OraMod

VPH based predictive model for oral cancer reoccurrence in the clinical practice

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Revision no.	Date of Issue	Author(s)	Brief Description of Change
1	22-06-2015	S. Burgarella (ST)	First draft (incomplete)
2	15-03-2016	M. Cereda, M. Berti, N. Serina, S. Burgarella (ST)	Second draft (almost complete with regard to ST's contribute; still missing final contributes by partners)
3	07-04-2016	F. Jung (Fraunhofer); A. Turetta (OneToNet); M. van de Wiel (VUmc); E. Martinelli	Contributes by Fraunhofer, OneToNet, VUmc, VCI, and UNIPR. Revised by Coordinator

Addressees of this document

This document should be distributed to all the personnel of OraMod Consortium partners, especially the technical partners that have developed the components of the OraMod system.
This document is Public, therefore it will be published on OraMod web site.

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List of abbreviations and acronyms

AIMD	Active Implantable Medical Device
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
ECG	ElectroCardioGram
EEA	European Economic Area
EHR	Electronic Health Record
FDA	Food and Drug Administration
GMPs	Good Manufacturing Practices
GUI	Graphical User Interface
IVD	*In Vitro* Diagnostic
IVDD	*In Vitro* Diagnostic Directive
JSON	JavaScript Object Notation
MDDS	Medical Device Data System
OSCC	Oral Squamous Cell Carcinoma
PACS	Picture Archiving and Communication System
PMA	Pre-Market Approval
QMS	Quality Management System
qRT-PCR	quantitative Reverse Transcription-Polymerase Chain Reaction
URD	User Requirements Document

1 Objective of the deliverable D8.3

This deliverable D8.3 - *Products certification guidelines* (responsible ST-Italy, month 30) - is an operational document whose objective is to identify - for both each new product developed within the OraMod project, and the OraMod system as a whole platform - the steps and actions to be performed in order to obtain the EC certification as medical device. Specific actions to be performed by the IP owners of such technologies are identified, and the relevant certification procedures are herein collected.

In WP8 - *Project Exploitation* - a specific task concerns the certification roadmap of the developed OraMod platform. This task T8.2 - *Medical device certification roadmap* (responsible ST-Italy, month 18-28) - does not require to the consortium partners a complete medical device certification of the developed platform within the timeframe of OraMod project: T8.2 requires the definition of all the required steps that the potential manufacturer of OraMod platform will have to do in order to put it into the medical device market. The output of task T8.2 is this deliverable, D8.3: a document of guidelines and procedures for certification of the OraMod platform, as well as of each developed component, as a medical device, with related costs and timings estimations.

The healthcare products market is global, but the industry is heavily and differently regulated in all important market areas. Products must comply with EU Directives in order to be put on the European Economic Area market, to the FDA's requirements for the United States market, etc. Task T8.2 is devoted to specify the actions necessary to achieve the certifications for the developed technologies to be used in clinical settings. The task relies on the results of T2.4 - *Technology standards identification* - where the relevant technology standards were identified to allow adoption of OraMod in the hospitals.

T8.2 has been led by ST-Italy and has involved Fraunhofer, OneToNet, VUmc, VCI, and UNIPR experts in medical devices certification.

2 Regulatory framework for the OraMod system

2.1 Regulatory elements in the OraMod system

After a preliminary investigation between ST-Italy (responsible for task T8.2), the project Coordinator and the other technological partners of the Consortium (Fraunhofer, OneToNet, VCI, and VUmc), the project framework shown in Figure 2.1 has been defined, from the regulatory point of view.

From a regulatory point of view, all the components developed by the Consortium for the OraMod system have been grouped into the following three elements:

1) The **image analysis software** developed by Fraunhofer Institute: from a regulatory point of view, this element is independent from the rest of the system, because a PACS (Picture Archiving and Communication System) server is set between it and the OraMod network platform. This element can be ideally substituted by a similar product developed by third parties.

2) The **qRT-PCR** (quantitative Reverse Transcription-Polymerase Chain Reaction) **system** developed by ST-Italy, which is composed by the Q3-Plus instrument, the consumable Lab-on-Chip cartridge, and the software running on a PC. From a regulatory point of view, this element is independent from the rest of the system as well, because the interface between the qRT-PCR system and the OraMod network platform is a JSON (JavaScript Object Notation) file sent by Q3-Plus software to the OraMod network platform. This element can be ideally substituted by a similar product developed by third parties.

3) All the rest of the developed components are part of the so called **OraMod network platform**. This platform is composed of the following parts:
    a. the ***back-end***, that is the network platform developed by OneToNet;
    b. the ***front-end***, that is the graphical user interface (GUI) developed by VCI;
    c. the ***models***, that have been developed by VUmc and can be implemented as standalone algorithms or as formulas included in the GUI code.

These three elements (image analysis software, qRT-PCR system and OraMod network platform) will follow independent regulatory paths, in terms of either medical device or *in vitro* diagnostic device certification roadmap, before they can be put on the market. At the end, these three paths will converge into a unique solution, that will be represented by a certified **OraMod system** having as “accessories” a certified image analysis software, a certified qRT-PCR system and a certified OraMod network platform.

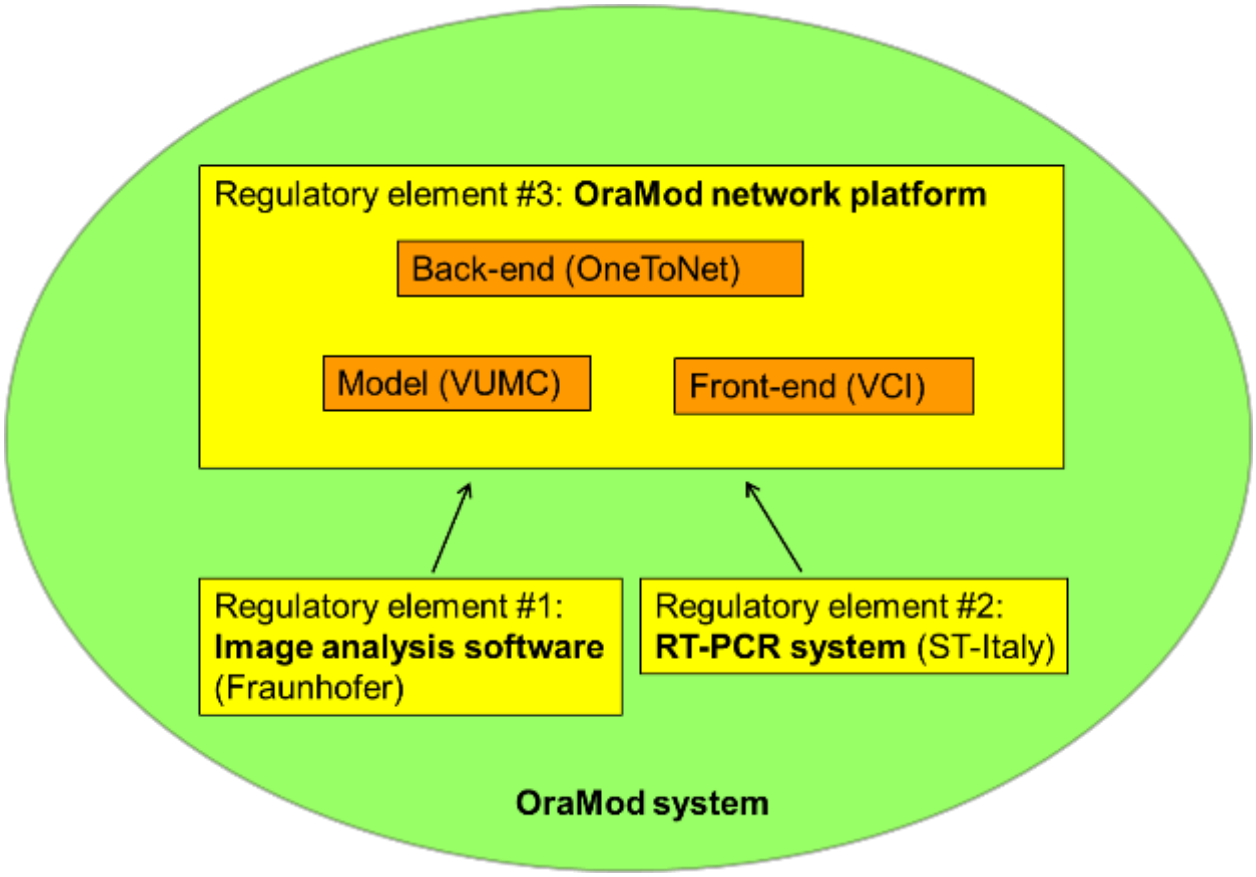


Figure 2.1: the OraMod system and its regulatory elements.

This scenario is further complicated by the fact that different regulations exist in different geographical markets. Thus, the three regulatory elements (image analysis software, qRT-PCR system and OraMod network platform) have to be analyzed in terms of regulatory evaluation for the market(s) of interest:

- The first market of interest is the European market of course, therefore the EU legislation has to be considered in order to obtain the CE mark.
- The second market of interest is the American one, thus the US regulations have to be considered in order to obtain the FDA approval.

In all cases, defining the **intended use** of a device is always the first step of its regulatory *iter*: it means 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. The intended use determines the following certification path to be pursued and regulatory requirements to be applied.
Thus, it is the legal manufacturer who decides if, and how, to certify its own device.

2.1.1 The Image analysis software

The image analysis software developed by Fraunhofer Institute has to meet the requirements of the *standalone medical device software*, due to its intended use. The medical software certification affects the software life cycle, its performances, the analysis of the risks connected to its use, etc., according to

the legislation of the market of interest. The partner Fraunhofer has been in charge of evaluating the certification roadmap for its image analysis software, according to the EU and US legislations, supported by ST-Italy.

2.1.2 The qRT-PCR system

The qRT-PCR system developed by ST-Italy has to meet the requirements of the *in vitro diagnostic (IVD) medical device*. The IVD certification affects the safety of the equipment, the performances of the test, the analysis of the risks connected to its use, etc., according to the legislation of the market of interest. The software running on PC has to be considered as a *medical device software*, with the specific requirements concerning this software category. The partner ST-Italy has been in charge of evaluating the certification roadmap for its qRT-PCR system, according to the EU and US legislations.

2.1.3 The OraMod network platform (back-end, front-end, model)

The OraMod network platform developed by OneToNet, VCI and VUmc can be defined as an *electronic clinical record including predictive models*, due to its intended use. The certification roadmap for this element has needed a deep investigation by the partners involved (OneToNet, VCI, VUmc, and ST-Italy as responsible for the task T8.2). These partners have been in charge of evaluating the certification roadmap for the OraMod network platform, according to the EU and US legislations.

3 Certification roadmap for the Image analysis software

3.1 Definition of the intended use

The OraMod image analysis software is to be used by a clinical expert for the purpose of image biomarker extraction, which is one of the basis of the OraMod prediction models.

The software helps the doctor to retrieve the medical image data from a clinical PACS system, process it locally and finally forward the extracted image features to the OraMod network platform.

The software combines manual and fully automatic extraction tools in order to make the feature process as swift and convenient as possible.

As defined by the OraMod protocol, using the software the clinical expert does a segmentation of the primary tumor and all lymph nodes with a major axis greater than 1cm.

The image analysis software automatically extracts relevant features from these segmentations and the clinician enriches this information by expert knowledge about possible invasions by the disease.

Once the feature extraction process is complete, the extracted data can be transferred to the OraMod network platform for further processing. All of the information sent to the OraMod system is eyed and validated by the clinical expert.

This information can be used for the training of the OraMod prediction models, or when such models already exist, the models can use this information to do a prediction about the recurrence and survival chance of the patient. These predictions are solely based on the OraMod system and the used model algorithms.

3.2 The regulatory context

From a regulatory point of view, the Image analysis software of Fraunhofer Institute is independent from the rest of the system, because a PACS server is set between it and the OraMod network platform. Thus, this element can be ideally substituted by a similar product developed by third parties. One of the objectives of task 8.2 has been the evaluation of the certification roadmap for the Image analysis software, according to the EU and US legislations.

According to an article published on European Medical Device Technology (EMDT) in 2012, this is the summary of similarities and differences between the EU and US regulation of medical-related software (full article available at http://www.emdt.co.uk/article/comparing-eu-and-us-approaches-regulating-clinical-decision-support-software-brief-summary-e):

Similarities

- Software is divided into two categories: (1) stand-alone software and (2) accessories.
- Software that comes pre-installed on the device when the device is placed on the market is not regulated as a separate medical device.
- Accessory software is regulated at the same level as the device to which it connects.
- General-purpose software used in a healthcare setting is not regulated, unless its specific intended use is that of a medical device.

Differences

- Software that merely performs storage, archiving, communication, "simple search" or lossless compression of medical data is not regulated in the European Union. In the United States, however, this software would be regulated as a Class I medical device data system (commonly referred to as an MDDS device), if any of the data is obtained electronically from a medical device.
- In the European Union, the default classification for stand-alone software that is not otherwise classified under the medical device directives is Class I—the lowest-risk classification. In the United States, however, the default classification is Class III, which includes devices that present the greatest risk in the eyes of US FDA.

The Image analysis software is not incorporated in a device, thus it is a **standalone software**.

3.2.1 EU regulations

In the European Union, a software used in healthcare can be a medical device, an IVD medical device, both of them, or neither of them (in this last case, not requiring any certification), depending on its intended use.

In the EU, a medical device has to meet the requirements of the Medical Device Directives 93/42/EEC and 2007/47/EC.
While an IVD medical device has to comply with the IVD Directive 98/79/EC.

According to Article 1.2a of Medical Device Directive 93/42/EEC, "'medical device' means 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, monitoring, treatment, alleviation of or compensation for an injury or handicap,
— investigation, replacement or modification of the anatomy or of a physiological process,
— control of conception,
and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means".

In the document named "*EU - medical-information-system-guideline"*, dated 2012-10-31, there is a guideline for qualification and classification of standalone software with a medical purpose (Figure 3.1). It is the translation from Swedish of the original report *"Medicinskainformationssystem – vägledning för kvalificering och klassificering av programvaror med medicinskt syfte"*, issued by the Swedish Medical Products Agency in June 2009.

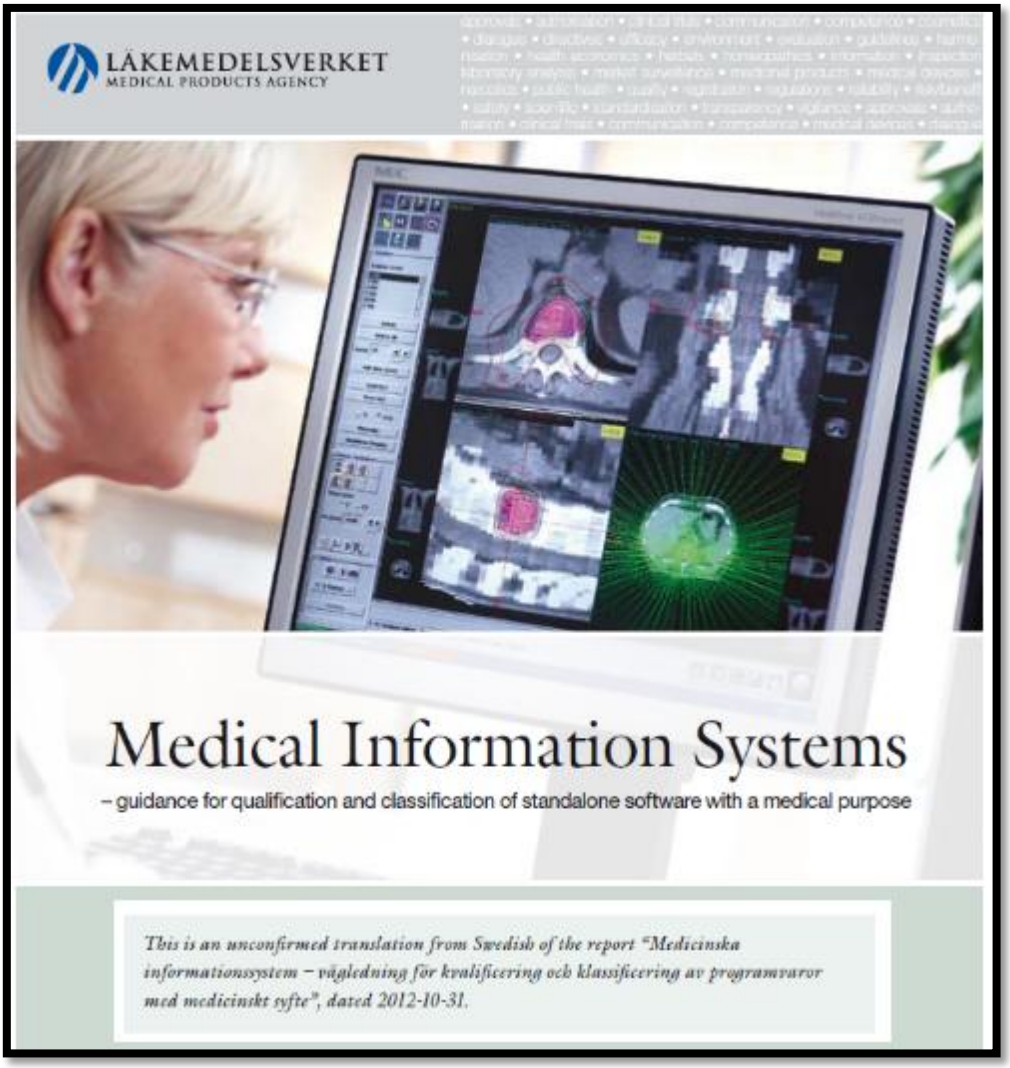


Figure 3.1: translation from Swedish of the report "Medicinskainformationssystem – vägledning för kvalificering och klassificering av programvaror med medicinskt syfte".

In its preface, it is stated that the latest update of Directive 93/42/EEC on medical devices, which came into force on 21 March 2010 by the amending Directive 2007/47/EC, clarifies that the directive also applies to so called standalone software and that they can be medical devices. Not much more is mentioned in the regulatory text about the requirements for standalone software and how to determine whether the software is a medical device or not. To help manufacturers, organizations and authorities, some Swedish interested parties, led by the Medical Products Agency, proposed this guideline for standalone software. The document was published in June 2009 and was positively received in Sweden and internationally.

The decision diagram shown in Figure 3.2 gives some guidance regarding the necessary steps to qualify standalone software as medical device, according to this document.

