNE / G-MED is the same as described in paragraph 3.5.1.1. for other medical devices.

3.5.2.2. EC type examination (Annex V)

The intervention of LNE / G-MED is the same as described in paragraph 3.5.1.2. for other medical devices.

3.5.2.3. Full quality assurance system (Annex IV except sections 4 and 6)

The intervention of LNE / G-MED is the same as described in paragraph 3.5.1.3. for other medical devices.

3.5.2.4. EC verification (Annex VI)

The intervention of LNE / G-MED is the same as described in paragraph 3.5.1.4. for other medical devices.

3.5.2.5. Quality assurance of production (Annex VII)

The intervention of LNE / G-MED is the same as described in paragraph 3.5.1.5. for other medical devices.

3.5.2.6. Quality assurance for products

Not foreseen in directive 98/79/EC.

3.5.2.7. EC declaration of conformity (Annex III except section 6)

No intervention of a Notified Body in the regulatory frame.

3.5.2.8. Verification of manufactured products

These mandatory procedure is only applicable for in vitro diagnostic devices referred to annex II, list A of the directive 98/79/EC.

The manufacturer shall forward to LNE / G-MED, without delay after the conclusion of the controls and tests it has carried out, the relevant reports on the tests done on each batch of devices. Furthermore, it shall make the samples of manufactured devices available to LNE / G-MED in accordance with pre-agreed modalities.

If LNE / G-MED discover in these batches anomalies which reveal a non-conformity to essential requirements, it must inform the manufacturer within a pre-agreed time frame; the manufacturer has the obligation not to put the concerned batch on the market.
3.5.2.9. Particular case of software

Considerations given in paragraph 3.5.1.8. for other medical devices are also applicable here. The NB-MED/2.2/Rec 4 recommendation covers also the case of in vitro diagnostic devices falling under directive 98/79/EC.

3.6. Horizontal themes

3.6.1. Risk analysis

Whatever the pro method chosen to validate design, and whether the involvement of a Notified Body is required or not, a risk analysis must have been carried out and documented by the manufacturer (directives 93/42/EEC and 98/79/EC).

The results of this analysis must appear in the technical dossier submitted to the Notified Body when one or other of the following modules has been chosen:

- examination of the design (see paragraphs 3.5.1.1. and 3.5.2.1.),
- type examination (see paragraphs 3.5.1.2. and 3.5.2.2.).

They must appear in the design specification documents which are part of the elements of the quality systems. This documentation must be kept up to date, and the Notified Body may have access to it during the audits and checks it carries out when approving the full quality assurance system when the manufacturer has chosen this assessment procedure (see paragraphs 3.5.1.3. and 3.5.2.3.).

Finally, they must appear in the technical documentation held available for the Competent Authorities as laid down under the EC declaration of conformity, when this procedure is applicable, i.e. for class I and class IIa devices (see paragraph 3.5.1.7.), and for in vitro diagnostic medical devices (see paragraph 3.5.2.7.).

The risk analysis is done by the designer of the device. It is a fundamental risk control aspect of the design process.

Its purpose is to identify the "hazards"¹ associated with the use of the device and to estimate the corresponding "risks"².

¹ A "hazard" is defined as a potential source of damage (physical injury and/or damage to health, or damage to the environment or property) (EN 14971)

² A "risk" is defined as the probable frequency of a damage causing harm "and" the seriousness of the damage (EN 14971).

The way in which a risk analysis may be carried out and recorded is not described in the European directives.

However, an European standard entitled: "Medical devices : risks management" (EN 14971) has been prepared by CEN.
As for any other standard, its application is not mandatory, but it can prove very useful, firstly to the manufacturer during the design phase of a device, and secondly to the whole "Notify Body / manufacturer" group for EC certification, as it provides a recognized basis for discussion.

These EN 14971 standard on risk management go beyond to risk analysis and treat also risk control and acceptability of risks which can’t be reduced.

It must be quoted also EN IEC 60 601-1-4 standards regarding the safety of programmable electrical medical systems.

3.6.2. Clinical evaluation

Following considerations don’t apply to in vitro diagnostic medical devices (directive 98/79/EC).

3.6.2.1. Guiding principles

The European directives specify that (90/385/EEC and 93/42/EEC, essential requirements, part 1):

« the devices must be designed and manufactured in such a way that... they will not compromise the clinical condition or the safety of patients... when they are used in the conditions and for the purposes intended, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient... »

« the devices must achieve the performances intended by the manufacturer... and be suitable for one or more of the functions... specified by the manufacturer. »

« any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.»

They add (directive 93/42/EEC, annex X : clinical evaluation):

« As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances... and the assessment of undesirable side-effects must be based on clinical data, in particular in the case of implantable devices and devices in class III. »

- These clinical data are made up:
  - either of a compilation of the relevant scientific literature whether or not combined with a critical evaluation of this collection,
  - or of the results of all the clinical investigations made...

As each case is individual, the directives cannot specify in advance when the collected scientific literature is enough and when specific clinical investigations are needed.
It is up to the Notified Body to assess whether any compilation of scientific literature provided by the manufacturer is sufficient, or if he needs the results of specific clinical investigations.

That is why, each time a manufacturer considers approaching LNE / G-MED to obtain the required certificates, he would be well-advised to consult LNE / G-MED as early as possible on this point. Where necessary, LNE / G-MED will get the opinion of an expert in the relevant medical field, and will then state the nature of the clinical data required, in the manner described in paragraph 3.7.

The MEDDEV 2.7.1 guide gives the methodology for clinical data evaluation.

Words and expressions hereafter defined are taken from european standards or recommendations elaborated by the coordination of Notified Bodies.

**CLINICAL DATA** (NB-MED/2.7/Rec 3) : data relevant to the clinical safety and performance of the device. This may include data resulting from clinical investigations, retrospective studies on the concerned device, information from the scientific literature or from the medical practice.

**CLINICAL EVIDENCE** (NB-MED/2.7/Rec 1) : **CLINICAL EVIDENCE** is gained when a qualified expert is able to conclude that the examined medical device complies to the following requirements :

1. the **PERFORMANCES** of the device, when used according to the destination and the conditions for utilisation claimed by the manufacturer comply with those indicated in §2 of annex 1 (directive 90/385/EEC) or to §3 of annex I (directive 93/42/EEC).
2. the undesirable side effects, under normal conditions of use, represent an acceptable **RISK** when weighed against the benefits to the patient.

**HAZARD** (EN 14971) : potential source of **HARM**.

**HARM** (EN 14971) : physical injury or damage to the health of people, or damage to property on the environment.

**RISK** (EN 14971) : combination of the probability of occurrence of harm and the severity of that **HARM**.

**DESTINATION** (Directive 93/42/EEC) : utilisation to which the device is intended for according to the indications given by the manufacturer in labelling, instruction for use and/or informative documents.

**PERFORMANCE OF DEVICE** (EN14155) : action of a particular medical device by reference to its foreseen utilisation when it is correctly use on the appropriate subjects.

**CLINICAL INVESTIGATION** (EN14155) : any systematic study on human being done for checking of security and the **PERFORMANCES** of a particular medical device under normal conditions of utilisation.

**CLINICAL INVESTIGATION PLAN** (EN14155 part 2) : document containing detailed informations related to motivation exposed, objectives, design and analyses proposed, methodology and **CLINICAL INVESTIGATION** operation.
The manufacturer’s dossier must allow LNE / G-MED to identify without ambiguity the concerned device, its use and its PERFORMANCES as claimed by the manufacturer. It must give LNE / G-MED trust in the fact that the manufacturer satisfy to applicable requirements of the corresponding directive (shortly recalled in introduction) in matter of CLINICAL EVIDENCE.

The following elements are then necessary. The omissions resulting from particular situations (device existing before the directives, large recognized experience,…) must be explicitly justified.

It is suggested to adopt the indicated order for marking the reading of dossier easier.

A. Device identification
   A.1 Trade identification (including the software version)
   A.2 Generic group (GMDN* nomenclature)
   A.3 Class (if applicable according directive)

* Global Medical Devices Nomenclature. This nomenclature at the final phase is intended to be worldwide adopted.

B. DESTINATION(S) claimed by the manufacturer

C. PERFORMANCES claimed by the manufacturer

D. Indications

E. Eventual contra indications

F. Expected effects
   F.1 Benefits expected for the patient
   F.2 RISKS linked to the use according to the manufacturer’s instructions
      
      Here are considered the residual RISKS, after implementation of security dispositions ; the RISKS for the patient, users, third parties and environment have to be taken into account ; the risks linked with other aspects of life cycle of the device like manufacturing or its elimination are taken into account in the risk analysis.

   F.3 Foreseen able undesirable secondary effects

G. Results of RISKS analysis (See NB-MED/2.7/Rec 3 and MEDDEV 2.7.1)

During the risk analysis done by the manufacturer implementing directive 93/42/EEC¹, certain HAZARDS of clinical nature have been identified and the corresponding RISKS evaluated ; here the objective is to give the corresponding information. It is suggested to classify these information on 3 levels :

- HAZARDS related to type of medical application and to the therapeutic procedure
- HAZARDS related to technical solutions adopted for the considered device
- HAZARDS specific to particular characteristics of the considered device.

¹ Risks analysis is not foreseen in the dispositions of directive 90/385/EEC (active implantable). Nevertheless, a such risks analysis is strongly recommended in order to better assure conformity to essential requirements.
These HAZARDS and RISKS of clinical nature constitute important parameters for guiding clinical data research. These data find their origin either in the scientific literature either in particular CLINICAL INVESTIGATION results realised for that purpose.

H. Data originating from scientific literature

These data must be available for LNE / G-MED. It is preferable to indicate in the submitted dossier all references used as well as the published abstract of the corresponding articles. It is also recommended to present a copy of the main articles on which the manufacturer’s conclusions are based, the other articles being available for LNE / G-MED on request.

The wording must be taken in a broad sense because these data may also be issued from a previous use broadly recognized, from the own manufacturer experience or from clinical investigations organized for studying a non specific aspect of the concerned device.