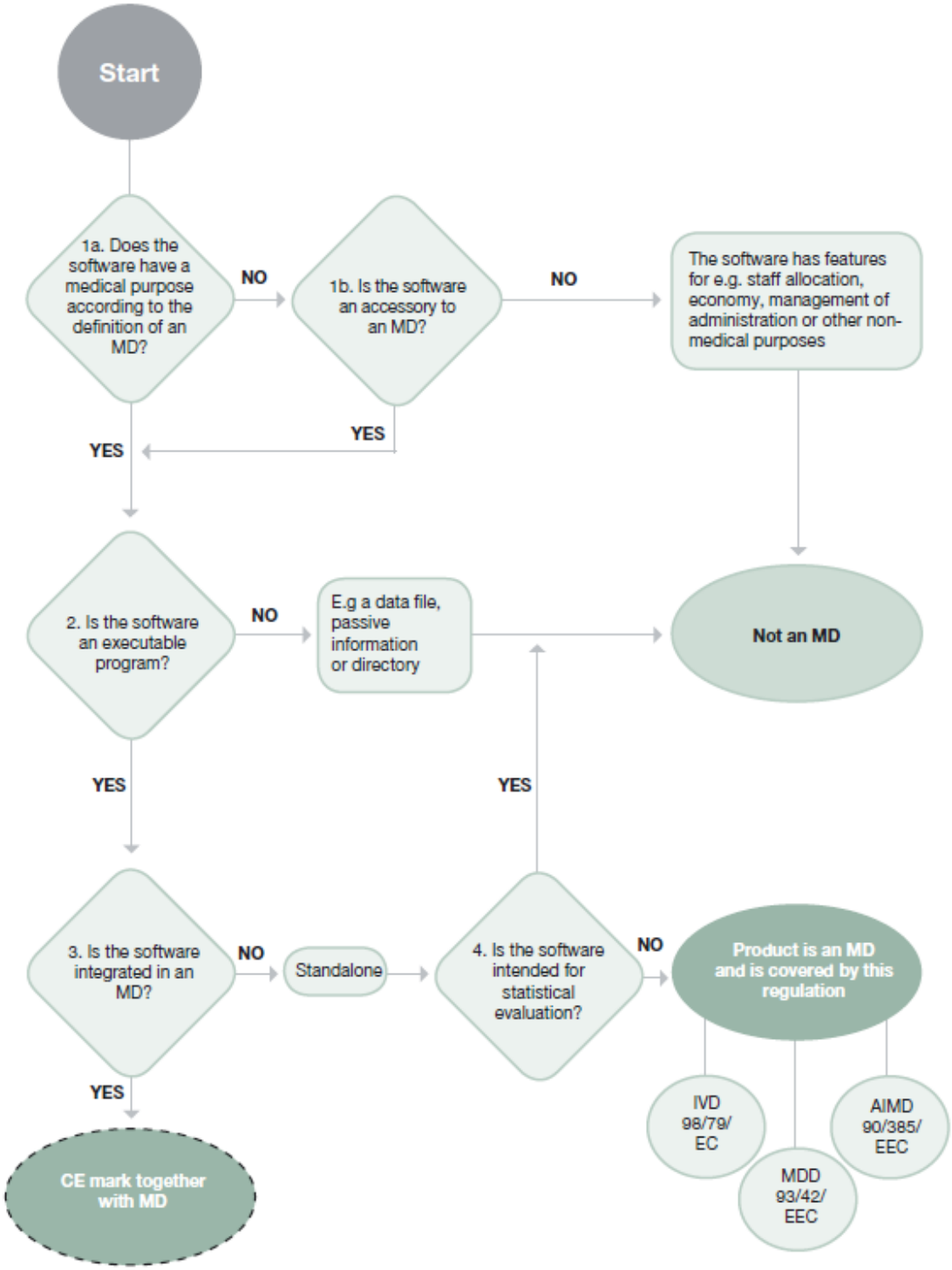
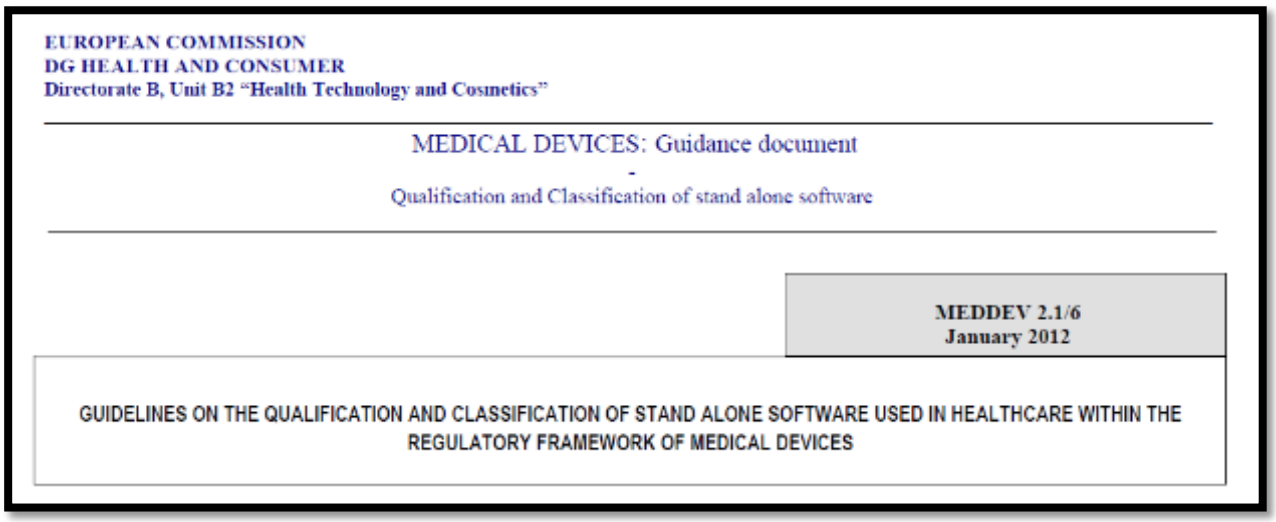


Figure 3.2: decision diagrams to classify standalone software.

After positive acceptance of this guideline, the Swedish Medical Products Agency initiated an EU guideline for standalone software. The Agency participated in the work together with other EU authorities and industry organizations; the resulting document was issued in January 2012 by the European Commission, DG Health and Consumer, referred to as "*MEDDEV 2.1/6 - guidelines on the*

qualification and classification of standalone software used in healthcare within the regulatory framework of medical devices" (Figure 3.3).


EUROPEAN COMMISSION
DG HEALTH AND CONSUMER
Directorate B, Unit B2 "Health Technology and Cosmetics"

MEDICAL DEVICES: Guidance document
-
Qualification and Classification of stand alone software

MEDDEV 2.1/6
January 2012

GUIDELINES ON THE QUALIFICATION AND CLASSIFICATION OF STAND ALONE SOFTWARE USED IN HEALTHCARE WITHIN THE REGULATORY FRAMEWORK OF MEDICAL DEVICES

Figure 3.3: MEDDEV 2.1/6 - guideline on standalone software, issued by the European Commission.

The purpose of this document is to define the criteria for the qualification of standalone software, when used in healthcare setting, as a medical device and the application of the classification criteria to such software. For the purpose of this guideline, standalone software means software which is not incorporated in a medical device when it is placed on the market or made available for use.

Software can be used for a large variety of medical purposes. In that respect, the arguments do not differ from those used for other medical devices. Standalone software can directly control an apparatus (e.g. radiotherapy treatment), can provide immediate decision triggering information (e.g. blood glucose meters), or can provide support for healthcare professionals (e.g. ECG interpretation). Not all standalone software used within healthcare can be qualified as a medical device. Standalone software may run on different operating systems or in virtual environments. These operating systems or virtual environments do not impact the qualification criteria. Standalone software might also be an accessory of a medical device. The risk related to a malfunction of the standalone software used within healthcare is in itself not a criterion for its qualification or not as a medical device. It is, therefore, necessary to clarify some criteria for the qualification of standalone software as medical devices.

The decision diagram shown in Figure 3.4 is taken from MEDDEV 2.1/6 and gives some guidance regarding the necessary steps to qualify standalone software as medical device. Table 3.1 explains the decision steps shown in Figure 3.4.

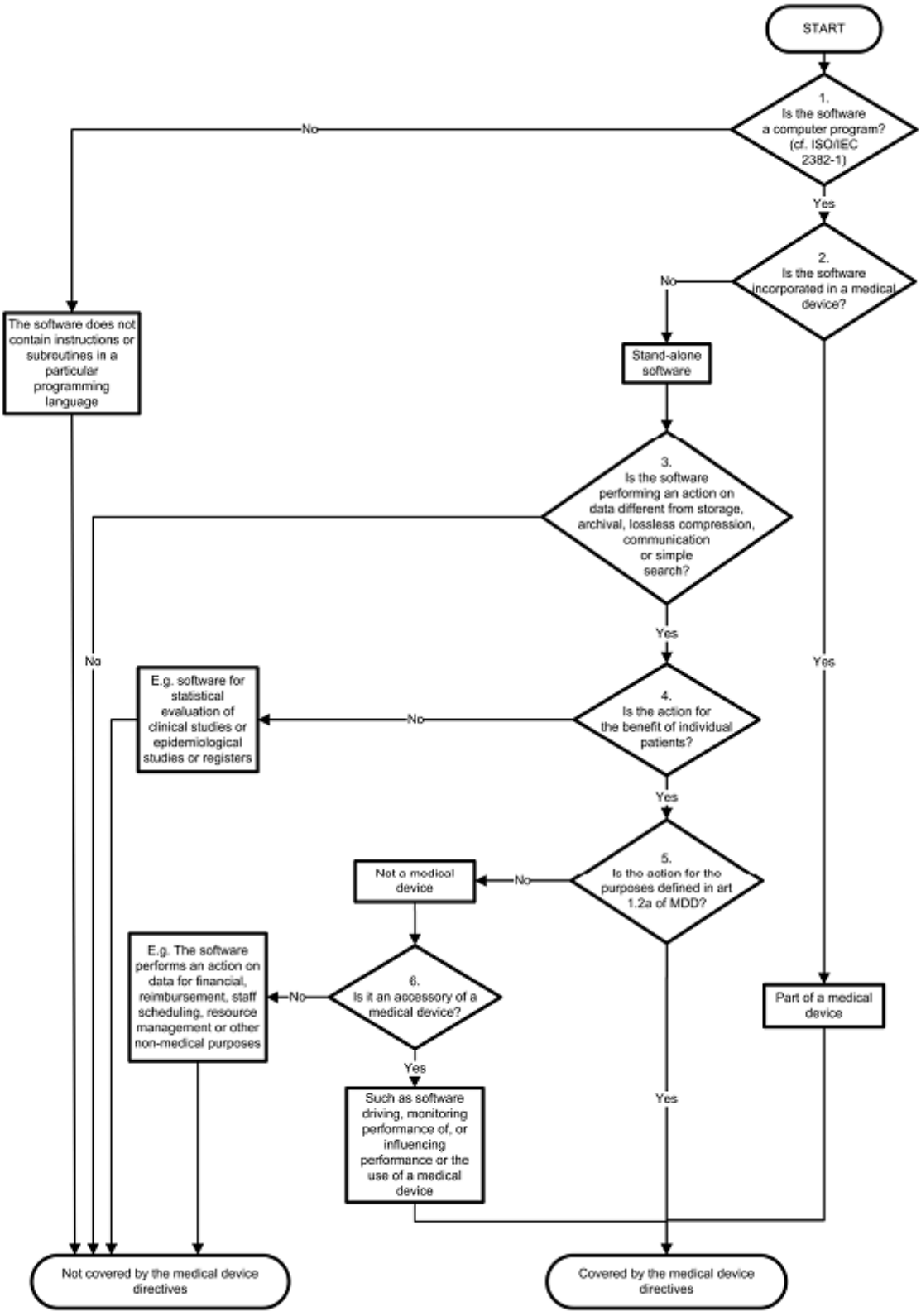


Figure 3.4: decision diagram to assist qualification of software as medical device.

Decision step # 1: if the standalone software is a computer program, then it may be a medical device. If the software is not a computer program, then it is a digital document and therefore not a medical device.

Decision step # 2: if the software is incorporated into a medical device rather than standalone software, it must be considered as part of that medical device in the regulatory process of that device. If it is standalone software, proceed to decision step 3.
Decision step # 3: if the software does not perform an action on data, or performs an action limited to storage, archival, communication, simple search or lossless compression (i.e. using a compression procedure that allows the exact reconstruction of the original data) it is not a medical device. Altering the representation of data for embellishment purposes does not make the software a medical device. In other cases, including where the software alters the representation of data for a medical purpose, it could be a medical device.
Decision step # 4: an example of software for the benefit of individual patients is software intended to be used for the evaluation of patient data to support or influence the medical care provided to that patient. Examples of software which are not considered as being for the benefit of individual patients are those which aggregate population data, provide generic diagnostic or treatment pathways, scientific literature, medical atlases, models and templates as well as software for epidemiologic studies or registers.
Decision step # 5: if the manufacturer specifically intends the software to be used for any of the purposes listed in Article 1.2a of Directive 93/42/EEC, then the software shall be qualified as a medical device. However, if only a non-medical purpose is intended by the manufacturer, such as invoicing or staff planning, it is not a medical device.
Decision step # 6: if the software is an accessory to a medical device, it is not a medical device itself, but it falls under Directive 93/42/EEC.

Table 3.1: decision steps to qualify standalone software.

To summarize: standalone software must have a medical purpose to be qualified as medical device. It should be noted that only the intended purpose as described by the manufacturer of the product is relevant for the qualification and classification of any device and not by virtue of the way it may be called. Standalone software that does not meet the definition of a medical device or of an IVD medical device, but is intended by the manufacturer to be an accessory to a medical device, or an IVD medical device, falls respectively under the scope of Medical Devices Directive 93/42/EEC or In-Vitro Diagnostic Directive 98/79/EC. It is to be noted that to be qualified as an IVD medical device, standalone software must first fulfill the definition of a medical device. Where a given product does not fall under the definition of medical device, or is excluded by the scope of the Directives, other Community and/or national legislation may be applicable.

In Annex 1 of MEDDEV 2.1/6, there are some examples of qualification for software used in the healthcare environment. One of such examples is Clinical Decision Support software: they are computer-based tools which combine medical knowledge databases and algorithms with patient specific data. They are intended to provide healthcare professionals and/or users with recommendations for diagnosis, prognosis, monitoring and treatment of individual patients. Based on steps 3, 4, and 5 of Figure 3.4, they are qualified as medical device, and therefore need to be CE marked. As instance, Computer Aided Detection systems are intended to provide information that may suggest or exclude

medical conditions and, therefore, qualified as medical devices. For example, such systems would be able to automatically read X-ray images or interpret ECGs. This example is very similar to the Image analysis software by Fraunhofer.

The **image analysis software** developed by Fraunhofer Institute can thus be classified as a clinical decision support software **Medical Device**, according to the EU legislation. Hence, it has to meet the requirements of Medical Device Directive 93/42/EEC and 2007/47/EEC, and needs to be CE marked.

2007/47/EEC Directive, that amended 93/42/EEC Directive, introduces also the standalone software in Annex IX of 93/42 EEC Directive. Annex IX states the classification criteria for medical devices; it contains 18 rules for classification of a medical device, based on its intended use, duration of contact with the human body, degree of invasiveness, and special situations.
The classification of a medical device determines its conformity assessment route, as from Figure 3.5. Most medical devices need that a Notified Body assesses its certification procedure, depending on the classification of the device itself; only Class I medical devices do not require a Notified Body. A Notified Body is a third party independent certification organization, which the competent authority has designated to carry out the conformity assessment procedures described in the annexes to a Directive. Manufacturers are free to apply to any designated Notified Body in the EU to carry out the desired conformity assessment procedure, regardless of which Member State that Notified Body is designated in. Figure 3.6 lists some of the Notified Bodies in the EU for Directive 93/42/EEC on Medical Devices.

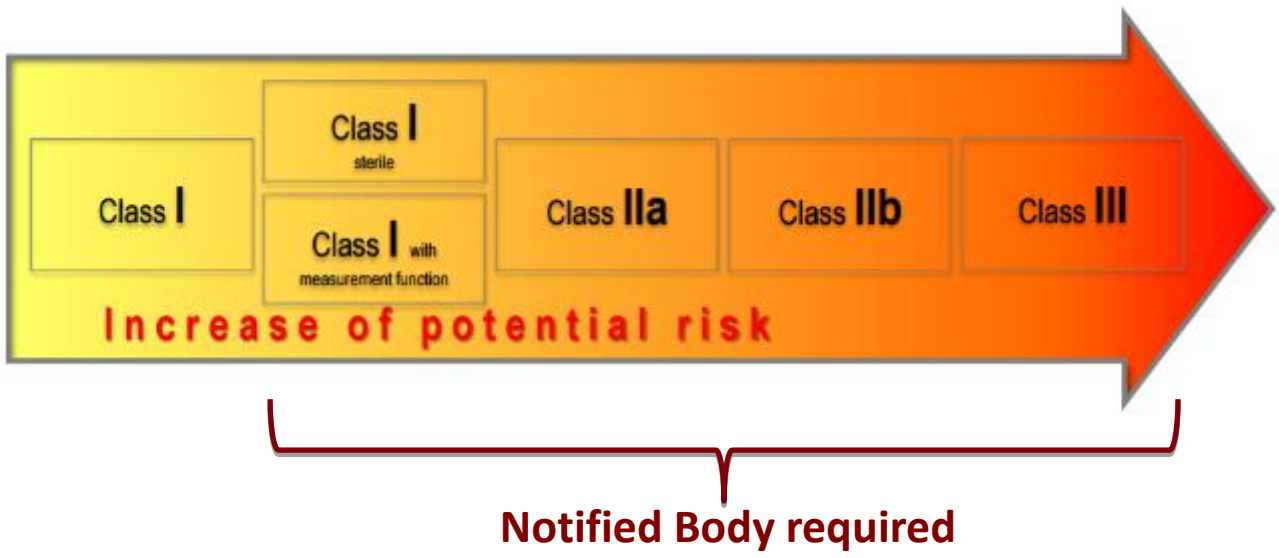


Figure 3.5: the classes of Medical Devices.

Body type ▲	Name ▲	Country
NB 0805	THERAPEUTIC GOODS ADMINISTRATION	Australia **(MRA)**
NB 0408	TÜV AUSTRIA SERVICES GMBH	Austria
NB 0636	PRÜFSTELLE FÜR MEDIZINPRODUKTE GRAZ	Austria
NB 1639	SGS Belgium NV	Belgium
NB 1014	ELEKTROTECHNICKÝ ZKUŠEBNÍ ÚSTAV, s.p.	Czech Republic
NB 1023	INSTITUT PRO TESTOVÁNI A CERTIFIKACI, a. s.	Czech Republic
NB 0543	Presafe Denmark A/S	Denmark
NB 0537	VTT Expert Services Oy	Finland
NB 0598	SGS FIMKO OY	Finland
NB 0459	Laboratoire national d'essais / G-MED	France
NB 0044	TÜV NORD CERT GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany
NB 0124	DEKRA Certification GmbH	Germany
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0297	DQS Medizinprodukte GmbH	Germany
NB 0432	Materialprüfungsamt Nordrhein-Westfalen (MPA NRW)	Germany
NB 0481	ECM-ZERTIFIZIERUNGSGESELLSCHAFT FÜR MEDIZINPRODUKTE IN EUROPA MBH	Germany
NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0494	SLG PRÜF UND ZERTIFIZIERUNGS GMBH	Germany
NB 0535	BSI Group Deutschland GmbH	Germany
NB 0633	BERLIN CERT PRÜF- UND ZERTIFIZIERSTELLE FÜR MEDIZINPRODUKTE GMBH AN DER TECHNISCHEN UNIVERSITÄT BERLIN	Germany
NB 0653	NATIONAL EVALUATION CENTER OF QUALITY AND TECHNOLOGY IN HEALTH S.A.- EKAPTY	Greece
NB 1008	TÜV Rheinland InterCert Muszaki Felügyeleti és Tanúsító Korlátolt Felelosségu Társaság	Hungary
NB 1011	Országos Gógyszerészeti és Élelmezés-egészségügyi Intézet Eszközminősítő és Kórháztechnikai Igazgatóság (National Institute of Pharmacy and Nutrition)	Hungary
NB 1979	SGS Hungária Minoségellenorzo, Kereskedelmi és Szolgáltató Kft.	Hungary
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy
NB 0068	IRCM ISTITUTO DI RICERCHE E COLLAUDI MASINI S.R.L.	Italy
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy
NB 0426	ITALCERT SRL	Italy
NB 0476	KIWA CERMET ITALIA S.P.A.	Italy
NB 0477	Eurofins Product Testing Italy S.r.l.	Italy
NB 0546	CERTIQUALITY S.R.L. - ISTITUTO DI CERTIFICAZIONE DELLA QUALITA'	Italy
NB 1370	BUREAU VERITAS ITALIA S.P.A.	Italy
NB 1936	TUV Rheinland Italia SRL	Italy

Figure 3.6: some Notified Bodies in the EU for Directive 93/42/EEC on Medical Devices.

An amendment introduced by Directive 2007/47/EEC explicitly added in Annex IX of Directive 93/42/EEC that "standalone software" meeting the definition of a medical device "is considered to be an active medical device". This means that rules 9, 10, 11 and 12 of Annex IX may apply. Figure 3.7 shows a

graphical summary of such rules, taken from MEDDEV 2.4/1 Rev.9 (a guidance document issued by the EC, containing guidelines for application of the classification rules for medical devices, as set out in Annex IX):

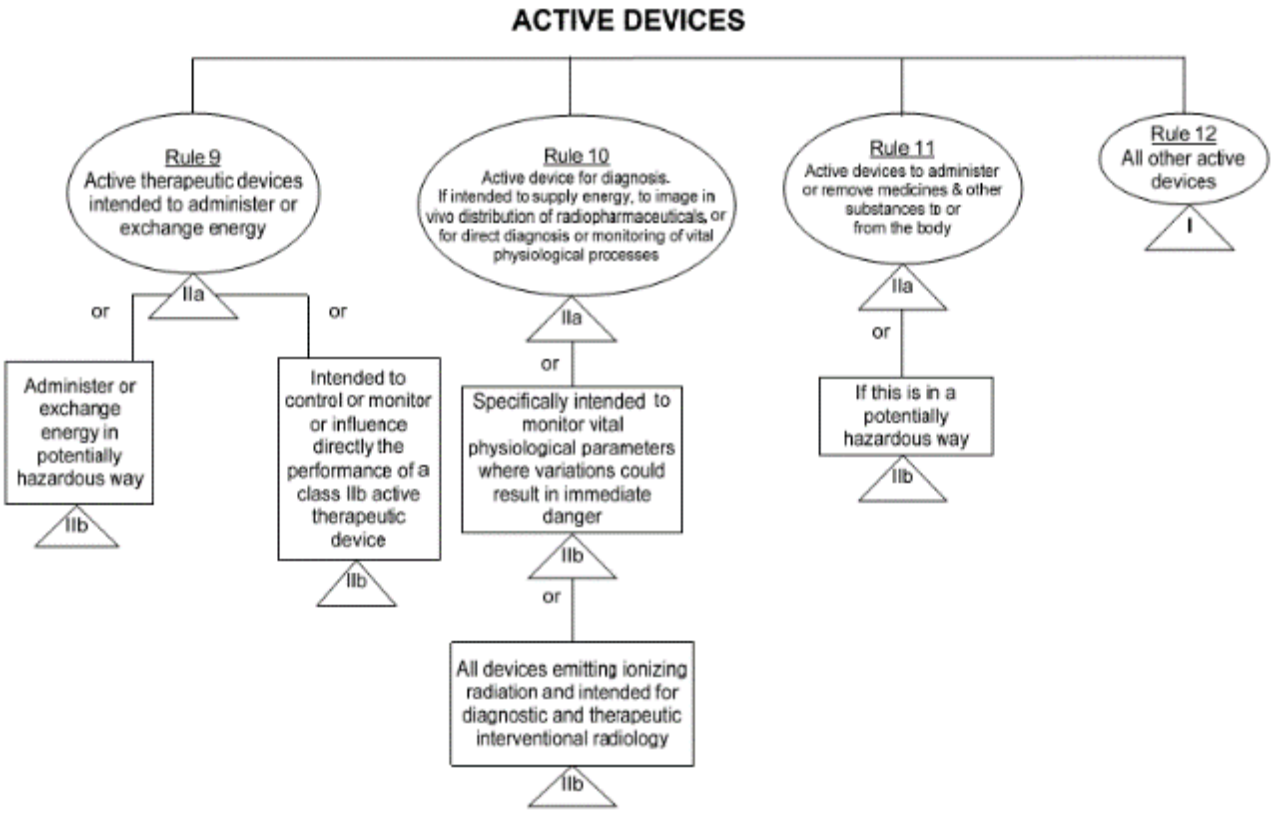


Figure 3.7: classification rules from 9 to 12 on active medical devices.

Standalone software which drives a medical device falling into a rule from 9 to 11, or influences the use of such device, falls automatically into the same class as the device it drives. Rule 12 states that all other active devices are in Class I. Class I standalone software can also come with a measuring function (example: orthopaedic planning software to measure interpedicular distance or sagittal diameter of the spinal canal), as MEDDEV 2.1/6 clarifies. Due to its intended use (see par. 3.1), we believe that the image analysis software developed by Fraunhofer falls within rule 10 “active device for diagnosis”; thus it can be classified as a **Class IIa Medical Device, standalone software**, according to the EU legislation. Nevertheless, it will be the future legal manufacturer’s only responsibility to classify this product, based on the exact intended use he will write down, and to decide the consequent certification path to follow before being able to put this software on the market. The classification herein proposed is not in any way binding, and has been made according to the best of our present knowledge.

The European CE medical device approval process can be divided into the following steps:

Step # 1: Determine if your product is a medical device.

Step # 2: Determine which EU Medical Device Directive applies to your device: 93/42/EEC – Medical Devices Directive (MDD) or 90/385/EEC - Active Implantable Medical Devices Directive (AIMDD).

Step # 3: Determine classification of your device using Annex IX of the MDD: Class I (non-sterile, non-measuring), Class I (sterile, measuring), Class IIa, Class IIb or Class III/AIMD. Active implantable medical devices are subject to the same regulatory requirements as Class III devices.
Step # 4: For all devices except Class I (non-sterile, non-measuring), implement Quality Management System (QMS) in accordance with Annex II or V of the MDD. Most companies apply the ISO 13485 standard to achieve QMS compliance (see par. 3.5).
Step # 5: Prepare a Technical File that provides detailed information on your medical device demonstrating compliance with MDD 93/42/EEC. For Class III/AIMD devices, a more detailed Design Dossier has to be prepared instead. Moreover, class III/AIMD devices will likely required clinical study data (existing clinical data may be acceptable). Clinical trials in Europe must be pre-approved by a European Competent Authority.
Step # 6: Appoint an Authorized Representative (EC Rep) located in Europe. They should be qualified to handle regulatory issues. Place EC REP name and address on Instructions for Use and packaging.
Step # 7: For all devices except Class I (non-sterile, non-measuring), your QMS and Technical File or Design Dossier must be audited by a **Notified Body**, a third party accredited by European authorities to audit medical device companies and products.
Step # 8: For all devices except Class I (non-sterile, non-measuring), you will be issued a European CE Marking Certificate for your device and an ISO 13485 certificate for your facility following successful completion of your Notified Body audit. CE Marking certificates are typically valid for 3 years. ISO 13485 certification must be renewed every year.
Step # 9: All Class I devices must be registered with the Competent Authority where your EC REP is based. Most EU member states do not require registration of Class IIa, IIb or III devices.
Step # 10: Prepare a Declaration of Conformity, a legally binding document prepared by the manufacturer stating that the device is in compliance with the applicable Directive. You may now affix the CE Marking.

Table 3.2: sequential steps for CE medical devices approval process.

These steps are schematized in the following figure 3.8:

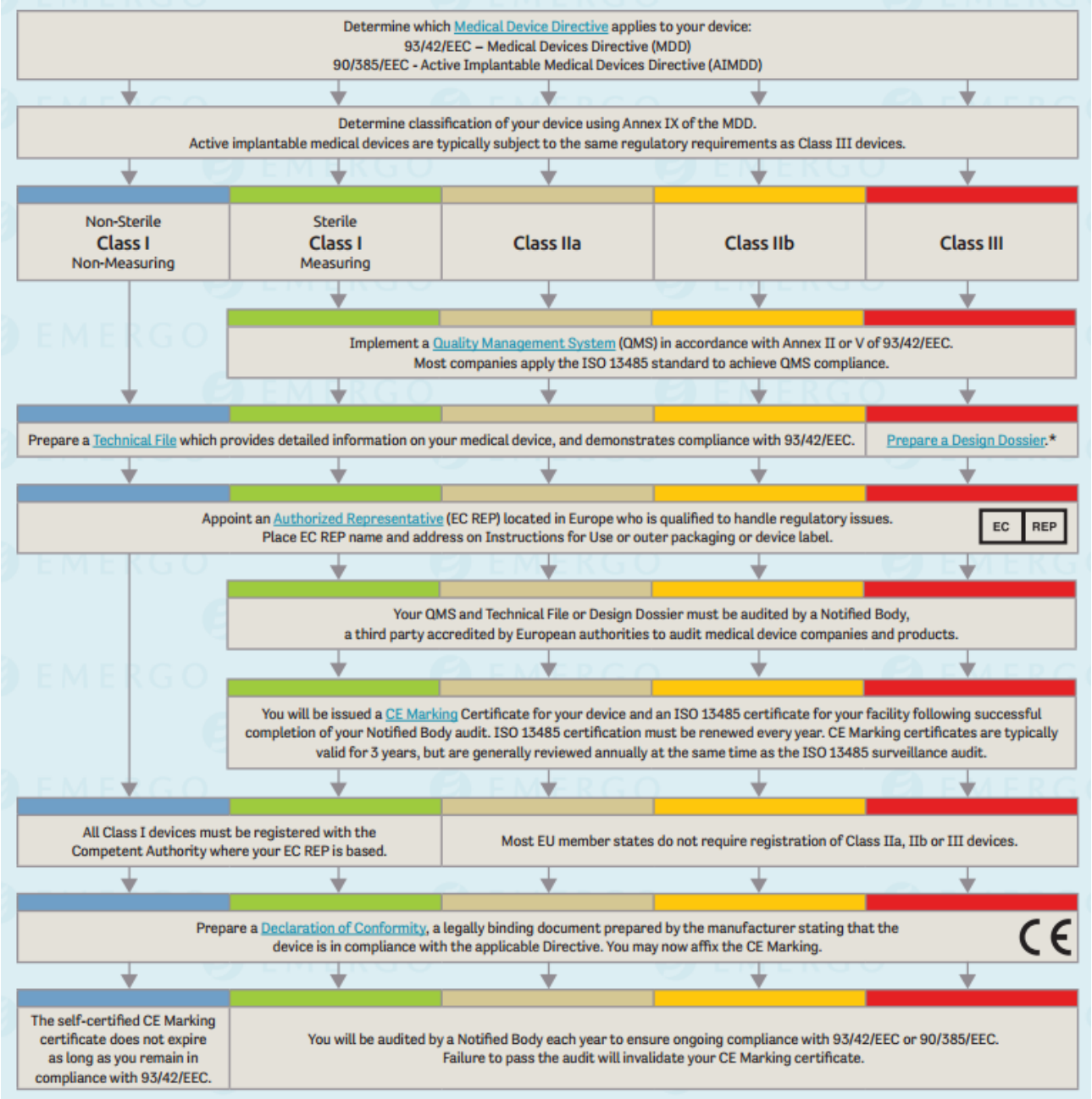


Figure 3.8: scheme of CE medical devices approval process.

More in detail, the manufacturer first has to declare conformity with the provisions of the Directive and Regulations and ensure that his product complies with relevant Essential Requirements – essentially, health and safety requirements. All medical devices must comply with the relevant Essential Requirements delineated in Annex I of the Medical Devices Directive 93/42/EEC. Compliance with the Essential Requirements is generally demonstrated by means of compliance with European Norm (EN) harmonized standards. While standards are voluntary, compliance with harmonized standards presume compliance with the relevant Essential Requirements and facilitates review by the Notified Body (when necessary).

In addition to this, an appropriate route to conformity assessment (Annexes II through VII of MDD) must be selected. The route is, in part, determined by device classification. For Class IIa products (like the Image analysis software), the declaration of conformity to Essential Requirements must be backed up with a conformity assessment by a **Notified Body**. This assessment may, at the manufacturer's choice, consist of:

a. Audit of the full quality assurance system (Annex II of MDD) ISO 13485;

   or

b. Preparation of the technical documentation to support the EC declaration of conformity, as set out in Annex VII, coupled with either:

   - Examination and testing of each product or homogenous batch of products (Annex IV; non-sterile products only);

     or

   - Audit of the production quality assurance system (Annex V) ISO 13485 (excluding Design);

     or

   - Audit of final inspection and testing (Annex VI) ISO 13485 (excluding Design & Manufacture).

Once the manufacturer has received certification from the Notified Body, he may CE mark his products in combination with the number of the Notified Body, and place the products on the EEA market.

Figure 3.9 schematizes this specific CE marking route for Class IIa medical devices, like the Image analysis software by Fraunhofer:

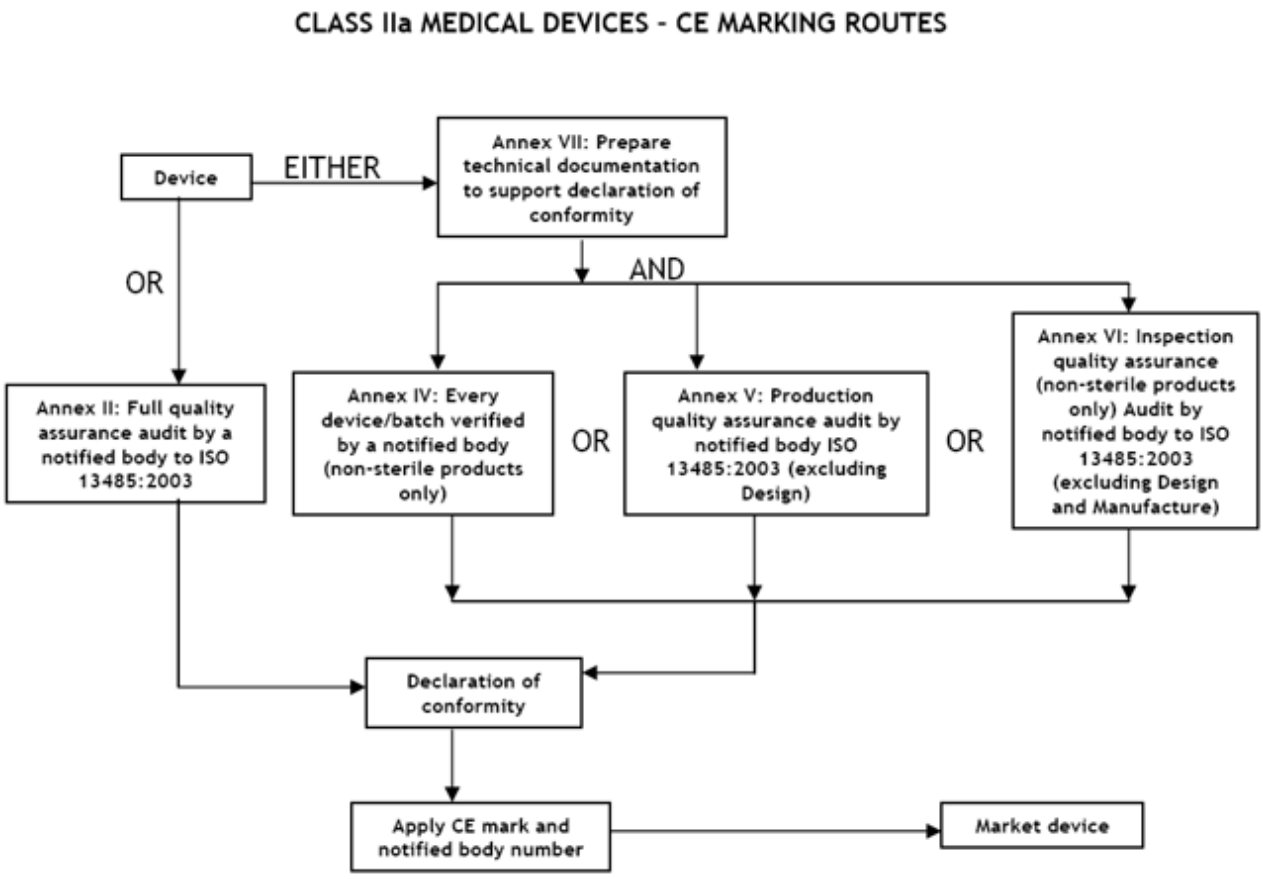


Figure 3.9: CE marking route for Class IIa Medical Devices.

Since the 2007/47/EEC amendment, a clinical evaluation in accordance with Annex X of Directive 93/42/EEC must be conducted for all medical devices. Confirmation of conformity with the requirements concerning the characteristics and performances referred to in sections 1 and 3 of Annex I ("Essential Requirements") of Directive 93/42/EEC under the normal conditions of use of the device, and the evaluation of undesirable side-effects, must be based on clinical data. Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device, in order to verify the clinical safety and performance of the device. Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device. It is first performed during the conformity assessment process leading to the marketing of a medical device, and then repeated periodically as new clinical safety and performance information about the device is obtained during its use. This information is fed into the ongoing risk analysis and may result in changes to the Instructions for Use. Figure 3.10 schematizes the steps to be followed when performing a clinical evaluation:

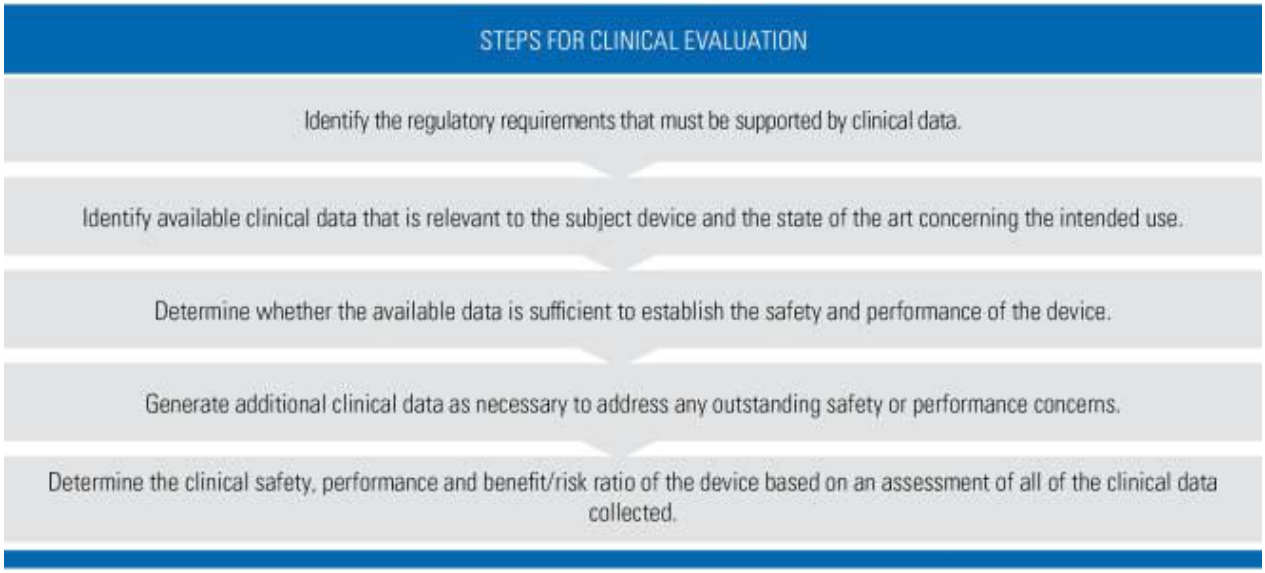


Figure 3.10: steps of a clinical evaluation.

The results of this process are documented in a clinical evaluation report. The clinical evaluation report and the clinical data on which it is based serve as the clinical evidence that supports the marketing of the device. The clinical evidence, along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Requirements and is part of the technical documentation of a medical device. Further details on clinical evaluation can be found in the guidance document "*MEDDEV 2.7.1 – Clinical evaluation: a guide for manufacturers and notified bodies"*, issued by the European Commission in 2009.