It is further recommended to indicate, as far as possible, the method used for research and choice of literature data.

Note: The other preclinical data (issued from clinical trials of biocompatibility...) constitute other parts of the technical documentation submitted by the manufacturer.

I. Data originating from particular CLINICAL INVESTIGATIONS

I.1 Indicate if CLINICAL INVESTIGATIONS has been necessary and justify the corresponding decision.

When clinical or pre-clinical data issued from scientific literature is insufficient for establishing CLINICAL EVIDENCE for the concerned device, the manufacturer may be induced to do particular CLINICAL INVESTIGATIONS (trials) for obtaining complementary data judged necessary. It is asked to the manufacturer to justify the decision he has taken to perform or not such CLINICAL INVESTIGATIONS.

I.2 CLINICAL INVESTIGATIONS process

I.2.1 Conformity to harmonised european standards
The respect of the harmonised european standard EN 14155 is not mandatory, but give presumption of conformity to the corresponding requirements of directives. For information, it is asked to indicate if the respect of such standards has been tried to be obtained.

It must be taken in mind that legal or regulatory requirements may exist in the countries where these clinical investigations are done. These dispositions have for objective to protect human being which undergo these investigations.

I.2.2 CLINICAL INVESTIGATIONS PLANS
It is asked to join the CLINICAL INVESTIGATIONS PLAN(S).

Note: The proof character of clinical data submitted is largely depending from the scientific rigour with which the CLINICAL INVESTIGATIONS PLANS have been elaborated and implemented.
I.3  **CLINICAL INVESTIGATIONS** results – critical analysis from the manufacturer

In the general case, the raw results are not asked; however it is not excluded that LNE / G-MED asks for communication of the results, in whole or in part if necessary, in order to highlight a particular point. But it is asked to join a dated and signed report by the principal investigator, which presents the results of investigations and their critical analysis carried out – or get carried out – by the manufacturer.

This report must show if deviations or amendments to the CLINICAL INVESTIGATION PLAN have been made and what are the consequences of these deviations or amendments for interpreting the results.

It must also point out if objectives of investigation are considered to be reached and what conclusions the manufacturer have drawn from the investigation.

J. Data synthesis and final evaluation

The combination of data taken from the literature review and the results of clinical investigation done, constitute the basic material for final evaluation.

*An synthesis report must be presented by the manufacturer.*

*This report must clearly indicate the conclusions drawn by the manufacturer concerning CLINICAL EVIDENCE and must particularly mention if:*

- the device reaches the claimed CLINICAL PERFORMANCES,
- the expected benefits for the patient justify the RISKS linked with the device utilisation in the conditions of use intended by the manufacturer taking into account the « state of the art generally recognized ».

*The synthesis report must justify the conclusions.*

**LNE / G-MED may consult a medical expert (or more) who is practitioner in the concerned medical speciality and that LNE / G-MED considers as qualified.**

This medical expert acts as an advisory specialist. His qualification is recognized and maintained by LNE / G-MED on the basis of certain criteria. These criteria are defined and monitored by LNE / G-MED’s "its Scientific and Medical Committee".

The medical expert is required to apply standard rules of confidentiality in order to protect the manufacturer’s intellectual and industrial property.

He is also required, so as to maintain the necessary independence and impartiality, to declare any shared interest with the manufacturer of the device in question.

He is chosen and appointed by LNE / G-MED, which can at any time remove him from the dossier in question.
3.6.2.2. Practical procedure

In practice, the following cases may occur:

3.6.2.2.1. The notion of "clinical data" and hence clinical evaluation, is inapplicable:

This is relevant notably where the device, strictly speaking, has no clinical performances, because there is no interaction with the patient.

The characteristics specific to the device are sufficient to establish its conformity or its non-conformity with the essential requirements.

Examples: accessories that have no direct effect on the patient (sterilizers used in hospitals, negatoscopes...).

3.6.2.2.2. The clinical evidence is obviously acquired from the start:

In this case, the clinical data put forward by the manufacturer can simply consist of a declaration by the latter and a reference to previous use. Where applicable, this declaration will be combined with the indication of the corrective actions carried out during the previous life of the device or an analogous devices.

3.6.2.2.3. The manufacturer provides sufficient data drawn from the scientific literature

Insofar as these data are sufficient to acquire CLINICAL EVIDENCE, results of specific clinical investigations are not necessary.

3.6.2.2.4. The data consist of a clinical review.

3.6.2.2.5. Data from the scientific literature are unavailable or insufficient:

- In this case, results of clinical investigations are necessary.

These must be –or have been– organized and performed in such a way as to provide all the results or the additional results that the "evaluating expert" needs to acquire the CLINICAL EVIDENCE.
• The manufacturer is then faced with three problems:
  
  • the first with regard to observance of the rules and regulations by the promoter and the investigators,
  
  • the second with regard to the nature and content of the preclinical data when these are necessary (establishment of technical safety, establishment of biocompatibility, in vitro studies, animal tests,…),
  
  • the third with regard to the content of the clinical investigation plan as this plan must be designed in such a way as to give the manufacturer a reasonable a priori certainty that the results will be enough for the evaluator.

Standard EN ISO 14155 part 2 gives a methodology for setting up a clinical investigation plan on solid scientific and ethic basis.

3.6.2.2.5.1. Compliance with the regulations relating to the preparation and the conduct of clinical investigations

• For the preparation of clinical investigations, the relevant regulation is organized as follows:

  In Europe, the medical devices directives lay down provisions applicable in all the countries of the European Economic Area in order to be authorized to undertake clinical investigations intended to confirm the conformity of devices with essential requirements (article 15 of directive 93/42/EEC and article 10 of modified directive 90/385/EEC).

  Compliance with these provisions, as transposed to the country (or countries) where investigations are intended, brings together the sponsor of the investigations and the Competent Authority of the country (or countries).

  Furthermore the directive 2001 / 20 / EC which defines the conditions to be fulfilled for clinical investigations on human being, is also applicable to medical devices.

  In France, the application order for law n° 94/43 of 18 January 1994 transposing the European directives contains these provisions.

  In addition, in France, the revised Huriet and Sérusclat Law and its corresponding orders contain the more general provisions to be observed each time a person undergoes biomedical research. These provisions are intended for the protection of these persons and apply whatever the goal of the research (increase in biological knowledge, study of a process or a medicinal product or a device, whether for the purpose of placing on the market or not).

  In France, it is the French Agency for Sanitary Safety of Health Products (AFSSAPS), which is the Competent Authority (i.e. the administrative authority responsible for the correct application of the provisions of the directives in question).

  The declarations and information necessary under the application order for the Law of 18 January 1994 (provisions corresponding to article 15 of directive 93/42/EEC) together with those that are necessary under the Huriet and Sérusclat Law, should be provided to the Competent Authority.

LNE / G-MED does not have the authority to intervene in this relationship.
for the conduct of these clinical investigations,

The directives gives the provisions for the purpose of ensuring the protection of the subjects who take part in them, and also in order to guarantee the scientific quality of the results, as these will constitute the clinical data used for assessment (annex X of directive 93/42/EEC and annex VIII of directive 90/385/EEC).

These conditions must be met, whatever the country in which the investigations concerned take place.
When these conditions are not met, the results of these investigations may be considered as not admissible by the Notified Bodies.

Compliance with harmonized european standard EN 540 "Clinical investigations of medical devices on human subjects" or EN ISO 14155 part 1, in the conduct of investigations, entails the presumption of conformity with these conditions, thus with the corresponding annexes in the directives.

3.6.2.2.5.2. Preclinical data and contents of the clinical investigation plan

Part 1 of standard EN 14155, contains certain minimal prescriptions related to these questions.

However, the content and the origin of the preclinical data (when these are required), together with the content of the clinical investigation programme in terms of objectives set, and specific resources and methods, are simply a matter of the particular case in question.

3.6.2.3. Examination of the clinical data

The examination of clinical data for evaluation purposes is, for LNE / G-MED, the main part of the activities involved in clinical evaluation.
It is carried out, when necessary, for the purpose of acquiring the "clinical evidence" defined in paragraph 3.6.2.1.

It falls within the modules corresponding to the "examination of the design" (annex II, point 4 of directive 93/42/EEC) or the "EC type examination" (annex III of directives 93/42/EEC and 90/385/EEC).

It is done by LNE / G-MED and under its responsibility.

3.6.3. Devices placed on the market in sterile condition

The following provisions are specific to directive 93/42/EEC.

Whatever the class to which the device in question belongs, and whatever the test method chosen by the manufacturer, directive 93/42/EEC stipulates that the latter must arrange for the approval of the aspects of the quality assurance system which are intended to secure and maintain the sterile state.

The requirements and procedures for such approval are, solely for the aspects defined in the previous paragraphs 3 and 4 –respectively entitled "quality system" and "surveillance", in annex V of directive (Production quality assurance).
In practice, two possibilities may arise:

3.6.3.1. First eventuality:

The manufacturer has chosen a conformity assessment procedure which includes the approval of his production quality assurance system (by annex II or V): the aspects associated with sterility are then covered under the general production process (cf. chapter "special processes"), to the extent that this approval has taken into account all the aspects of the validation of the sterilisation processes used.

3.6.3.2. Second eventuality:

The manufacturer has chosen a conformity assessment procedure which does not include the approval of his production quality assurance system (by annex IV, VI or VII of directive 93/42/EEC): the aspects associated with sterility must then undergo the necessary additional procedure to meet the requirements described in the first paragraph.

In any case, LNE / G-MED possesses all the skills and experience required for this approval.

- List of the main standards with regard to sterility:

Refers to list indicated in annex A of the present guide.

3.6.4. Establishing biocompatibility

Directive 93/42/EEC lays down, in the Essential Requirements (Annex I paragraph 7.1), that « …Particular attention must be paid to:

- the choice of materials used, particularly as regards toxicity…,
- the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device ».