3.2.2 US regulations

In the US, the regulatory framework is somewhat more complex. The Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 *et seq.*) establishes a comprehensive system for the regulation of medical devices intended for human use. If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the FD&C Act, it will be regulated by the Food and Drug Administration (FDA, the US federal agency that is responsible for regulation of medical devices, drugs, food safety etc.) as a medical device, and is subject to premarketing and postmarketing regulatory controls. A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Section 513 of the FD&C Act establishes three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of safety and effectiveness. The three

classes and the requirements which apply to them are:

1. Class I, General Controls
   - With Exemptions
   - Without Exemptions

2. Class II, General Controls and Special Controls
   - With Exemptions
   - Without Exemptions

3. Class III, General Controls and Premarket Approval.

All classes of devices are subject to General Controls. General Controls are the baseline requirements of the FD&C Act, and include requirements for registration, listing, labeling, adverse event reporting, and good manufacturing practices (GMPs) (quality system requirements).
Special Controls are controls that, in addition to General Controls, are applicable to a class II device. FDA classifies into class II the devices for which General Controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish Special Controls to provide such assurance. Special Controls are usually device-specific and include performance standards, postmarket surveillance, patient registries, special labeling requirements, premarket data requirements.
Devices that are not within a type marketed before the date of the Medical Device Amendments of 1976 – referred to “preamendments devices” – are classified into class III automatically. In addition, the FDA classifies into class III the devices intended to be used in supporting or sustaining human life or preventing impairment of human health, or that may present a potential unreasonable risk of illness or injury, or are new and present unknown safety or effectiveness issues or risks; for which General Controls and Special Controls are considered insufficient to provide reasonable assurance of the safety and effectiveness, or for which there is insufficient information to make such a determination.

The class to which a device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance/approval to market. If a device is classified as Class I or II, and if it is not exempt, a Premarket Notification 510(k) will be required for marketing. All devices classified as exempt are subject to the limitations on exemptions. Limitations of device exemptions are covered in the Code of Federal Regulations (CFR) under 21 CFR xxx.9, where xxx refers to Parts 862-892. Most Class I devices and a few Class II devices are exempt from the premarket notification 510(k), thus for them the submission of a 510(k) and marketing clearance from FDA are not required before marketing the device in the U.S.. Devices exempt from 510(k) are:

- preamendment devices not significantly changed or modified; or
- Class I/II devices specifically exempted by regulation.

The term "preamendment device" refers to devices legally marketed in the U.S. before May 28, 1976 (that is, prior to the passage of the medical device amendments) and which have not been:

- significantly changed or modified since then; and
- for which a regulation requiring a premarket approval (PMA) application has not been published by FDA.

For Class III devices, a PMA application is required, unless the device is a preamendment device (or substantially equivalent to such a device) and PMAs have not been called for. In this case, a 510(k) will

be the route to market.
More details will be given in par. 4.2.2.

Device classification depends on the intended use of the device and also upon indications for use. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea". Indications for use can be found in the device's labeling, but may also be conveyed orally during sale of the product. In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.
Most medical devices can be classified by finding the matching description of the device in Title 21 of the Code of Federal Regulations (CFR), Parts 862-892. FDA has classified and described over 1700 distinct types of devices and organized them in the CFR into 16 medical specialty "panels", such as Cardiovascular devices or Ear, Nose, and Throat devices. For each of the devices classified by the FDA, the CFR gives a general description including the intended use, the class to which the device belongs (i.e., Class I, II, or III), and information about marketing requirements.

Any software that meets the legal definition of a medical device is a medical device, and is known as Medical Device Software. If the software is a Device, then it is still a Device regardless of the means by which the software is delivered to the end user. Since the Image analysis software by Fraunhofer Institute is “intended for use in the diagnosis of disease”, then it is a **Medical Device Software**. Medical Device Software can appear in many forms:

- Software that is a component of a medical device;
- Software that is an accessory to a medical device;
- Standalone software, also known as “software only devices”; which is software intended to run on general purpose computers. This is the case of the Image analysis software by Fraunhofer.

FDA has historically regulated a few types of stand-alone software, like picture archiving and communication systems, radiation treatment planning software and drug dose calculators. FDA has generally classified other types of standalone software as an accessory to a classified medical device, for example interpretive ECG and BIS (bispectral index) for depth of anesthesia.

FDA issued a final guidance on Mobile Medical Apps on September 25, 2013. FDA only regulates mobile apps that are intended to be used as an accessory to a regulated medical device or to transform a mobile platform into a regulated medical device.

FDA, the Office of the National Coordinator for Health IT (ONC), and the Federal Communications Commission released a June 2014 report on the future of a nationwide health infrastructure. Key conclusions were:

- a limited, narrowly-tailored approach that primarily relies on ONC-coordinated activities and private sector capabilities is prudent;
- that no new or additional areas of FDA oversight are needed;
- a better approach is to foster the development of a culture of safety and quality; leverage standards and best practices; employ industry-led testing and certification; and selectively use tools such as voluntary listing, reporting, and training.

Consistent with the Mobile Medical Apps guidance, where health information technology enters into

"traditional medical device" space, FDA regulates it as a medical device. This includes, for example, new types of imaging analysis software (like the Image Analysis Software developed by Fraunhofer for the OraMod project), phone-based controllers for devices such as infusion, pumps, glucose meters, and physiological monitors, extending the range of and data provided by remote monitoring systems.

On October 12, 2014, FDA finalized its "Content of Premarket Submissions for Management of cybersecurity in Medical Devices". FDA expects that manufacturers will develop cybersecurity controls to assure medical device cybersecurity and maintain medical device functionality and safety. This needs to occur during the device design phase, as part of defining design inputs.

Regarding Clinical Decision Support software (as the Image analysis software by Fraunhofer is), FDA has been promising further guidance on this topic. Sophisticated algorithms based on statistical analysis of large datasets, potentially incorporating machine learning, that make predictions about the likelihood of a particular disease or outcome, are considered as medical devices.

Useful references are the following ones:

Mobile Medical App Guidance:
http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm263366.pdf

Guidance on software in premarket submissions:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf

Cybersecurity Guidance:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM356190.pdf

Wireless Guidance:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077272.pdf

In the document named "*US - general principles of software validation"* issued by FDA in 2002, there is a guidance regarding the general principles for medical software validation. The guidance also includes references to the parts of the Code of Federal Regulations (CFR) that have to be considered. It outlines general validation principles that the FDA considers to be applicable to the validation of medical device software or the validation of software used to design, develop, or manufacture medical devices.

This guidance describes how certain provisions of the medical device Quality System regulation apply to software and the agency's current approach to evaluating a software validation system. For example, this document lists elements that are acceptable to the FDA for the validation of software; however, it does not list all the activities and tasks that must, in all instances, be done to comply with the law. The scope of this guidance is somewhat broader than the scope of validation in the strictest definition of that term. Planning, verification, testing, traceability, configuration management, and many other aspects of good software engineering discussed in this guidance are important activities that all together help to support a final conclusion that software is validated. This guidance recommends an integration of software life cycle management and risk management activities. Based on the intended use and the

safety risk associated with the software to be developed, the software developer should determine the specific approach, the combination of techniques to be used, and the level of effort to be applied. While this guidance does not recommend any specific life cycle model or any specific technique or method, it does recommend that software validation and verification activities be conducted throughout the entire software life cycle.

When the software is developed by someone other than the device manufacturer (e.g., off-the-shelf software), the software developer may not be directly responsible for compliance with FDA regulations. In that case, the party with regulatory responsibility (i.e., the device manufacturer) needs to assess the adequacy of the off-the-shelf software developer's activities and determine what additional efforts are needed to establish that the software is validated for the device manufacturer's intended use.

This guidance applies to:

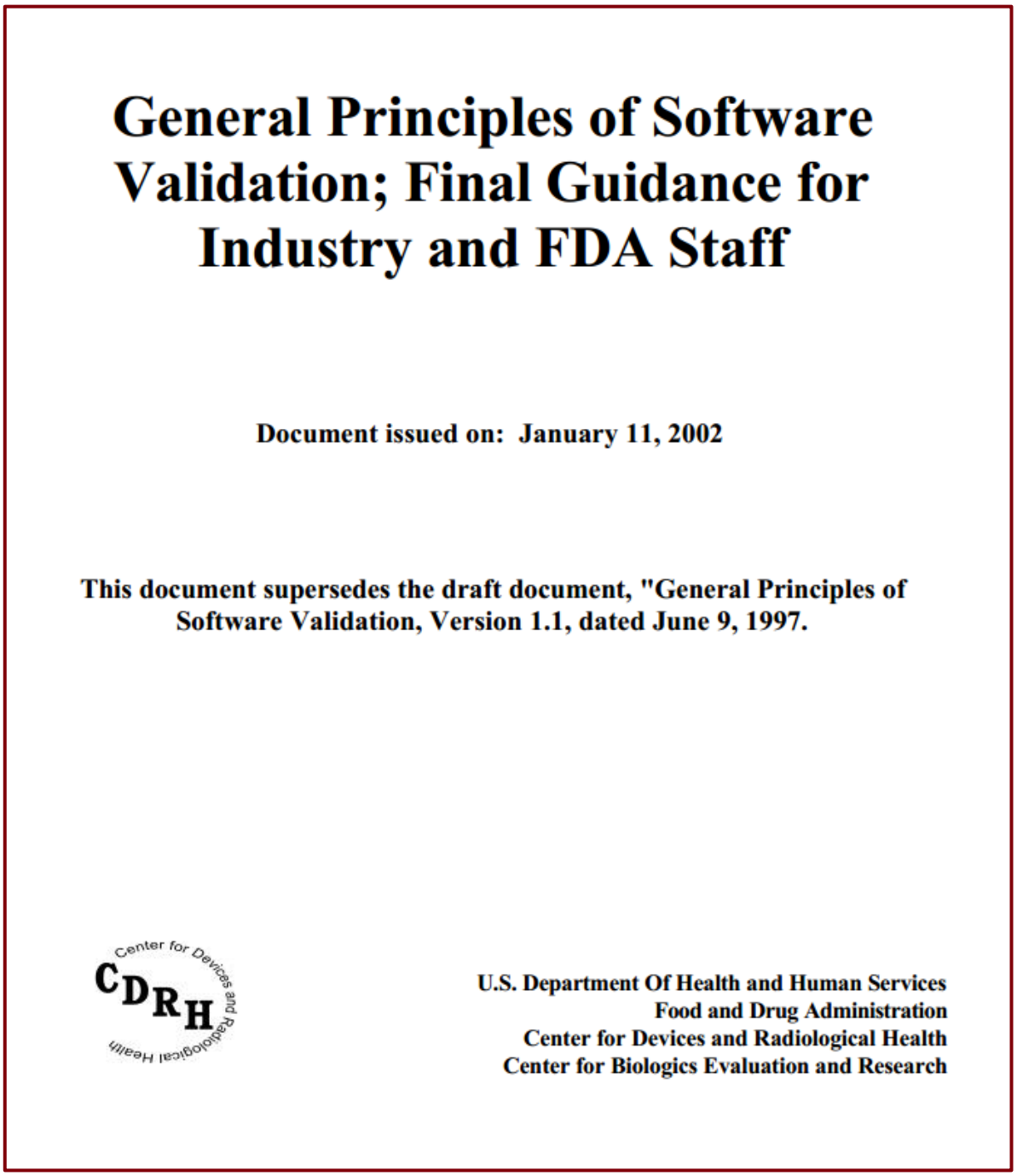
- Software used as a component, part, or accessory of a medical device;
- Software that is itself a medical device (e.g., blood establishment software);
- Software used in the production of a device (e.g., programmable logic controllers in manufacturing equipment); and
- Software used in implementation of the device manufacturer's quality system (e.g., software that records and maintains the device history record).

This document is based on generally recognized software validation principles and, therefore, can be applied to any software. For FDA purposes, this guidance applies to any software related to a regulated medical device, as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) and by current FDA software and regulatory policy.

Software verification provides objective evidence that the design outputs of a particular phase of the software development life cycle meet all the specified requirements for that phase. Software verification looks for consistency, completeness, and correctness of the software and its supporting documentation, as it is being developed, and provides support for a subsequent conclusion that software is validated. Software testing is one of many verification activities intended to confirm that software development output meets its input requirements. Other verification activities include various static and dynamic analyses, code and document inspections, walkthroughs, and other techniques.

Software validation is a part of the design validation for a finished device, but is not separately defined in the Quality System regulation. For purposes of this guidance, FDA considers software validation to be "confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled." In practice, software validation activities may occur both during, as well as at the end of the software development life cycle to ensure that all requirements have been fulfilled. Since software is usually part of a larger hardware system, the validation of software typically includes evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements. A conclusion that software is validated is highly dependent upon comprehensive software testing, inspections, analyses, and other verification tasks performed at each stage of the software development life cycle. Testing of device software functionality in a simulated use environment, and user site testing are typically included as components of an overall design validation program for a software automated device.

Software validation is a critical tool used to assure the quality of device software and software automated operations. Software validation can increase the usability and reliability of the device, resulting in decreased failure rates, fewer recalls and corrective actions, less risk to patients and users, and reduced liability to device manufacturers. Software validation can also reduce long-term costs by making it easier and less costly to reliably modify software and revalidate software changes. Software maintenance can represent a very large percentage of the total cost of software over its entire life cycle. An established comprehensive software validation process helps to reduce the long-term cost of software, by reducing the cost of validation for each subsequent release of the software.



General Principles of Software Validation; Final Guidance for Industry and FDA Staff

Document issued on: January 11, 2002

This document supersedes the draft document, "General Principles of Software Validation, Version 1.1, dated June 9, 1997.

Center for Devices and Radiological Health
CDRH

U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Figure 3.11: cover of the FDA guidance on software validation.

Further guidance on the specific application covered by the Image Analysis software can be found in a document called "*Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions*", issued by FDA in 2012 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm187294.pdf).

3.3 Product classification according to EU and US legislation

As already said in the previous paragraphs, we believe that the Image analysis software by Fraunhofer can be classified as a **Class IIa Medical Device** standalone software according to **EU legislation**. Thus, its future legal manufacturer will need an assessment by a Notified Body in order to obtain the CE mark.

While it can be classified as a **Class II Medical Device** Software according to **US legislation**, needing a **510(k) Premarket Notification** and **GMP compliance**. This classification has been done by analogy with two similar categories of Medical Device Softwares identified by FDA: "Lung Computed Tomography System, Computer-Aided Detection" (definition: "To assist radiologists in the review of multi-slice computed tomography (msct) exams of the chest and highlight potential nodules that the radiologist should review", http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=5047) and "Chest X-Ray Computer Aided Detection" (definition: "To assist radiologists in the review of chest radiographic images and highlight potential nodules that the radiologist should review", http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=5056), both with Regulation Number: 892.2050. Their intended use is very similar to the one of the Image Analysis Software by Fraunhofer, so we assume their classification can be translated to our case. Those Medical Device Softwares are subject to both General Controls and Specials Controls, being Class II devices; moreover, they are not exempt from 510(k) submission, so they need to undergo a 510(k) Premarket Notification, neither are they exempt from GMPs.

However, as already said, the classifications herein proposed are not in any way binding: it will be the future legal manufacturer's only responsibility to classify this product, based on the exact intended use he will write down, and to decide the consequent certification route to follow.

3.4 Timing and costs to obtain certification

In order to obtain the CE certification as a Class IIa Medical Device for a standalone software, the first main activity to be performed is a documental one, that is, preparing a proper Technical File. Software testing according to ISO 62304 (see par. 3.5 and 3.6) must be carried out as well. We estimate that around 3 months are needed to perform these activities, from the moment when the software has reached the necessary maturity and reliability (even if, ideally, the Technical File should be set up in the right way since the very beginning of the development process of a medical device).
Auditing by a Notified Body is then necessary, as already said; we estimate that around 3-5 months are necessary for this step.
Thus, a total time of around 6-8 months should be needed for certification of the Image analysis software as a Class IIa Medical Device in the EU.

Regarding the costs for CE marking of a Class IIa Medical Device, 3 months of personnel cost have to be considered to perform the abovementioned activities, of course.
Moreover, since a Notified Body has to be involved, there are Certification Fees charged by Notified Bodies to be considered. The fees charged by a Notified Body, which is in general a profit-driven organization in the private sector, vary from Notified Body to Notified Body, from country to country. Last, there are Official Fees charged by governmental EEA Competent Authorities, which are in general non-profit governmental agencies in the public sector; they normally charge fees for the processing and administration of the registration/notification of MDs/IVDs. The procedures and official fees vary from Member State to Member State, but typically are just in the range of 100-500 €. We estimate all these fees, including especially the ones charged by the Notified Body, to be in the range of 12000-24000 € for a Class IIa Medical Device.

A proper Technical File and a proper software testing need to be done also for obtaining FDA clearance to market a Class II Medical Device in the US. We can estimate around 3 months here as well, without the need for re-doing the activities if one has already performed them for CE marking.
Moreover, in the US one has to consider also the timing needed for FDA review of the 510(k) Premarket Notification submission. FDA typically reviews the 510(k)s in a 90-day timeline. After a positive answer by FDA, the medical device can be then put into US market.
So, the total time for certification of a Class II Medical Device in the US can be estimated at around 6 months.

Regarding the costs in the US, besides the same personnel cost as for the EU scenario, there are some fees to be paid. When submitting a 510(k) Premarket Notification, the standard fee to be paid for the FDA review is USD 5228 in 2016. All types of 510(k)s (Traditional, Abbreviated, and Special) are subject to this fee. If the legal manufacturer is a “small business”, defined as a business “having no more than 500 employees, including affiliates”, it can pay the small business fee, which is 50 % of the standard fee (USD 2614 in 2016). Moreover, owners or operators of places of business (also called establishments or facilities) that are involved in the production and distribution of medical devices intended for use in the US are required to register annually with the FDA. This process is known as establishment registration. The annual establishment registration fee for 2016 is USD 3845. There are no waivers or reductions for small establishments, businesses, or groups: all establishments must pay this establishment registration fee.

3.5 List of applicable international standards

The medical software certification affects the software life cycle, its performances, the analysis of risks connected to its use, etc. One way to comply with the essential requirements of the regulations is to follow harmonized standards. If one fulfills a requirement in a harmonized standard, it is then assumed that the corresponding requirement is fulfilled in the European directive and in the corresponding US regulations. The harmonized standards are excellent and useful tools for demonstrating conformity with the requirements in the medical device directives.

Standards for software, manufacturing of IT systems and installation of IT networks have been developed. Some of these consensus documents are described in this paragraph with emphasis on

purpose, scope and for whom they are aimed. The following is the list of applicable international standards for the Image analysis software developed by Fraunhofer Institute.

ISO 13485:2012 : Medical devices – Quality management systems – Requirements for regulatory purposes

The standard specifies requirements for a quality management system where the organization needs to demonstrate the ability to provide medical devices and related services to continually satisfy customer demands and regulatory requirements applicable for medical devices and related services. The primary goal of ISO 13485:2012 is to facilitate the harmonization of the legal requirements on quality management systems for medical devices. As a result, it includes a number of specific requirements for medical devices and excludes some of the requirements in ISO 9001 that are not applicable. All requirements in ISO 13485:2012 are applicable to organizations that provide medical devices, irrespectively of organizational structure or size. The standard covers manufacturing, design, final quality control and final testing. Documentation requirements, management responsibility, resource management, product realization, measurement, analysis and improvement are included.

ISO 27799:2008 : Health informatics – Information security management in health using ISO/IEC 27002

The standard defines guidance to support interpretation and application of ISO/IEC 27002 (*Information technology – Security techniques – Code of practice for information security management*) and is a complement to that standard. The specified set of detailed security measures in the standard is intended to aid health care providers to ensure an appropriate security level to sustain confidentiality, accuracy and accessibility for personal information within health care.

ISO 14971:2012 : Medical devices – Application of risk management to medical devices

ISO 14971 is primarily aimed for manufacturers of medical devices that need to comply with the essential requirements in the Directive 93/42/EEC on medical devices. This standard describes a process for management and mitigation of risks associated with development and monitoring of medical devices. ISO 14971 is helpful for the manufacturer to analyze, assess and evaluate any risks related to their products, and to mitigate those risks as well as monitoring the efficiency of the mitigation measures. The standard describes different processes to manage risks, mainly for the patient, but also for operators, other persons, other equipment and environment. It is important that the risk assessment concept is also understood by health care providers in order to justify various measures for patients and the public. The decision to use a medical device for a certain clinical procedure requires that any residual risks, as described by the manufacturer in the instructions for use, must be weighed against the expected benefits for a procedure in each individual case. The requirements in this standard apply to all phases in the life cycle of a medical device and also apply to risk management of IVD medical devices. The standard does not require that the manufacturer has a functional quality management system implemented. Risk management can on the other hand be integrated in a quality management system.