The nature and origin of the data required for establishing conformity with this essential requirement, when this is applicable, can only be determined in respect of the particular device in question. That is why it can only be to the manufacturer’s advantage to consult LNE / G-MED on this point as early as possible in the procedure, each time a problem of biocompatibility is likely to arise.

Indeed, LNE / G-MED has internal skills in matter of biocompatibility. Moreover, LNE / G-MED can call upon outside skills belonging to specialist laboratories in this field with whom LNE / G-MED has made agreements.

- List of the main biocompatibility standards

Refers to list indicated in annex A of the present guide.
3.6.5. Establishing microbiological safety

Paragraph 8 of the essential requirement headed "Infection and microbial contamination" in directive 93/42/EEC, is also intended to cover risks associated with viruses and other non conventional transmissible agents when it is relevant to take these risks into account.

That is why, beyond the aspects associated with traditional sterilization, it may be necessary to demonstrate viral inactivation in certain cases.

These cases mostly involve devices which are manufactured using tissue, cells or other products derived from tissues of animal origin (or, where applicable, biotechnologically produced).

Here again, the nature and origin of the data required for establishing conformity can only be determined according to the particular treated device, and it can only be to the manufacturer’s advantage to refer to LNE / G-MED on this point.

Concerning the examination of the data provided by the manufacturer and their assessment, LNE / G-MED can call on acknowledged outside expertise.

- List of the main relevant standards and other applicable documents

Concerning medical devices produced from non-viable derivates of animal tissues, the situation is complex and evolutive due to the emerging risk of new variant of Creutzweld-Jacob disease when starting from bovine, caprine or ovine tissues infected by transmissible animal spongiform encephalopathies.

European standards EN 12442-1, EN 12442-2 and EN 12442-3 in this matter are useful. They will be revised soon and then replaced by EN 22442.

The website of the European Commission (works of Scientific Committees) have published the decision of European Commission related to medical devices and to transmissible spongiform encephalopathies.

National dispositions for microbiological safety have to be taken into account in the frame of essential requirements.

3.6.6. Device which have a measurement function

Directive 93/42/EEC, in its essential requirement (annex I, paragraph 10), attributes particular objectives to the measurement functions built into the devices, in respect of accuracy, scales of measurement and units used.

- Conformity to this requirement is established :

  • for class III devices, at the time of the "examination of the design" of the product (annex II, paragraph 4) or at the time of the "type examination" (annex III). Approval of the quality system is also involved,

  • for class IIb devices, at the time of the type examination and/or through approval of the quality system,
• for class IIa devices, through annex IV (EC verification) or annex II (full quality assurance system) or annex V (production quality assurance) or annex VI (product quality assurance),
• for class I devices, it is mandatory, as for devices placed on the market in a sterile condition, to employ a Notified Body. The latter’s role is then to apply annex IV, annex V or annex VI; the application of these annexes is then restricted solely to the aspects of manufacture linked with the conformity of products to metrological requirements.

3.6.7. Devices containing medicinal products

An essential requirement of directive 93/42/EEC lays down (annex I, point 7.4) that:

« where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in article 1 of directive 65/65/EEC and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in directive 75/318/EEC. »

In this case, the Notified Body must consult, with regard to the aspects referred to above, "one of the Competent Authority for drugs appointed by the Member States in accordance with directive 65/65/EEC revised by directive 2001 / 83 / EC, before taking a decision ". In France, this Body is AFSSAPS.

Verification of "usefulness" is linked here with the reasons for which the medicinal substance is used with the intention of enabling (or helping) the device to attain the performances which are attributed to it by the manufacturer of the device.

Verification of "safety" involves ensuring that the potential risks inherent in the use of the substance are justified taking into account the "intended purpose" of the device.

The Notified Body remains responsible for its final decision regarding the device concerned. It may choose the Competent Authority for drugs from all those appointed by EEA Member States.
In accordance with the terms of the Commission’s guidelines regarding this particular subject, (MEDDEV 2.1/3 rev 2), LNE / G-MED proceeds as follows:

- Checking that the data provided by the manufacturer contain data regarding this verification, together with data regarding the information that the device manufacturer must provide to the user (when this verification is relevant).
- Choice of the Competent Authority for drugs to consult; this choice takes several factors into account, including geographical factors, the manufacturer’s wishes, the identity of the Authority which, where applicable, granted the product licenses for the medicinal substance,…
- Consultation of the Competent Authority for drugs regarding:
  - the contractual aspects (delivery times, costs, confidentiality…),
  - provision of the necessary data with, where applicable, justified request for additional data,
  - assessment of the data by the Competent Authority for drugs,
- Examination of the opinion of the Competent Authority for drugs,
- LNE / G-MED’s decision in the light of the opinion of the Competent Authority for drugs (this decision may, where applicable, involve stating the technical obstacles or non-conformities to be removed for certification to be possible).
- LNE / G-MED informs the Competent Authority for drugs consulted of the decision it has taken. If this decision differs from the opinion reached by the Competent Authority for drugs, LNE / G-MED provides the latter and the applicant with explanations.