ISO/TR 80002-1:2009 : Medical device software – Guidance on the application of ISO 14971 to medical device software

This is a technical report that covers manufacturers' risk management and software development when software is part of a medical device or a system and describes how to apply ISO 14971 (see above) together with the IEC 62304 standard (see below). The report gives a good description in quite a simple way, of how a software designer of medical devices can adopt a proactive instead of a reactive approach to mitigate problems.

EN 62304:2007 : Medical device software – Software life cycle processes

This standard applies for both manufacturers and users. It demonstrates a systematic approach for design and maintenance of medical device software. It defines the life cycle requirements for medical device software. The set of processes, activities, and tasks described in this standard establishes a common framework for medical device software life cycle processes. It applies to the development and maintenance of medical device software when software is itself a medical device or when software is an embedded or integral part of the final medical device. This standard does not cover validation and final release of the medical device, even when the medical device consists entirely of software.

EN 80001-1 : Application of risk management for IT-networks incorporating medical devices

Medical devices are often part of IT networks to achieve desired performance (e.g. interoperability). This standard is typically aimed for health care providers and is intended to be used as guide when a health care provider has acquired a medical device and plans to implement it in an IT network. The standard defines roles, areas of responsibility and activities that are essential to risk management of IT networks that include medical devices and deals with safety, efficiency, and data and system security. The standard is applicable for all parts in the life cycle of an IT network with medical devices. The risk analysis has clear references to ISO 14971 and also defines a medical IT network which is helpful for how to determine and delimitate the application. Hospitals that are going to apply the standard, and collaborate with vendors that are aware of the content, can provide a safer network with the identified and communicated residual risks. For medical devices with software connected to a network, this allows for the intended use to be fulfilled in a safer way.

EN 62366:2008 : Medical devices – Application of usability engineering to medical devices

This standard describes a process for a manufacturer to analyze, specify, design, verify and validate the usability, since this is closely related to the safe use of a medical device. It is a process standard intended to evaluate and mitigate risks from problems arising at correct use and foreseeable use error of a medical device, i.e. normal use. It is also useful for identification, but not for evaluation or mitigation, of risks due to abnormal use.

3.6 Software development: compliance with IEC 62304 standard

The international standard IEC 62304 "*Medical device software - Software life cycle processes*" specifies life cycle requirements for the development of medical software and software within medical devices. It can be used as a benchmark to comply with regulatory requirements from both the EU and US markets. This standard helps to monitor the software engineering processes and methods used to develop medical software/firmware, in order to ensure quality. Quality here means that the software/firmware works as expected, thus ensuring safety. Establishing the safety and effectiveness of a medical device containing software, or being a software itself (as in this case), requires knowledge of what the software is intended to do and demonstration that the use of the software fulfills those intentions without causing any unacceptable risks.

This standard provides a framework of life cycle processes with activities and tasks necessary for the safe design and maintenance of medical device software. This standard provides requirements for each life cycle process. Each life cycle process is further divided into a set of activities, with most activities further divided into a set of tasks.

As a basic foundation, it is assumed that medical device software is developed and maintained within a quality management system and a risk management system. The risk management process is already very well addressed by the International Standard ISO 14971 (see par. 3.5 and 4.10).

The IEC 62304, as every standard, explains what has to be done, but now how to do it. Moreover, a standard does not give one a direct access to the market (as a norm would do instead), but increases the possibilities of doing it.
It is based on software engineering principles, establishing that a quality software development may sequentially include:

1. Feasibility analysis:
   - User Requirements Document (URD): the feasibility analysis starts with the preparation of this document. Its aim is to define what the system (not necessarily only the software) has to do. The use cases are defined here, that is, all the possible interactions between the system and external actors. The definition of User Requirements can come from a customer, or be performed internally by the manufacturer.
   - Project plan definition.
   - Verification and validation plan definition.
   - Risk management analysis has to be started in this phase.
2. Design: meaning both architectural and detailed design, with static and/or dynamic modelling.
3. Implementation.
4. Verification/validation.
5. Maintenance: a software maintenance plan has to be established, which shall address procedures for:
   - Receiving,
   - Documenting,
   - Evaluating,
   - Resolving, and
   - Tracking

   any feedback arising after release of the software.

Some other processes are transversal to the above-mentioned sequential phases, in particular:

a. Risk analysis: a Risk management file shall be created, complying with ISO 14971 standard "*Medical devices - Application of risk management to medical devices".* For each potential cause where the software contributes to a hazardous situation documented in the risk management file, the manufacturer shall define and document risk control measures. Further details will be given at par. 4.10.

b. Requirements traceability: a method has to be established in order to give evidence that:
   - All the items specified in the URD document have been implemented;
   - All the items specified in the URD document have been tested;
   - All the highlighted risks have been correctly mitigated;
   - All the software mitigation measures have been correctly implemented;
   - All the feedbacks requiring modification have been correctly evaluated;
   - …

   That is, all the inputs provided have been considered and analyzed.

3.7 Performance evaluation

A clinical evaluation in accordance with Annex X of Directive 93/42/EEC must be conducted for all medical devices, as already said at par. 3.2.1.

3.8 Risk analysis: compliance with ISO 14971 standard

A risk analysis has to be performed for a medical device, in accordance with ISO 14971-2012: "*Medical devices – Application of risk management to medical devices*" (see par. 3.5). All the questions regarding the Device Analysis for Safety (DAS) have to be answered, according to Annex C ("Questions that can be used to identify medical device characteristics that could impact on safety") and Annex H ("Guidance on risk management for in vitro diagnostic medical devices") of the ISO 14971 standard.

A complete example is given at par. 4.10, where a detailed risk analysis for the "Q3-Plus OraMod qRT-PCR assay" is shown.

4 Certification roadmap for the qRT-PCR system

4.1 Definition of the intended use

The "Q3-Plus OraMod qRT-PCR assay" is intended for the *in vitro* detection and relative quantification of 12 target human messenger RNAs (mRNAs) in clinical specimens, including tissue biopsies and fresh frozen Oral Squamous Cell Carcinoma (OSCC) tumor samples. The test is intended to be used on the Q3-Plus instrument using the Q3-Plus OraMod Software. The assay utilizes a real-time, quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR) for the amplification of 12 target mRNAs plus 1 reference mRNA recovered from clinical specimens, and fluorogenic target-specific hybridization for the detection and relative quantification of the amplified mRNAs.

The "Q3-Plus OraMod qRT-PCR assay" is an *in vitro* diagnostic test for the detection and relative quantification of 12 target mRNAs as an aid to prognosis in the evaluation of patients with OSCC.

The assay is intended to be used in conjunction with the OraMod system: the assay results are for use as part of a multi-test algorithm being the core of the OraMod system, which calculates the probability of patient survival, OSCC recurrence, and OSCC N-staging.

Assay results are not intended to be used as the sole basis for patient management decisions.

The "Q3-Plus OraMod qRT-PCR assay" is intended for use by trained laboratory personnel who are proficient in performing qRT-PCR assays.

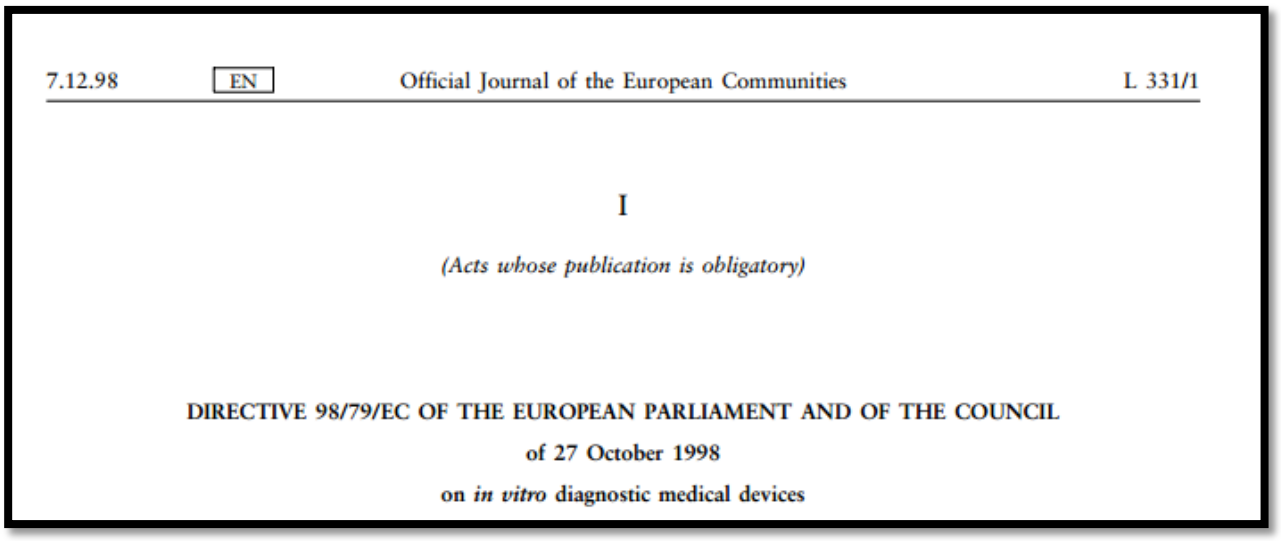
The specimen preparation must be performed according to the workflow procedures described in the package insert.

4.2 The regulatory context

4.2.1 EU regulations

The "Q3-Plus OraMod qRT-PCR assay" is an ***In Vitro* Diagnostic Medical Device (IVD)**.

Directive 98/79/EC of the European Parliament and of the Council on IVD Medical Devices (IVDD) provides the current EU regulatory framework for IVDs. It establishes minimum requirements that are binding on all EU Member States and must be included in the respective national laws to ensure free trade of all IVD Medical Devices under its scope, while supporting the highest level of protection of human health and safety. The CE Marking for IVDs is a legally binding statement by the manufacturer that their product has met all the requirements of the IVD Directive (IVDD 98/79/EC).



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(Acts whose publication is obligatory)

DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 27 October 1998

on *in vitro* diagnostic medical devices

Figure 4.1: cover of the 98/79/EC Directive on In Vitro Diagnostic Medical Devices (IVDD).

An IVD Medical Device is defined in article 1.2b of Directive 98/79/EC as "any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information: concerning a 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 IVD 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 IVD medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination".

From this definition it follows that in order to fall within the definition of an IVD medical device, the product must also meet the definition of a medical device.

A Notified Body is a third party independent certification organization which the competent authority has designated to carry out conformity assessment procedures according to a Directive. Contrary to medical devices, the majority of IVDs do not require the intervention of a Notified Body in the conformity assessment process. However, for some IVDs (the correct performance of which is perceived to be essential to health), involvement of a Notified Body is required. Manufacturers are free to apply to any designated Notified Body in the EU to carry out the desired conformity assessment procedure, regardless of which Member State that Notified Body is designated in. Figure 4.2 lists the Notified Bodies in the EU for Directive 98/79/EC:

Body type ▲	Name ▲	Country
NB 0408	TÜV AUSTRIA SERVICES GMBH	Austria
NB 1023	INSTITUT PRO TESTOVÁNI A CERTIFIKACI, a. s.	Czech Republic
NB 0543	Presafe Denmark A/S	Denmark
NB 0537	VTT Expert Services Oy	Finland
NB 0459	Laboratoire national d'essais / G-MED	France
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0535	BSI Group Deutschland GmbH	Germany
NB 1011	Országos Gógyszerészeti és Élelmezés-egészségügyi Intézet Eszközminősítő és Kórháztechnikai Igazgatóság (National Institute of Pharmacy and Nutrition)	Hungary
NB 1979	SGS Hungária Minoségellenorzo, Kereskedelmi és Szolgáltató Kft.	Hungary
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 0344	DEKRA Certification B.V.	Netherlands
NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland
NB 1293	EVPU a.s.	Slovakia
NB 2265	3EC International a.s.	Slovakia
NB 0318	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS	Spain
NB 1783	TURKISH STANDARDS INSTITUTION (TSE)	Turkey
NB 0086	BSI	United Kingdom
NB 0088	LLOYD'S REGISTER QUALITY ASSURANCE LTD (0088)	United Kingdom
NB 0120	SGS United Kingdom Limited	United Kingdom
NB 0843	UL INTERNATIONAL (UK) LTD	United Kingdom

Figure 4.2: the Notified Bodies in the EU for Directive 98/79/EC.

The IVD Directive (98/79/EC) groups IVDs into four categories (Figure 4.3). These categories are, in order of increasing perceived risk:

1. General/Other IVDs: all IVDs other than those covered by Annex II of IVDD and IVDs for self-testing;
2. IVDs for Self-Testing: devices intended by the manufacturer to be able to be used by lay persons in a home environment (for example devices for pregnancy and cholesterol home tests), excluding self-test devices covered in Annex II;
3. IVDs in Annex II List B of the Directive: which, amongst others, includes reagents and products for determination of some blood groups (anti-Duffy and anti-Kidd), as well as for detection of rubella, toxoplasmosis, cytomegalovirus, chlamydia, and devices for self-diagnosis of blood sugar;
4. IVDs in Annex II List A of the Directive: which includes reagents and products for determination of some blood groups (ABO system, rhesus, anti-Kell), as well as for detection of HIV 1 and 2, HTLV I and II, and hepatitis B, C and D.

ANNEX II

LIST OF DEVICES REFERRED TO IN ARTICLE 9(2) AND (3)

List A

- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell,
- reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

List B

- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd,
- reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies,
- reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis,
- reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria,
- reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia,
- reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B,
- reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA,
- reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21,
- the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.

Figure 4.3: classification of IVDs in Directive 98/79/EC.

A Notified Body is required for CE-IVD certification of IVDs for Self-Testing, IVDs in Annex II List B, and IVDs in Annex II List A. No Notified Body is requested for certification of General IVDs (Figure 4.4).

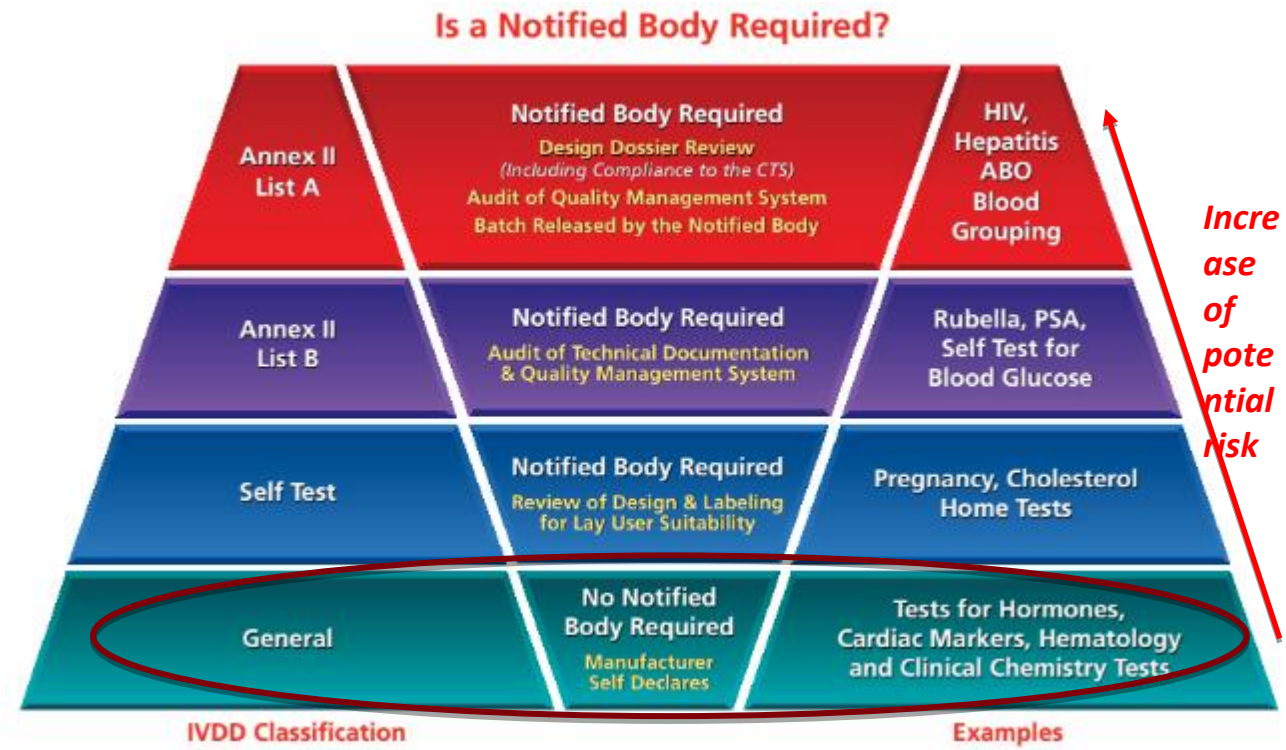


Figure 4.4: requirement for a Notified Body, depending on IVD classification.

In Annex I, the IVD Directive includes the essential requirements with which the IVDs must comply before being placed on the market. The essential requirements aim to ensure that the products do not compromise the health and safety of patients and users, and are designed and manufactured to achieve the performance specified by the manufacturer for the stated medical purpose. Not all the essential requirements will apply to all devices and it is up to the manufacturer of the device to assess which are appropriate for his particular product. Technical standards that have been harmonized under the European IVD Directive may be used to show conformity with the relevant essential requirements. Compliance with an appropriate harmonized European standard gives a presumption of conformity with the essential requirements to which the standard relates. The use of standards is not mandatory, although some European Directives make direct reference to them and therefore their application becomes obligatory.

Both the Medical Devices Directive (93/42/EEC) and the *In Vitro* Diagnostic Medical Device Directive (98/79/EC) require manufacturers or their authorized representatives or others placing medical device(s) on the European Economic Area (EEA) market, to provide certain information to the Competent Authorities in the EEA Member State where they have a registered place of business. These requirements have been transposed into national laws of the EEA Member States.

4.2.1.1 The conformity assessment process

In general terms, a manufacturer wishing to place their products on the market under the CE IVD Directive (IVDD 98/79/EC) must:

1. Determine the classification of the IVD device in accordance with Annex II of the Directive;
2. Ensure that the device meets the essential requirements specified in Annex I of the Directive;
3. Follow the appropriate conformity assessment procedure;
4. If appropriate (depending on the risk category of the device), ensure that an independent certification body (the Notified Body) is involved in the conformity assessment procedure.

Table 4.1 summarizes the conformity assessment process according to the CE IVD Directive.

The conformity assessment procedures include obligations with regard to experience gained in the post-production phase, including implementation of any necessary corrective actions. Manufacturers must maintain a vigilance system to notify the regulatory authorities of incidents that might lead to or might have led to death or serious health consequences, or to a systematic recall of a device.

Step # 1
Determine the classification of the IVD device in accordance with the European IVD Medical Devices Directive (IVDD 98/79/EC). The four classes are: General IVD, Self Test IVD, Annex II List B IVD, Annex II List A IVD.

Step # 2
For all devices except General IVDs, implement a Quality Management System (QMS) in accordance with Annex IV, V, VI or VII of the IVDD. Most companies apply the ISO 13485 standard to achieve QMS compliance.

Step # 3
Prepare a Technical File that provides detailed information demonstrating compliance with the IVD Directive 98/79/EC. The technical file must include information such as the device's design, intended use, risk assessment and route to conformity with requirements. Once completed, it must be made available to Competent Authorities upon request.

Step # 4
Appoint an Authorized Representative (EC REP) located in Europe and qualified to handle regulatory issues. Place EC REP name and address on Instructions for Use and packaging wherever sold in Europe.