The contents of the dossier must allow to assess the points mentioned in paragraph B3 of MEDDEV 2.1/3 rev 2

3.6.8. Devices previously considered (or included) as medicines for placing on the market

Certain devices that fall under directive 93/42/EEC were, before the latter came into force, treated as medicines for their placing on the market in certain Member States.

The situation in this respect varies from one Member State to another; however, within the European Economic Area, it will de facto be harmonized following the obligatory application of directive 93/42/EEC from June 1998.

For the CE marking of these products as medical devices, LNE / G-MED takes account of the technical and clinical knowledge prior to the application of directive 93/42/EEC, as well as the permits acquired.

3.7. Course of the procedure with LNE / G-MED

- To contact LNE / G-MED

LNE / G-MED
1, rue Gaston Boissier 75724 PARIS Cedex 15 – France
Tél. : + 33 1 40 43 37 00 – Télécopie : + 33 1 40 43 37 37
e-mail : info@gmed.fr
• Initial contact

LNE / G-MED send a "questionnaire" form to the manufacturer. One part of this questionnaire is dedicated to quality assurance system and an another part is dedicated to EC type examination. Only the provisions applicable to the service requested by the manufacturer have to be completed.

This questionnaire permit to produce an estimate and to evaluate the time required.

First, LNE / G-MED and the manufacturer check together that the concerned devices come under the directives for medical devices. They also check with classes these belong to.

If approval of a quality assurance system is chosen as one of the proof procedures, the first contact is also used to sum up existing factors (certificates already obtained or pending, audits performed…).

LNE / G-MED takes these existing factors into account when they were obtained from other Bodies, notably those it has recognized or which have been officially Notified in any one of the Member States of the EEA.

Where evaluation of conformity involves the "EC type examination", two principle situations are possible:

• The devices in question have never previously undergone any assessment procedure in another context.
  The engineer in charge of the dossier will then take into account the history of the devices, of the performances attributed by he manufacturer, of the standards applied in full or in part – notably harmonized european standards -, of the risks associated with the use of the devices, as well as tests done by the manufacturer or by a third party on behalf of the manufacturer.

• The devices in question have previously undergone certain regulatory assessment procedures in another context.
  As a result of these procedures, the tests or audits reports are examined by the LNE / G-MED engineer responsible for the dossier who will decide which additional assessments are necessary in order to cover all the relevant essential requirements of the directive which applies.

• On receipt of the "questionnaire" form duly completed, LNE / G-MED establishes an estimate for its services.

LNE / G-MED also provides a time estimate for start-up and completion.

• If the applicant accepts the estimate, LNE / G-MED submit to the manufacturer a contract proposal based on LNE / G-MED rules of certification.

• The evaluation phase

Depending on the kind of device in question and the means of proof chosen by the manufacturer, evaluation takes different forms.
However, it always involves LNE / G-MED carrying out audits, tests and document inspections, as defined by the directives and for the purpose of issuing the certificates required by the procedure for CE marking.

In the course of the evaluation phase, non-conformities may be detected:

- during examination of the technical dossier ("examination of the design", "type examination", ...) or during trials. The assessment report mentions the non-conformities and the engineer responsible for the dossier then informs the applicant so that he can take the necessary measures to eradicate the non-conformities,
- during evaluation of the quality systems. The audit report states any non-conformities detected. In concert with the auditors, the manufacturer determines how the non-conformities detected will be removed and how they will be recognized as removed (additional examination, additional audit,…).

In all circumstances, LNE / G-MED is attached to maintain a followed contract with the manufacturer in order to find the best solutions in the shortest possible time.

### Issuing certificates

When conformity with the annexes of the directives that the applicant has chosen as proof method, is recognized to have been attained, LNE / G-MED established the corresponding certificates and sends them to the applicant.

These certificates are in bilingual version (French / English).

Equipped with the necessary certificates issued by LNE / G-MED, the manufacturer will be able to establish his declarations of conformity and affix CE marking on the devices he wants to place on the market.

### Working language between the manufacturer and LNE / G-MED

This may be in French or English.

For a different language, LNE / G-MED should be consulted in advance.

### 4. CE marking

Devices, other than custom-made ones and those intended for clinical investigations, which are considered to meet the essential requirements which concern them, must have EC conformity marking when they are placed on the market.

CE marking must be affixed visibly, legibly and indelibly on the device or on the sterile packaging, when this is possible and appropriate, as well as in the instructions for use. Where applicable, CE marking must also appear on the sales packaging.

CE marking must be accompanied by the identification number of the Notified Body responsible for the implementation of the procedures covered in annexes II, IV, V and VI of directive 93/42/EEC or of the procedures covered in annexes II, IV and V of directive 90/385/EEC or of the procedures covered in annexes III, IV, V, VI and VII of directive 98/79/EC.
For class I devices that are not placed on the market in sterile condition and are not used for measuring, obviously no organization identification number is required.

**LNE / G-MED’s identification number is 0459.**

It is the manufacturer who affixes and is responsible for the affixing of the CE marking. For this, he must hold the necessary certificates issued by the Notified Body or Bodies he used, when the establishment of conformity requires him to make use of a Notified Body.

When he does not need to make use of a Notified Body, - EC declaration of conformity, described in annex VII of directive 93/42/EEC -, he must observe the provisions of the latter annex with regard to the establishment of the declaration of conformity and constitution of the necessary technical documentation.

- **The drawing of the CE marking is described in annex XII of directive 93/42/EEC an in annex X of directive 98/79/EC.**

  « The CE conformity marking shall consist of the initials «CE» taking the following form :

  ![CE marking diagram](image)

  - If the marking is reduced or enlarged, the proportions given in the above graduated drawing must be respected.
  - The various components of the CE marking must have substantially the same vertical dimension, which may not be less than 5 mm.
   This minimum dimension may be waived for small-scale devices. »

In addition, it is forbidden to show markings or writing which might cause third parties to confuse them with the meaning or the appearance of CE marking.

Other marks may be placed on the device, the packaging or the instructions which come with it, as long as they do not reduce the visibility and legibility of the CE marking.

**The fact, for a manufacturer to make improper use of CE marking to place a product on the market, is clearly forbidden and lays this manufacturer open to penalties, the nature and importance of which depend on each of the Member States in the territory on which the product was placed on the market.**
5. Maintaining the advantage of CE marking

This chapter describes the measures taken, as well as the obligations laid on the manufacturer, for the purpose of maintaining, over time, the advantage of CE marking for given devices.

Every device placed on the european market must conform to the essential requirements.

This means that in this regard, two objectives must be met:

**Objective 1:** Controlling changes in the model.

*When the design of a model is changed, or when its manufacture is changed,* the change must not have the effect of removing its conformity with the essential requirements.

**Objective 2:** Each copy must be the same as the model.

*Each copy* of a model whose design has been approved by a Notified Body through application of one of the measurement procedures laid down in the directives or, where applicable, whose design has been declared in conformity by the manufacturer himself, must be made in such a way that it remains identical to the model.

For this reason, the proof methods contain provisions that are intended to ensure the permanent maintenance of this conformity.

5.1. Full quality assurance system

5.1.1. If the examination of the design of the product has been done

« Changes to the approved design must receive further approval from the Notified Body which issued the EC design-examination certificate wherever the changes could affect conformity with the essential requirements of the directive or with the conditions prescribed for use of the product.

The applicant shall inform the Notified Body which issued the EC design-examination certificate of any such changes made to the approved design.

This additional approval must take the form of a supplement to the EC design-examination certificate. »

*(Directive 93/42/EEC annex II, section 4.4)*

In addition, for diagnostic in vitro medical devices listed in annex II, list A, the manufacturer shall inform « immediately the Notified Body if it has obtained information about changes to the pathogen and markers of infections to be tested, in particular as a consequence of biological complexity and variability. In this connection, the manufacturer shall inform the Notified Body whether any such a change is likely to affect the performance of the concerned device. » (Directive 98/79/EC annex IV, point 4.5)

The manufacturer is responsible for declaring changes in the design to the Notified Body, when these changes meet the conditions referred to above.

The size of the changes which entail an obligation to make such a declaration is thus a matter of judgement.
However, it may be said that if one or other of the following circumstances were to arise, a declaration should be made:

- change in the "intended purpose" (indication or use intended by the manufacturer),
- change in design having an impact on the results of the risk analysis or on the clinical data,
- change in design having an impact on the declared performances,
- substantial change in the instructions for use.

It goes without saying that LNE / G-MED, in the event of a declaration of change in design for a device that has undergone a design-examination, only examines the consequences of the change in terms of essential requirements, to the extent that such an examination is relevant.

In addition, the certificate issued by the Notified Body for a given design is valid for a maximum period of five years (article 11, section 11 of directive 93/42/EEC and article 9 point 10 of directive 98/79/EC).

This certificate may be extended following a request made at the time agreed in the contract signed by the two parties.

**WARNING**: in the case covered here, the provisions above are obviously added to those of paragraph 5.1.2. below, as a design-examination is always combined with approval of the full quality assurance system, an approval which must necessarily be given by the same Notified body.

5.1.2. General cases

« The manufacturer must inform the Notified Body which approved the quality system of any plan for substantial changes to the quality system or the product range covered.

The Notified Body must assess the changes proposes and verify whether after these changes the quality system still meets the requirements referred to in section 3.2.

It must notify the manufacturer of its decision. This decision must contain the conclusions of the inspection and a reasoned assessment. »
In addition, to check that the manufacturer applies his approved quality system permanently to all products placed on the market which are supposed to have originated in this system, the directives stipulate:

« The aim of surveillance is to ensure that the manufacturer duly fulfils the obligations imposed by the approved quality system.

The manufacturer must authorize the Notified Body to carry out all the necessary inspections and supply it with all the relevant information, in particular :

The Notified Body must periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system and must supply the manufacturer with an assessment report.

In addition, the Notified Body may pay unannounced visits to the manufacturer.

At the time of such visits, the Notified Body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly.