Step # 5
For all devices except General IVDs, QMS and Technical File must be audited by a European Notified Body. A CE marking certificate for the device will be issued upon successful completion of the Notified Body audit.

Step # 6
Prepare a Declaration of Conformity, a legally binding document prepared by the manufacturer stating that your IVD is in compliance with the applicable Directive.

Step # 7
The CE mark must be affixed in a visible, legible and indelible form on the device (where practicable and appropriate) and on the instructions for use. It must also appear on the sales packaging. The relevant notified body number (where one has been used) should accompany the CE marking.

Step # 8
The IVD device must be registered with the European Competent Authority (Ministry of Health) where the Authorized Representative is based. Additional notifications to other countries may be required.

Table 4.1: conformity assessment process according to the CE IVD Directive.

With the intended use proposed in the OraMod project (par. 4.1), the "Q3-Plus OraMod qRT-PCR assay" can be classified as a **General IVD device**, since the specific application is neither a Self-Test, nor is included in Annex II. Thus, no Notified Body has to be involved in the conformity assessment procedure, and the legal manufacturer will be able to proceed through a self-certification route in which he self-affixes the CE Mark as a legally binding attestation. The conformity assessment process for General IVDs is shown in Figure 4.5:

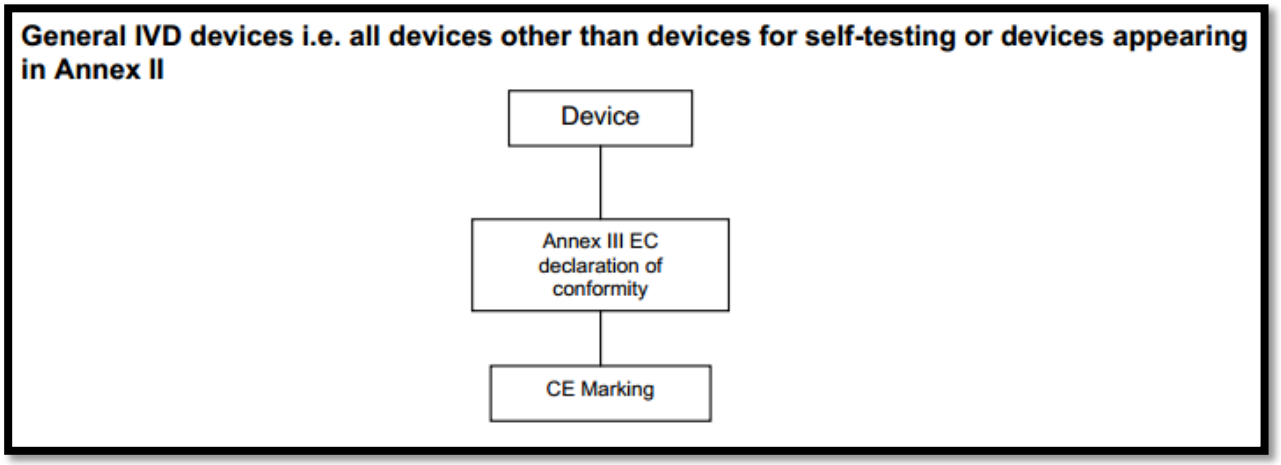


Figure 4.5: conformity assessment process for the "Q3-Plus OraMod qRT-PCR assay".

4.2.1.2 Proposal of a new European Regulation on IVDs

Following a public consultation in summer 2010 and publication of its results in February 2011, a proposal for a harmonized European "Regulation on In Vitro Diagnostic Medical Devices" was drawn up by the commission and presented on September 26, 2012. The new Regulation taken into consideration will introduce significant changes. The old IVD Directive will be replaced by an EU Regulation which will come into effect directly in all EU Member States, without requiring transposition into national law.

The classification system for IVDs will be changed significantly and will be based on classification rules, instead of the current positive lists. That is, in the future IVDs will be divided into four classes of risk: A (lowest risk), B, C and D (highest risk). Even for class A devices, verification of the measuring function, sterilization process or design of near-patient testing by a Notified Body will be mandatory as far as

applicable. This basically means that many devices will be in a higher risk class than now, and thus they will be subject to assessment or more in-depth assessment by a Notified Body in the future. To clarify the impact of this change, one has to consider that while at present only 10-20% of IVD products require an assessment by a Notified Body, with the new IVD Regulation only 10-20% of IVD products will NOT require a Notified Body assessment: all the remaining 80-90% of IVD devices will require a Notified Body. In the case of new applications for conformity assessment of high-risk devices, the proposal introduces an obligation for Notified Bodies to notify an expert committee. The expert committee will have the power to request the Notified Body to submit a preliminary assessment. Furthermore, companion diagnostics will be included into the regulation and special requirements will be defined for near-patient (point of care) testing. Compared to the current situation, the scope of applications will be extended on those produced and used within one health institution, if they are classified into the highest risk class (class D).

Thus, it is very likely that IVD assays similar to the "Q3-Plus OraMod qRT-PCR assay" will require an assessment by a Notified Body in the future. However, some years will pass before the adoption of this new IVD Regulation; moreover, after that there will be a transition period of 3 years during which the present Directive will be still valid. Therefore, we consider that the "Q3-Plus OraMod qRT-PCR assay" will have to comply with the already described requirements of the present IVD Directive 98/79/EC.

4.2.2 US regulations

The reference to IVDs in the US Code of Federal Regulations (CFR) is 21 CFR 809.3. According to the FDA, "IVD products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its *sequelae*. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are (medical) devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), and may also be biological products subject to section 351 of the Public Health Service Act".
Like other medical devices, IVDs are subject to premarket and postmarket controls.

FDA classifies IVD products into Class I, II, or III, as for medical devices (see par. 3.2.2), based on their risks and the level of regulatory control that is necessary to assure safety and effectiveness. Class I devices generally pose the lowest risk to the patient and/or user, and Class III devices pose the highest risk.

The Code of Federal Regulations lists the classification of existing IVDs in 21 CFR 862, 21 CFR 864, and 21 CFR 866.

IVDs, and all other medical devices, are subject to General Controls. General Controls are the basic provisions of the May 28, 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act, that provide the FDA with the means of regulating devices to ensure their safety and effectiveness. The General Controls in the Amendments apply to all medical devices, including IVDs. They include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices.

The Good Manufacturing Practices (GMPs) requirements are part of the Quality System Regulation. They require that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution in the United States. The QS Regulation is contained in 21 CFR 820.

IVD products have special labeling requirements under 21 CFR 809, Subpart B, In Vitro Diagnostic Products for Human Use. Before a manufacturer obtains clearance or approval for an IVD product, they must label the product in accordance with labeling regulations.

The Medical Device Reporting (MDR) regulations require manufacturers who have received complaints of device malfunctions, serious injuries or deaths associated with medical devices to notify FDA of the incident. MDR regulations require User Facilities (e.g. hospitals, laboratories) to report suspected medical device related deaths to both the FDA and the manufacturers. User facilities must report medical device-related serious injuries to the manufacturer.

4.2.2.1 The "Pre-Submission" Process for IVDs

A Pre-Submission Process includes a formal written request from an applicant for feedback from the FDA, which is provided in the form of a formal written response or, if the manufacture chooses, a meeting or teleconference in which the feedback is documented in meeting minutes. A Pre-Submission meeting is a meeting or teleconference in which the FDA provides its substantive feedback on the Pre-Submission.

A Pre-Submission provides the opportunity for an applicant to obtain FDA's feedback prior to submission of an Investigational Device Exemption (IDE) or marketing application. The request must include specific questions regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements). A Pre-Submission is appropriate when FDA's feedback on specific questions is necessary to guide product development and/or application preparation.

The FDA encourages use of the Pre-Submission program under circumstances such as the following:

- The device involves new technology, a new intended use, or a new analyte and it will be helpful to familiarize the FDA with the novel features in advance of the submission;
- Assistance is needed in defining possible regulatory pathways;
- The studies involve complex data and/or statistical approaches;
- The predicate or reference method is unclear or uncertain; or
- The new device is a multiplex device capable of simultaneously testing a large number of analyses.

A sponsor should submit a Pre-Submission if they would like the FDA's thoughts on their studies or proposals prior to starting their studies. The potential benefits of submitting a Pre-Submission are:

- To begin a dialogue with FDA and promote greater understanding;
- To reduce the cost of research studies by focusing on the important information needed for FDA approval (or clearance) and eliminating unnecessary or burdensome studies; and
- To speed the review process for the future marketing application, since FDA will already be familiar with the device.

Pre-Submissions and meetings are strictly voluntary, and any comments or recommendations made in the review of protocols or during these meetings are not binding on the manufacturer or the Agency.

4.2.2.2 The Investigational Device Exemption (IDE)

An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data to support 510(k) submission or premarket approval. An IDE permits devices to be shipped lawfully for the purpose of conducting investigations, without complying with requirements of the Food, Drug, and Cosmetic Act that apply to devices in commercial distribution. Many IVDs are exempt from IDE requirements.

4.2.2.3 The Premarket Notification [510(k)]

Each person who wants to market in the US a Class I, II, and some III IVD devices intended for human use, for which a Premarket Approval (PMA) is not required, must submit a 510(k) to FDA unless the device is exempt from 510(k) requirements of the Federal Food, Drug, and Cosmetic Act. A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent (SE), to a legally marketed device that is not subject to premarket approval, called the "predicate device". A 510(k) must be submitted to FDA at least 90 days before marketing, unless the device is exempt from 510(k) requirements. FDA reviews 510(k) submissions in a 90-day timeline. If there are unaddressed scientific issues, the review scientists can ask for additional information and put the submission temporarily on hold. If FDA finds the information provided by the sponsor meets the standard of equivalency, the product is cleared for marketing in the United States. If FDA finds that there is no predicate for the device, or that the new device does not have equivalent performance to the identified predicate, then the device is found not substantially equivalent. There is no 510(k) form, but instead a format for the submission is described in 21 CFR 807.

Review of a 510(k) is based on the evaluation of the analytical performance characteristics of the new device compared to the predicate, including:

- Bias or inaccuracy of the new device;
- Imprecision of the new device; and
- Analytical specificity and sensitivity.

The types of studies required to demonstrate substantial equivalence include the following:

- In the majority of cases, analytical studies using clinical samples (sometimes supplemented by carefully selected artificial samples) will suffice.
- For some IVDs, the link between analytical performance and clinical performance is not well defined. In these circumstances, clinical information may be required.
- FDA rarely requires prospective clinical studies for IVDs, but regularly requests clinical samples with sufficient laboratory and/or clinical characterization to allow an assessment of the clinical validity of a new device. This is usually expressed in terms of clinical sensitivity and clinical specificity or agreement.

The "New 510(k) Paradigm" issued in 1998 presents device manufacturers with two new optional approaches for obtaining marketing clearance for devices subject to 510(k) requirements:

- "Special 510(k): Device Modification" option, for manufacturers who modify their own already legally-marketed device;
- "Abbreviated 510(k)" option when a guidance document exists, a Special Control has been established, or FDA has recognized a relevant consensus standard for the device.

A manufacturer considering either a special or abbreviated 510(k) should first consult 21 CFR 807.81(a)(3).

4.2.2.4 The Premarket Approval (PMA)

A PMA is an application submitted to FDA to request approval to market, or continue marketing, a class III medical device. PMA approval is based on scientific evidence providing a reasonable assurance that the device is safe and effective for its intended use or uses. For IVDs, there is a unique link between safety and effectiveness since the safety of the device is not generally related to contact between the device and patient. For IVD products, the safety of the device relates to the impact of the device's performance, and in particular on the impact of false negative and false positive results, on patient health. FDA reviews PMA submissions in a 180-day timeline. If there are unaddressed scientific issues, the review scientists can ask for additional information and put the submission temporarily on hold. If a product is the first of a kind, or if it presents unusual issues of safety and effectiveness, it is generally reviewed before it is approved by an advisory panel of outside experts. Approval of a PMA requires review of the manufacturing processes, an inspection of the manufacturing facility, a bioresearch monitoring audit of clinical data sites, as well as comprehensive review of the premarket data. If FDA finds that a product is safe and effective, it receives an official approval order for marketing in the United States. If FDA finds that a product is not safe and effective, it may be non-approved. A manufacturer considering a PMA should consult 21 CFR 814.

For most PMAs, sponsors identify surrogate endpoints and establish the device performance (clinical sensitivity and specificity or agreement) with relation to the identified endpoints in corollary studies using randomly collected clinical studies.

4.2.2.5 The De Novo Classification for IVD Devices

Prior to the FDA Modernization Act of 1997 (FDAMA), all devices on the market as of May 28, 1976 were classified according to their risk. Any device that was not classified was automatically assigned to Class III, requiring a premarket approval (PMA) application. A device could be moved out of Class III only through a cumbersome reclassification process. FDAMA amended Section 513(f) of the Act, to provide a new mechanism for classifying new Class III devices for which there is no predicate device. It allows the recipient of an NSE (not substantially equivalent) letter to request a risk-based classification determination to be made for the device. In some cases, this allows a manufacturer to use the De Novo process to submit a 510(k) for a new IVD that would otherwise have to get to market via the PMA process.

4.3 Product classification according to EU and US legislation

The "Q3-Plus OraMod qRT-PCR assay" can be classified as a **General IVD Device** according to the present **EU legislation**, as already said at par. 4.2.1.1. Thus, its legal manufacturer will be able to proceed with a self-declaration in order to obtain the CE-IVD mark, without any need for assessment by a Notified Body.

While we believe it can be classified as a **Class II IVD Device** according to **US regulation**, needing a **510(k) Premarket Notification** and **GMP compliance**. This classification has been done by analogy with a similar diagnostic kit, cleared by FDA in 2013, called "PROSIGNA™ BREAST CANCER PROGNOSTIC GENE SIGNATURE ASSAY" (manufacturer: Nanostring Technologies) (510(K) Number: K130010; Regulation Number: 866.6040, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K130010). It is a gene expression profiling test system for breast cancer tumor, to provide a risk assessment for distant recurrence of breast cancer. The result is indicated for use only as a prognostic marker by physicians along with a number of other factors to assess the risk of recurrence of breast cancer. This intended use is very similar to the one of the "Q3-Plus OraMod qRT-PCR Assay", so we assume its classification can be translated to our case. That assay is subject to both General Controls and Specials Controls, being a Class II device; moreover, it is not exempt from 510(k) submission, so it had to undergo a 510(k) Premarket Notification, neither is it exempt from GMPs.

However, as already said, the classifications herein proposed are not in any way binding: it will be the future legal manufacturer's only responsibility to classify this product, based on the exact intended use he will write down, and to decide the consequent certification route to undertake.

4.4 Timing and costs to obtain certification

In order to obtain the CE-IVD certification for the "Q3-Plus OraMod qRT-PCR assay", some activities have to be performed for the software part (already described at par. 3.4), that is, preparation of a proper Technical File and execution of software testing according to ISO 62304. Such activities can be estimated as requiring around 3 months, as already said.
Moreover, in this case some tests on the hardware part (the Q3-Plus instrument) are needed as well. These tests on the instrument serve essentially (in the specific case of Q3-Plus, due to its characteristics) to demonstrate its electrical safety, electromagnetic compatibility, and photobiological safety. Such tests should be preferably conducted by a third party being a Notified Body for the Directives of interest, that would also check the Technical File produced. These tests on the hardware are very similar to the ones already performed by ST for the CE certification of the Q3-Plus instrument as laboratory instrumentation for research only, which will be described more in detail at par. 4.6. Based on this experience, we estimate that around 3 months are needed to perform these tests.
Hence, we can consider around 6 months in total for the CE-IVD certification of a General IVD Device, as the "Q3-Plus OraMod qRT-PCR assay" is, where no Notified Body has to check all the documentation at the end and thus the manufacturer can proceed with a self-declaration after these 6 months.

Regarding the costs for CE-IVD marking of the "Q3-Plus OraMod qRT-PCR assay", General IVD Device, we calculate around 15000 € for execution of the tests on the hardware, consequent reporting, and revision of the technical documentation by a Notified Body, based on ST's previous experience.
Besides this cost, we must consider also the personnel cost for around 3 months of work.

The Technical File, software testing, and hardware tests at a Notified Body performed for CE-IVD certification can be exploited also for obtaining FDA clearance to market in the US. We can estimate around 6 months here as well, without the need for re-executing these activities.
Moreover, in the US one has to consider also the timing needed for FDA review of the 510(k) Premarket Notification submission, since the "Q3-Plus OraMod qRT-PCR assay" would be a Class II IVD device not exempt from 510(k) (par. 4.3). FDA typically reviews the 510(k)s in a 90-day timeline. After a positive answer by FDA, the IVD device can be then put into US market.
So, the total time for certification of the "Q3-Plus OraMod qRT-PCR assay" in the US can be estimated at around 9 months.

Regarding the costs in the US, besides the same costs as for the EU scenario (15000 € + 3 months of personnel cost), there are also some fees to be paid to FDA, as already said for the Image Analysis software (see par. 3.4). The standard fee to be paid for the FDA review of a 510(k) Premarket Notification is USD 5228 in 2016. If the legal manufacturer is a "small business", defined as a business "having no more than 500 employees, including affiliates", it can pay the small business fee, which is 50 % of the standard fee (USD 2614 in 2016). Moreover, owners or operators of places of business (also called establishments or facilities) that are involved in the production and distribution of IVD devices intended for use in the US are required to register annually with the FDA. This process is known as establishment registration, and the annual fee for this is USD 3845 in 2016. There are no waivers or reductions on this for small establishments, businesses, or groups.

4.5 List of applicable international standards

One way to comply with the essential requirements of the regulations is to follow harmonized standards. If one fulfills a requirement in a harmonized standard, it is then assumed that the corresponding requirement is fulfilled in the European directive and corresponding US regulations. The following is the list of applicable international standards for the qRT-PCR system developed by ST-Italy.

List of applicable standards from the International Organization for Standardization (ISO, www.iso.org):

For the manufacturer of the IVD product:

- **ISO 13485**: Medical devices - Quality management systems - Requirements for regulatory purposes.

For the IVD product:

- **ISO 14971**: Medical devices - Application of risk management to medical devices.
- **ISO 18113-1**: In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 1: Terms, definitions and general requirements.
- **ISO 18113-2**: In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 2: In vitro diagnostic reagents for professional use.
- **ISO 18113-3**: In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 3: In vitro diagnostic instruments for professional use.

- **ISO 15193**: In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for content and presentation of reference measurement procedures.
- **ISO 15194**: In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for certified reference materials and the content of supporting documentation.

List of applicable standards from the International Electrotechnical Commission (IEC, www.iec.ch):

For the instrument:

- **IEC 61010-1**: Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 1: General requirements.
- **IEC 61010-2-101**: Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment.
- **IEC 61010-2-081**: Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-081: Particular requirements for automatic and semi-automatic laboratory equipment for analysis and other purposes.
- **IEC 61326-1**: Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 1: General requirements.
- **IEC 61326-2-6**: Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 2-6: Particular requirements - In vitro diagnostic (IVD) medical equipment.
- **IEC 62471**: Photobiological safety of lamps and lamp systems.

For the software:

- **IEC 62304**: Medical device software - Software life cycle processes.

For the IVD product:

- **IEC 62366**: Medical devices - Application of usability engineering to medical devices.

4.6 Instrument development: compliance with safety and compatibility standards

The first step performed in the regulation of the qRT-PCR platform has been the EC Declaration of Conformity as laboratory instrumentation for research use only of the “Q3-Plus” qRT-PCR instrument.

The “Q3-Plus” qRT-PCR instrument is an instrument designed to be used specifically with the Q3 cartridge and the Q3 software, in order to develop Application-Specific Kits for *In Vitro* Diagnostics (IVD) based on real-time PCR. Figure 4.6 illustrates the system integration of qRT-PCR platform: the Q3-Plus qRT-PCR instrument, together with the Q3 application-specific cartridge and the Q3 application-specific software (like the OraMod-dedicated, closed software developed within this project, and described in D6.3 - *qRT-PCR and lab-on-chip*), is used to set up an application-specific CE IVD assay like the “Q3-Plus OraMod qRT-PCR assay”.

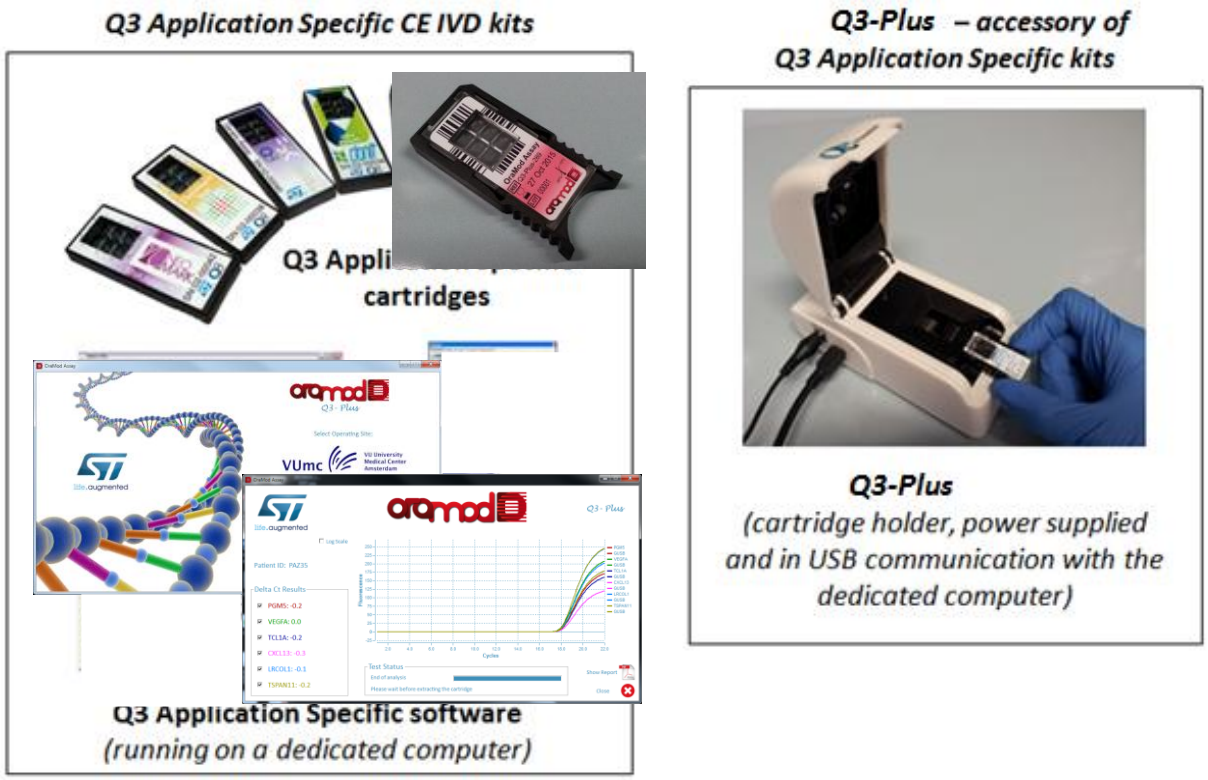


Figure 4.6: qRT-PCR platform integration: the qRT-PCR instrument (product name: "Q3-Plus") is an accessory of application-specific assays.

The Q3-Plus qRT-PCR instrument is a mechanical, optical and electrical instrument, designed to be used specifically with the Q3 cartridge and the Q3 software, and acting as holder of the cartridge, controller of the thermal process on the cartridge, optical fluorescent signals source and reader. The qRT-PCR instrument product configuration includes its power supply and its USB cable for computer connection.
In order to fulfill the above-mentioned functions, the qRT-PCR instrument is composed of dedicated mechanical, optical and electrical components.

The assembly of the mechanical components performs the following functions:

1. holding and alignment of the cartridge, respect to the optical module and the electronic components;
2. cooling by air flow the active area of the cartridge during the cooling phases of the thermal cycling procedure;
3. holding of the optical components and isolating them from external light exposure;
4. holding of the electrical components;
5. holding all the components of the qRT-PCR instrument in a single assembly, isolating them from the external environment, while leaving inlet and outlet openings for air flow and connections with the power supply and with the dedicated computer.

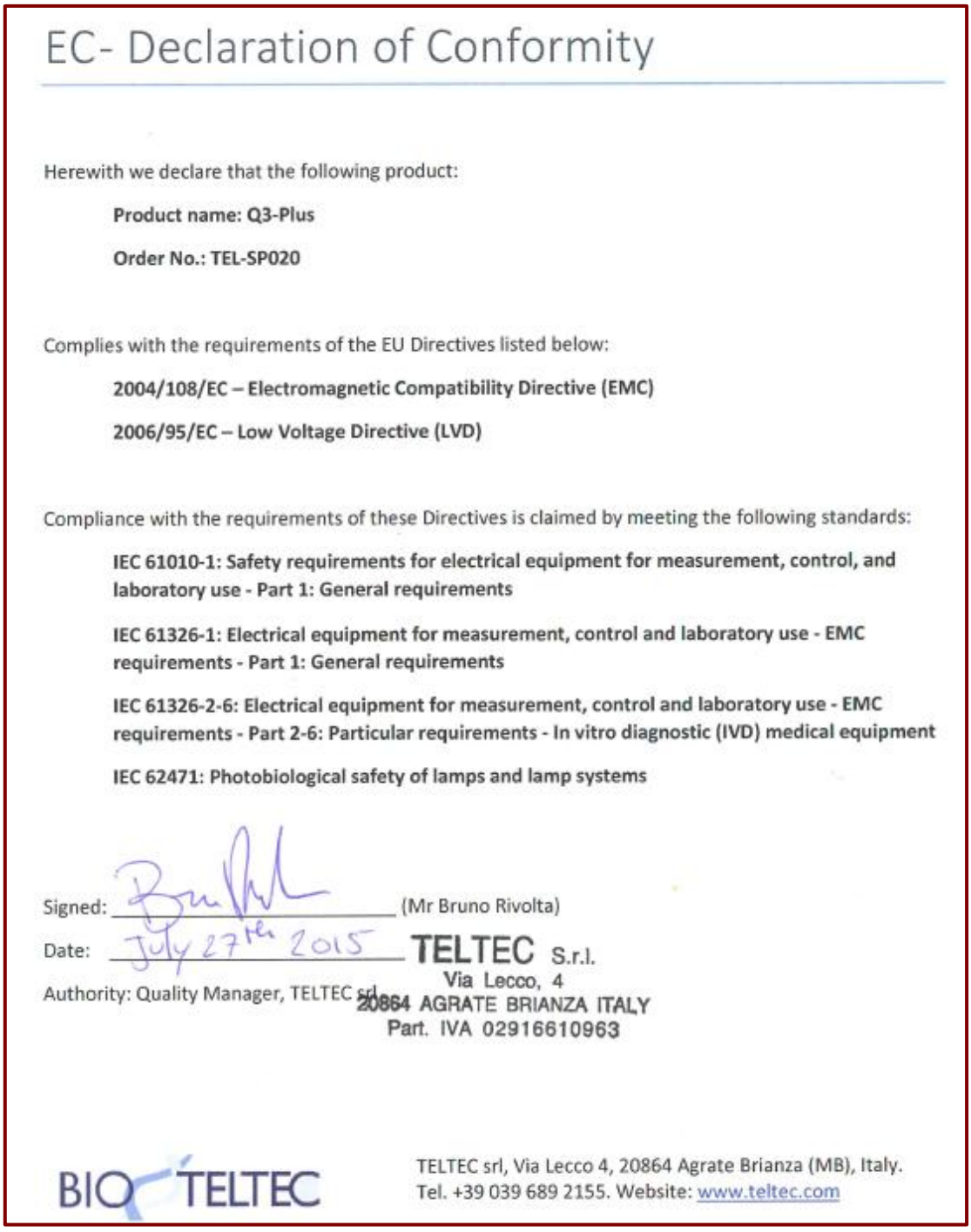
The assembly of the optical components performs the following functions:

1. providing light sources for optical excitations of the fluorophores in the cartridge;
2. providing light source filtering for selected light waves excitations of the fluorophores in the cartridge;
3. providing selected light waves filtering of the fluorophores emission signals;
4. acquiring the filtered fluorophores emission signals;
5. providing illumination to the bar code printed on the cartridge label;
6. reading the bar code on the cartridge label.

The assembly of the electrical components performs the following functions:

1. managing the power of the qRT-PCR instrument;
2. managing the thermal cycling in terms of chip heating and chip cooling;
3. receiving from Q3 software the parameters for thermal cycling process and for image acquisition process;
4. controlling the temperature of the chip;
5. managing the powering of the whole system and controlling the internal electronic connections;
6. performing the internal instrument calibration;
7. performing the cartridge calibration;
8. powering and managing the LED illumination system;
9. powering and managing the image acquisitions by CMOS image sensors;
10. sending to the Q3 software, running on a personal computer, the output of the thermal cycling, in terms of fluorescence values as functions of reaction time.

The first version of qRT-PCR instrument, designed by ST-Italy and manufactured by an ST's selected partner, has obtained the CE mark as laboratory instrumentation for research use only in April 2014. The product name registered by the manufacturer in the EC declaration of conformity is "Q3-Evo Reader". The second, updated version of **qRT-PCR instrument**, designed by ST-Italy and manufactured by an ST's selected partner, has obtained the **CE mark as laboratory instrumentation for research use only** in July 2015. The product name registered by the manufacturer in the EC declaration of conformity is "Q3-Plus" (Figure 4.7). The CE mark for research use only has been required in order to use the qRT-PCR instrument in all the clinical research settings (UNIPR, UDUS, and VUmc) involved in the OraMod project, for both the validation studies and the clinical studies. Moreover, this CE mark is a **fundamental pre-requisite for the future CE-IVD certification** of the "Q3-Plus OraMod qRT-PCR assay".



EC- Declaration of Conformity

Herewith we declare that the following product:

Product name: Q3-Plus

Order No.: TEL-SP020

Complies with the requirements of the EU Directives listed below:

2004/108/EC – Electromagnetic Compatibility Directive (EMC)

2006/95/EC – Low Voltage Directive (LVD)

Compliance with the requirements of these Directives is claimed by meeting the following standards:

IEC 61010-1: Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 1: General requirements

IEC 61326-1: Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 1: General requirements

IEC 61326-2-6: Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 2-6: Particular requirements - In vitro diagnostic (IVD) medical equipment

IEC 62471: Photobiological safety of lamps and lamp systems

Signed: _____ (Mr Bruno Rivolta)

Date: July 27th 2015

Authority: Quality Manager, TELTEC srl

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Figure 4.7: the EC - Declaration of Conformity for the "Q3-Plus" qRT-PCR instrument.

The qRT-PCR instrument complies with the requirements of the EU Directives listed below:

- 2004/108/EC – Electromagnetic Compatibility Directive (EMC)
- 2006/95/EC – Low Voltage Directive (LVD)

The compliance with the requirements of these Directives has been verified by meeting the following international standards:

- IEC 61010-1: Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 1: General requirements

- IEC 61326-1: Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 1: General requirements
- IEC 61326-2-6: Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 2-6: Particular requirements - In vitro diagnostic (IVD) medical equipment
- IEC 62471: Photobiological safety of lamps and lamp systems.

Compliance with the above-mentioned standards has been verified by the accredited laboratory IMQ (IMQ S.p.A. - Via Quintiliano 43, 20138 Milano, Italy; www.imq.it; Notified Body number: 0051). IMQ is Italy's most important Notified Body and a European leader in conformity assessments and laboratory tests for the electrical, electronic, gas and energy industries.

4.7 Cartridge development: compliance with quality standards

The Lab-on-chip cartridge is manufactured in accordance with ST's quality procedures, which guarantee a very high level of quality ad repeatability, typical of semiconductor industry. The cartridge has followed a maturity *iter* according to ST's internal standards, which the company applies to all of its products. When the cartridge has reached a sufficient level of maturity according to those standards (May 2014), a medium-scale industrial production has been put in place inside ST; involving ST sites in Agrate Brianza, Italy (silicon chip production) and Malta (cartridge assembly and final quality controls). Part of the production, and the whole process of assembly and final quality controls, have been occurring inside the above-mentioned ST's production sites and are continuously on-going. The plastic materials composing the cartridge are acquired from external companies specialized in injection molding for biomedical applications.

The cartridge is identified by the ST product code "RTPCR06D/GC".

4.8 Software development: compliance with IEC 62304 standard

For the development of both the firmware embedded inside the Q3-Plus instrument, and the OraMod-dedicated "closed" software running on PC, ST has been following the international standard IEC 62304 (see par. 3.6 and 4.5).

4.9 Performance evaluation

Directive 98/79/EC on IVD devices requires in Annex III, Annex IV, and Annex V, that the manufacturer provides evidence in his technical documentation that the IVD performs as claimed. Such evidence can be shown by data already available to the manufacturer, or by scientific literature, or by data originating from performance evaluation studies in a clinical or other appropriate environment, in accordance with the intended use. If a performance evaluation study is necessary and appropriate to support performance claims of the IVD, the European Standard EN 13612:2002 "*Performance evaluation of in vitro diagnostic medical devices*" describes how the manufacturer can fulfill his obligation to conduct a scientifically sound performance evaluation study. The evaluation plan is adapted to the nature of the IVD and its intended use, taking into account the various recommendations given in standards and scientific literature.

4.10 Risk analysis: compliance with ISO 14971 standard

A risk analysis has to be conducted in order to certify a medical device or and IVD device. ST has already conducted a preliminary risk analysis for the "Q3-Plus OraMod qRT-PCR assay", according to the requirements of the ISO 14971 standard (*Medical devices - Application of risk management to medical devices*). All the questions regarding the Device Analysis for Safety (DAS) have been answered, according to Annex C (Questions that can be used to identify medical device characteristics that could impact on safety) and Annex H (Guidance on risk management for in vitro diagnostic medical devices) of the ISO 14971 standard. Table 4.2 and table 4.3 show the checklists defined by these two annexes.

1. *What is the intended use and how is the medical device to be used?*
2. *Is the medical device intended to be implanted?*
3. *Is the medical device intended to be in contact with the patient or other persons?*
4. *What materials or components are utilized in the medical device or are used with, or are in contact with, the medical device?*
5. *Is energy delivered to or extracted from the patient?*
6. *Are substances delivered to or extracted from the patient?*
7. *Are biological materials processed by the medical device for subsequent re-use, transfusion or transplantation?*
8. *Is the medical device supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable?*
9. *Is the medical device intended to be routinely cleaned and disinfected by the user?*
10. *Is the medical device intended to modify the patient environment?*
11. *Are measurements taken?*
12. *Is the medical device interpretative?*
13. *Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies?*
14. *Are there unwanted outputs of energy or substances?*
15. *Is the medical device susceptible to environmental influences?*
16. *Does the medical device influence the environment?*
17. *Are there essential consumables or accessories associated with the medical device?*
18. *Is maintenance or calibration necessary?*
19. *Does the medical device contain software?*
20. *Does the medical device have a restricted shelf-life?*
21. *Are there any delayed or long-term use effects?*
22. *To what mechanical forces will the medical device be subjected?*
23. *What determines the lifetime of the medical device?*
24. *Is the medical device intended for single use?*
25. *Is safe decommissioning or disposal of the medical device necessary?*
26. *How will information for safe use be provided?*
27. *Will new manufacturing processes need to be established or introduced?*
28. *Is successful application of the medical device critically dependent on human factors such as the user interface?*
29. *Does the medical device use an alarm system?*
30. *In what way(s) might the medical device be deliberately misused?*
31. *Does the medical device hold data critical to patient care?*
32. *Is the medical device intended to be mobile or portable?*
33. *Does the use of the medical device depend on essential performance?*

Table 4.2: checklist of Annex C of ISO 14971 - Questions that can be used to identify medical device characteristics that could impact on safety.

1. *What is the possibility that an incorrect result would be generated by the IVD medical device?* 2. *What is the possibility that the incorrect IVD examination result would be detected by a user/laboratory?* 3. *What is the possibility that the incorrect IVD examination result would be detected by the physician?* 4. *What is the possibility that a physician would act or fail to act on the result?* 5. *What is the possibility that a physician's action/inaction would cause or contribute to harm to the patient?* 6. *What is the severity of the resulting harm?*

Table 4.3: checklist of Annex H of ISO 14971 - Guidance on risk management for in vitro diagnostic medical devices.

Following Annex D (Risk concepts applied to medical devices) of the ISO 14971 standard, the Classification of Hazardous situations and Harms has been evaluated. In order to determine the Acceptance Index for each possible Hazardous and evaluate the acceptability of the risk, it is necessary to evaluate the Probability (P) that the single hazardous situation generates the Harm (H) associated and the Severity of the Harm (S). The information necessary to evaluate the probability must be derived from scientific data, clinical evaluations, evaluation of the potential accidents, available standards if any, and from experience and evaluation of similar conditions.

To represent the Severity of the harms (S) it has been decided to use 5 levels, representing an increasing severity of the consequences (Table 4.4), while to represent the Probability (P) of the event 6 levels have been used (Table 4.5).

SEVERITY OF THE HARM	*IMPACT OF THE EVENT*
Negligible	*Inconvenience or temporary discomfort.*
Minor	*Results in temporary injury or impairment not requiring professional medical intervention.*
Serious	*Results in injury or impairment requiring professional medical intervention.*
Critical	*Results in permanent impairment or life-threatening injury.*
Catastrophic	*Results in patient death.*

Table 4.4: Severity classification of the harm and consequent impact on patient.

PROBABILITY	*VALUE*
Frequent	$\geq 10^{-3}$
Probable	$< 10^{-3}$ *and* $\geq 10^{-4}$
Occasional	$< 10^{-4}$ *and* $\geq 10^{-5}$
Remote	$< 10^{-5}$ *and* $\geq 10^{-6}$
Improbable	$< 10^{-6}$

Table 4.5: Probability classification and estimation of an event leading to harm.

In order to evaluate the acceptance index of the Risk, the value of the probability P and the severity of the harm S are crossed in the Risk Index Matrix as follows (Table 4.6):

Risk Index		Negligible	Minor	Serious	Critical	Catastrophic
		B	L	M	S	C
Frequent	F	1	1	1	1	1
Probable	O	1	1	1	1	1
Occasional	U	2	2	1	1	1
Remote	R	3	2	2	1	1
Improbable	N	3	3	2	2	2

Table 4.6: Risk Index Matrix of the device (lower numbers indicate increased risk).

In the above table we define 3 areas, on the basis of the index of acceptance of the risks (Table 4.7):

1. Area of NOT Acceptable risks: value 1;
2. Area requiring Further Risk Reduction: value 2;
3. Area of Acceptable risks: value 3.

Risk Priority	Risk level of concern	Review of risk assessment	Acceptance of residual risk
1	UNACCEPTABLE without risk/benefit justification	Risk Analysis Group	Legal Manufacturer
2	INVESTIGATE further risk reduction		
3	ACCEPTABLE without further risk reduction	Risk Analysis Group	Risk Analysis Group, Project Manager

Table 4.7: Acceptance Risk Table of the device.

4.10.1 Specific risks evaluation

4.10.1.1 Energy hazards - Electromagnetic energy

1. Risk of Operator electrocution - The electrical hazards consider the factors that can cause an injury to the operator due to the exposition to voltage or current during the normal operation of the device or in fault condition. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Catastrophic (C)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Catastrophic (C)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the Q3-Plus instrument is powered at 12 V 1.5 A: these values can be considered quite safe. Moreover, the two power supplies provided with the Q3-Plus instrument are compliant respectively with the IEC 60601 and with the IEC 60950 (A1 + A11, A12 excluded).