It must provide the manufacturer with an inspection report and, if a test has been carried out, with a test report. »

It should be noted that the directive does not specify how often these periodic inspections by the Notified Body should take place. As the Notified Body is responsible for the issue conditions of its certificates, it is up to it to base its fundamental conviction on the inspection conditions that it finds most appropriate, without imposing improper burdens or restrictions on the manufacturer.

For its part, LNE / G-MED considers one inspection per year to be reasonable, a frequency that may vary upward or downward in accordance with the factors on which its fundamental conviction is based.

Likewise, it believes unannounced visits to be justifiable only if it has specific worries in the light of the context as a whole¹.

¹ This context extends to requests that may be made to it by a Competent Authority of a Member State, against the background of the exercise of the "safeguard clause", of vigilance or of market surveillance.

The nature of the inspection, or of the unannounced visit, carried out by LNE / G-MED, is restricted to that which may be considered necessary and sufficient in the light of the goal of the inspection or the visit and of its context.

The certificate of quality system is delivered for a 3 years validity. It may be reconducted on request introduced at the time agreed in the contract signed by the two parties.

5.2. Production quality assurance

The content of paragraph 5.1.2. above applies here, though its bearing is limited to the nature of the quality system initially approved (i.e. without taking control of design into account).
5.3. **Product quality assurance**

The content of paragraph 5.1.2. above applies here unchanged, though its bearing is limited to the nature of the quality system initially approved.

5.4. **EC type-examination**

> « The applicant must inform the Notified Body which issued the EC type-examination certificate of any significant change made to the approved product.

Changes to the approved product must receive further approval from the Notified Body which issued the EC type-examination certificate wherever the changes may affect conformity with the essential requirements or with the conditions prescribed for use of the product. This new approval must, where appropriate, take the form of a supplement to the initial EC type-examination certificate. »

As in the case of EC type-examination, the applicant, who here may be the manufacturer’s representative, is responsible for declaration.

The extent of change in a product which may require such a declaration is not specified in the directives, but in this regard the conclusions of paragraph 5.1.1. of this guide may be applied.

**LNE / G-MED’s role in this case is restricted to the additional examinations or tests strictly necessary to ensure that the consequences of the changes made do not entail the loss of conformity to the essential requirements.**

**In addition, the EC type-examination certificate issued by a Notified Body is valid for a maximum of five years.**

This certificate may be extended following a request made at the time agreed in the contract signed by the two parties.

In addition, for diagnostic in vitro medical devices listed in annex II, list A or list B, the manufacturer shall inform the Notified Body on changes of pathogen agent and infection markers, as stipulated in the paragraph 5.1.1. of the present guide.

5.5. **EC verification**

**Note:** This procedure must not be confused with the "verification of manufactured products" specific to certain in vitro diagnostic devices.

In this procedure, the Notified Body intervenes either for each copy placed on the market (unit verification), or for each batch released (statistical verification).

The question of the maintenance, during the time, of CE marking conditions does not occur in this case.

**However, for devices placed on the market in a sterile condition,** the conditions for maintaining CE marking as described in paragraph 5.2. of this guide apply for aspects regarding the securing and maintenance of sterility.
5.6. EC declaration of conformity

Here, the obligations the manufacturer has consist of keeping up-to-date technical documentation which is made available to the national authorities for inspection for a period five years at least after the manufacture of the last product marketed.

However, as before, for devices placed on the market in a sterile condition, the conditions for maintaining CE marking as described in paragraph 5.2. of this guide apply for aspects regarding the securing and maintenance of sterility.

5.7. Verification of manufactured products

In the case of in vitro diagnostic medical devices covered by annex II, list A, the manufacturer shall forward to the Notified Body without delay after the controls and tests the relevant reports on the tests carried out on the manufactured devices or each batch of devices. Furthermore, the manufacturer shall make the samples of manufactured devices or batches of devices available to the Notified Body in accordance with pre-agreed conditions and modalities.

The manufacturer may place the devices on the market, unless the Notified Body communicates to the manufacturer within the agreed time-frame but not later than 30 days after reception of the samples, any other decision, including in particular any condition of validity of delivered certificates.
ANNEX A

Standards list of "harmonised european standard" status,
the most recent at the date of publication of the present guide

Standards list of « harmonised european standard » status for directive 90/385/EEC :
http://europa.eu.int/comm/enterprise/newapproach/standardization/harmstds/reflist/implmedd.html

Standards list of « harmonised european standard » status for directive 93/42/EEC :

Standards list of « harmonised european standard » status for directive 98/79/EC :
ANNEX B

List of "Notified Bodies Recommendations" (NB-MED),
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- Conformity assessment of annex II, IVD’s designed and evaluated prior to adoption of Common Technical Specifications (CTS) NB-MED/2.5.5/Rec3(3)
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- Evaluation of clinical data NB-MED/2.7/Rec3(3)

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- CE marking of pre-MDD Devices NB-MED/2.13/Rec1(4)
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Other
- Voluntary certification at an intermediate stage of manufacture NB-MED/2.15/Rec1(3)