2. Risk of LED harm - During the test, the lid of the instrument could be accidentally opened. This operation, if done at the wrong moment, could cause a direct illumination of the human eye with the reader's LEDs. This could cause, in case of usage of high potential risk LEDs, severe injury to the operator. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the Q3-Plus instrument is equipped with pulsed LED light sources for fluorophores excitation, which comply with the international standard IEC 62471: Photobiological safety of lamps and lamp systems. In particular: for IEC 62471:2006, the device belongs to the exempt group at 20cm, with maximum exposure time=196s; for EN 62471:2008, the device belongs to the risk group 1 at 20cm.

Moreover, the user manual will report, as additional mitigation, not to open the lid of the Q3-Plus instrument during operation.

4.10.1.2 Energy hazards - Thermal energy

1. Risk of Operator burn (1) - The thermal hazard is related to the possibility that for an electrical fault or an over-current some of the components go in a condition of overheating and the device or a part of

it become very hot and/or go up in flames, resulting in burns for the patient. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the current delivered from the power supply is lower than 1.5 A at 12 V, that makes a dangerous overheating very improbable.

2. Risk of Operator burn (2) - This hazard is related to the possibility that the operator extracts the cartridge during the thermal cycling. This could cause a thermal injury if the operator touches the silicon while it is still hot. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the silicon die has been inserted inside a plastic holder by design, so that a minimum part of the silicon is exposed. In this way, the possibility to touch the dye is very low. In the user manual it shall be explicitly reported to not remove the cartridge from the instrument until the analysis is finished.

4.10.1.3 Energy hazards - Mechanical energy

1. Risk of Accidental shock - If the Q3-Plus instrument is accidentally shocked or moved, while performing an analysis, the liquid reagents may exit from it, compromising the result of the test. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: if some reagents should exit from the cartridge, the on-board reaction controls (reference gene reactions in the OraMod application) would fail. Therefore, the software would clearly indicate to repeat the test, and no wrong results could be produced. In the user manual it shall also be indicated that the Q3-Plus instrument cannot be moved when performing the test and every accidental shock shall be avoided. Moreover, it shall be indicated that the operator always has to wear gloves and a lab coat when staying near the Q3-Plus instrument, while this is performing an analysis. Finally, on the Q3-Plus instrument's base four suction cups have been inserted in order to increase the object stability.

2. Risk of Sharp die - Because of too much torsion on the cartridge or unwanted accidental fall, the silicon die may break. If broken, the silicon die, considering its thin thickness could become sharp. If not handled with care, the operator can be injured. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the silicon die has been inserted inside a plastic holder by design, so that none of its profiles are exposed. In this way, the die may break only if it should be strongly clashed against a hard, protruding object. In the user manual it shall be explicitly reported first to handle with care the cartridge and then, if a cartridge should break, to handle with care all the scraps resulting from its break. Moreover, the user manual shall report that the operator always has to wear gloves and a lab coat while holding a cartridge.

4.10.1.4 Biological hazards

1. Risk of Sample prep contamination - During the preparation of the sample to be analyzed in the Q3-Plus instrument, depending on the specific application, the sample can be contaminated by external agents. This contamination may result in a not correct output of the analysis because it starts from a not original sample. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Serious (M)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Serious (M)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: considering that this operation does not belong to ST-Italy's assignments, the legal manufacturer of the final "Q3-Plus OraMod qRT-PCR assay" shall be in charge of defining procedure and methods for the correct sample preparation, in order to avoid all the possible situations of contamination by external agents.

2. Risk of Unwanted contact with dangerous biological material - In the sample preparation phase, or if some liquid reagents leak out from the instrument (because of faulty cartridge sealing, or accidental shock to the Q3-Plus instrument), the operator could accidentally get in contact with dangerous biological material (bacteria, viruses and other pathological agents) which could cause, in the worst case, death or serious injury. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: by design, the reagents volumes are very low, therefore the associated risks are very low too; additionally, the sliding cover gives some protection from liquid spilling. Moreover, the samples loaded inside the Q3 cartridge are not raw specimens, but (in the OraMod-specific application) already purified RNA samples, that are not dangerous/infective anymore, if the purification has been properly

conducted. Regarding the risk during the sample preparation phase, considering that this operation does not belong to ST-Italy's assignments, the legal manufacturer of the final assay shall be in charge of defining the procedure and methods for the correct sample preparation, avoiding all the possible situations of contact and infections, especially with the most dangerous biological materials. Regarding the risk due to an accidental shock to the Q3-Plus instrument, it shall be indicated in the user manual that the Q3-Plus instrument cannot be moved when performing the test and every accidental shock shall be avoided. Moreover, it shall be indicated that the operator always has to wear gloves and a lab coat when staying near the Q3-Plus instrument, while this is performing an analysis. On the Q3-Plus instrument's base four suction cups have been inserted in order to increase the object stability.

3. Risk of Cartridge re-usage - The operator may use the same cartridge for two sequential tests. Considering that the sample used with the first test would contaminate the sample of the second test, the second test would give a not correct output. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: The user manual shall explicitly report that the Q3 Cartridge is disposable, in order to prevent any possible cross contamination between two different tests. Moreover, by design the Q3 Cartridge has a special embossing (holes for sample loading) inside the wax before use, which disappears after use; so that should the operator be going to re-use an already used cartridge, he/she should clearly perceive that it is an already used one. Finally, the Q3 Cartridge has on-board reaction controls: if the cartridge is re-used, typically the reference gene reactions would fail, because its reagents were exhausted during the previous test; therefore, the software would clearly indicate to repeat the test, and no wrong results could be produced.

4. Risk of Unsafe decommissioning - Depending on the biological substances used in the tests, the Q3 cartridges and the Q3-Plus instrument may contain dangerous biological materials for the humans and the environment. The Severity of the possible Harm depends on the specific application, that is, it depends on the specific kind of sample which is used and on the specific PCR reagents. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)

Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: by design, the reagents volumes are very low, therefore the associated risks are very low too. Additionally, by design the reagents are automatically sealed by the wax at the end of an analysis, and the sliding cover further protects from any possible liquid spilling. In the user manual it shall be explicitly written that only trained user shall use and manipulate the system. Also, it shall be reported that each Q3 Cartridge has to be safely disposed at the end of a test, in the hospital waste, in accordance with the applicable national and international laws. Moreover, it shall be indicated that the operator always has to wear gloves and a lab coat when disposing a used cartridge. Finally, it shall be reported that the Q3-Plus instrument shall be periodically cleaned and disinfected depending on the material used, and that at the end of its lifetime, it shall be safely disposed in accordance with the applicable national and international laws.

4.10.1.5 Operational hazards - Function

1. Risk of Software bug - Because of a software bug, the software may crash, or the output of the process may result in an incorrect value. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the software will be subject to a series of tests and validation phases. Moreover, the entire development of the source code will follow the IEC 62304 standard, in order to guarantee the lowest possible presence of bugs. Finally, should the software crash anyway, it would not give any output results at all and the analysis would have to be repeated, thus it is very improbable that wrong results are generated.

4.10.1.6 Operational hazards – Use error

1. Risk of Out of temperature range usage - It might happen that the operator uses the instrument out of its temperature range environment. This could cause a not correct thermal cycling process. As consequence, this could imply a not correct result of the test. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: a first mitigation is done using reference gene reactions as on-board reaction controls. If the thermal cycling is not run correctly, the controls would fail, therefore the software would clearly indicate to repeat the test, and no wrong results could be produced. A second mitigation consists in expliciting in the user manual the operating temperature range of the instrument.

2. Risk of Use of not original accessories - The operator might use cartridges which are not original and not tested with the Q3-Plus instrument. All the consequences cannot be predicted: a fluid leakage could happen, the cartridge could burn, the results could be wrong. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: In the user manual it has to be explicitly written that only original accessories can be used. Moreover, a bar code might be inserted on the Q3 Cartridge, containing relevant information. A check before starting the analysis could be automatically performed by the software; if the check fails because the bar code is not present or not original, the analysis would be stopped.

4.10.1.7 Informational hazards - Labeling

No labeling risks identified, because the label on the Q3 Cartridge and Q3-Plus instrument shall be made compliant by the legal manufacturer to the standards EN ISO 18113-1:2011 and, depending on the case, to its particulars. ST-Italy will only suggest to the final system integrator the labeling to be applied to the Q3-Plus instrument in order to be compliant with the 61010-1:2010 (3rd edition) as Generic Laboratory Equipment.

4.10.1.8 Informational hazards – Operating instructions

1. Risk of Not trained user on manipulating biological material - A user not trained may use the system. The operator and the environment may enter in contact with dangerous biological material. The Severity of the possible Harm depends on the specific application, that is, it depends on the specific kind of sample which is used and on the specific PCR reagents. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: the system shall be distributed to and used in laboratories where it is assumed that all the persons working inside have the right knowledge for manipulating biological materials. At the same time, on the user manual it shall be reported that the system has to be used by trained users in specialized laboratories.

2. Risk of Not trained user on using system - A user not specifically trained on the Q3-Plus System might try to use it without knowing how to run an analysis, yielding wrong results. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Critical (S)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	1 - Unacceptable
Residual Severity of the Harm	Critical (S)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	2 - Investigate

New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: In first instance a user manual shall be provided which will give all the information on how to correctly run an analysis session. At the same time, the software on PC side shall be designed and implemented in order to reduce to a minimum the interaction with the operator. This minimizes the human error factor and should guarantee the right result.

3. Risk of Interface and documentation language - The selected language supported by the software interface and used in writing the documentation shall be the English. The operator may not understand or speak this language, having some difficulties in using the system. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: Considering that the Q3-Plus system shall be used by trained operators, it can be assumed that the operator will have enough knowledge to understand English language, also because a lot of laboratory tools use this language. At the same time, the software interface shall give as less as possible interaction to the operator, in order to prevent any possible potential human error.

4.10.1.9 Informational hazards – Service and maintenance

1. Risk of CCC mechanical breaking or wear - After several insertions and extractions of the cartridges, the mechanical component of the instrument which holds the cartridge (named as “CCC”) may break or wear. In this situation, the cartridge could not be inserted/held correctly anymore and it would be impossible to run correctly the test. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)

Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: The software detects the presence/absence of the cartridge. If not present, the analysis cannot proceed, returning the relative warning via software to the operator. Moreover, the user manual shall report that after 500 analyses, the Q3-Plus instrument shall be sent to maintenance in order to change the CCC component with a new one. As additional control, a check will be put in place on software side, in order to guarantee that no more tests can be executed when the CCC component is considered too old because of the age or the number of analyses run.

2. Risk of CCC contact loss - After several insertions and extractions of the Cartridges, the electrical contact between Q3 Cartridge and Q3-Plus instrument might lose quality because of oxidation and mechanical movements. If the contact is totally absent, the Cartridge cannot communicate with the Q3-Plus instrument and the test cannot run. If the contact is partial, the heaters cannot work as expected and this could cause an incorrect result of the analysis. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Minor (L)
Initial Probability that the single hazardous situation generates the Harm associated	Occasional (U)
Initial Risk Index	2 - Investigate
Residual Severity of the Harm	Minor (L)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: if the contact is totally absent, the Q3-Plus instrument cannot communicate with the Cartridge. In this case, the software informs via user interface the operator about the cartridge missing. If the contact is partial, this would be still detected in most cases by the software; moreover, the legal manufacturer shall implement an “error correction”: this can be done through the on-board reaction controls, or using different validated solutions. Finally, the user manual shall report that periodic, ordinary maintenance has to be done by trained personnel.

3. Risk of Power supply connector breaking - After several insertions and extractions of the power supply plug in the Q3-Plus instrument connector, the connector may break. If the connector is broken, the Q3-Plus instrument cannot be powered on and the analysis cannot be performed. The Summary Risk Evaluation table is the following:

Initial Severity of the Harm	Negligible (B)
Initial Probability that the single hazardous situation generates the Harm associated	Remote (R)
Initial Risk Index	3 - Acceptable
Residual Severity of the Harm	Negligible (B)
Residual Probability that the single hazardous situation generates the Harm associated	Improbable (N)
Residual Risk Index	3 - Acceptable
New risk introduced with risk mitigation	No
(if yes) New risk name	

Risk mitigation: by design there is a specific LED inside the power-on button, in order to understand if the Q3-Plus instrument is correctly powered on. Moreover, the fan inside the instrument immediately switches on after the instrument has been turned on, making a clearly audible noise. The user manual will explain that, in case of a Q3-Plus instrument plugged into the electrical mains, switched on but with the LED and/or fan turned off, it will be necessary to return the product to maintenance.

4.11 Labelling

The labelling of medical devices and IVD devices has to comply with the EN 980:2008 standard: "*Symbols for use in the labelling of medical devices*". EN 980:2008 is the European standard for symbols used by medical device manufacturers. It provides guidance on meeting European Directive labelling requirements. All medical device manufacturers must use symbols to avoid mistranslation of essential information into multiple languages. EN 980:2008 aims to simplify labelling and ensure the consistent use of symbols across all medical devices. It also ensures that medical device manufacturers communicate clearly with customers and meet their product expectations. EN 980 is for use with the risk management standard EN ISO 14971; using the appropriate symbols can be an important element in risk reduction, a key part of risk management for medical devices.

As an example, Figure 4.8 shows the present label of the CE-marked, for research use only, Q3-Plus qRT-PCR instrument. It is applied to the bottom of each instrument.

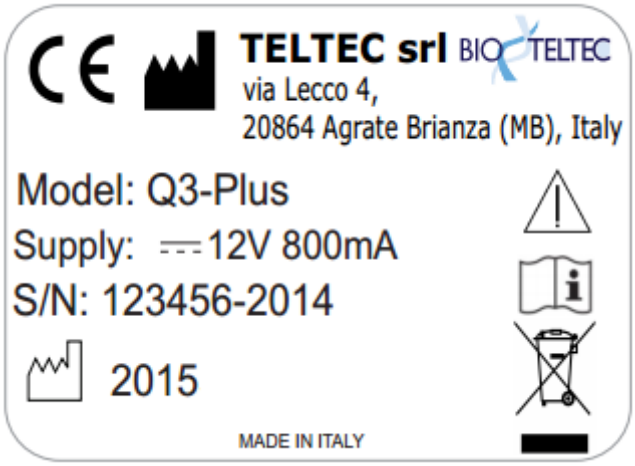


Figure 4.8: label of the Q3-Plus qRT-PCR instrument, CE marked for research use only.

5 Certification roadmap for the OraMod network platform

5.1 The regulatory context

As described in Figure 2.1, the OraMod network platform, which is the regulatory element #3 of the OraMod system, is composed of the back-end, the front-end and the core models. The ***back-end*** is the network platform developed by OneToNet. The ***front-end*** is the graphical user interface (GUI) developed by VCI. The ***models*** have been developed by VUmc and can be implemented as standalone algorithms or as formulas included in the GUI code.

From a regulatory point of view, the OraMod network platform can be defined as an *electronic clinical record including a predictive model*. We evaluated the certification roadmap for the OraMod network platform, according to the EU and US legislation.

The already mentioned EU guideline MEDDEV 2.1/6 on qualification and classification of standalone software used in healthcare (see par. 3.2.1) states: "Some standalone software may break down into a significant number of applications for the user where each of these applications is correlated with a module. Some of these modules have a medical purpose, some not… This raises the issue as to whether the whole product can be CE marked when not all applications have a medical purpose… The modules which are subject to the medical device Directives must comply with the requirements of the medical device Directives and must carry the CE marking. The non-medical device modules are not subject to the requirements for medical devices. It is the obligation of the manufacturer to identify the boundaries and the interfaces of the different modules. The boundaries of the modules which are subject to the medical device Directives should be clearly identified by the manufacturer and based on the intended use. If the modules which are subject to the medical device Directives are intended for use in combination with other modules of the whole software structure, other devices or equipment, the whole combination, including the connection system, must be safe and must not impair the specified performances of the modules which are subject to the medical device Directives."

Software that merely performs storage, archiving, communication, "simple search" or lossless compression of medical data, like the back-end plus the front-end of the OraMod network platform, is considered an Electronic Health Record (EHR), which is not regulated in the European Union. In the United States, however, this software would be regulated as a Class I medical device data system (commonly referred to as an MDDS device), if any of the data is obtained electronically from a medical device.

As the OraMod network platform includes also predictive models, it can be analyzed as a Clinical Decision Support software (CDS software) as well. A comparison between EU and US approaches to regulating clinical decision support software is shown in Figure 5.1 (source: http://www.emdt.co.uk/article/comparing-eu-and-us-approaches-regulating-clinical-decision-support-software-brief-summary-e).

Attribute	EU Regulatory Framework	US Regulatory Framework
Determines device status based on the manufacturer's intended uses	√	√
Regulates accessories to medical devices at the same level as the device	√	√
Regulates accessories and stand-alone software differently	√	√
Regulates software associated with IVD devices	√	√
Regulates software that merely performs storage, archival, communication, simple search or lossless compression of medical data	√	√
Regulates software that displays or converts data	√	√
Regulates software that analyses information and produces patient-specific results for clinical decision-making purposes	√	√
Regulates software based on independent modules as opposed to an overall system	√	x
Diagnostic services provided from outside of jurisdiction that may be regulated	√	x
Source of data irrelevant for determination of regulatory status	√	√ *
* US FDA has statutory authority to regulate but is currently developing a regulatory approach to regulation of data from nonmedical device sources.		

Figure 5.1: comparing EU and US approaches to regulating Clinical Decision Support software.

5.2 Back-end plus front-end: definition of the intended use

The main intended use of the back-end plus front-end of the OraMod network platform is to replace a patient's paper records.

With this software a clinician can enter, store and modify the patient's clinical data in the daily clinical practice, for the management of OSCC patients from the first visit down to the last follow-up.

Direct consequence of this purpose is the possibility to enable communication and facilitate interaction among all interested clinicians and all involved medical devices.

This Platform is substantially an EHR (Electronic Health Record system) able to store in an automatic way the data coming from all devices (Imaging, qRT-PCR) and collect data from all the Clinical Units involved in the project.

The EHR is also enforced by an innovative and easy to use user interface enabling to show data with a different aggregation and different point of view.

The intended use of the back-end plus front-end of the OraMod network platform is:

- to provide a more specific overview of total patient health including hospital admission, observational visit, surgical visit, clinical data, follow-up visit after a treatment;
- to improve the quality of care delivered to patients;
- to populate a data warehouse containing all information needed to build significant clinical trials;
- to give to a specialized board the possibility to discuss the situation of a patient with the same data in a collaborative environment.

5.2.1 EU regulations on EHRs: classification of back-end plus front-end

The **back-end plus front-end** of the OraMod network platform can be defined as an electronic health record (EHR), as said above. According to MEDDEV 2.1/6 - *Guidelines on the qualification and classification of stand-alone software used in healthcare within the regulatory framework of medical devices*, "if the software does not perform an action on data, or performs an action limited to storage, archival, communication, 'simple search' or lossless compression (*i.e.* using a compression procedure that allows the exact reconstruction of the original data) it is not a medical device. Altering the representation of data for embellishment purposes does not make the software a medical device". Thus, an EHR is **NOT a medical device** according to the EU Medical Device Directive.

Anyhow, where a given product does not fall under the definition of medical device, or is excluded by the scope of the Directives, other Community and/or national legislation may be applicable. And in fact, the situation in the EU at national level regarding EHRs is quite fragmented. A recent study funded by the Health Programme of the European Union and published in July 2014 provides an overview of the national laws on electronic health records within the EU Member States. The final report of the study is named "*EU - Legal study on electronic health records – Final report and recommendations"*. The cover page of the study is shown in Figure 5.2. This report was produced and funded under the EU Health Programme (2008-2013) in the frame of a direct service contract with the Consumers, Health and Food Executive Agency (Chafea) acting under the mandate of the European Commission.

At the webpage with address:

http://ec.europa.eu/health/ehealth/projects/nationallaws_electronichealthrecords_en.htm

it is possible to download also a specific country report for each EU Member State. These reports are not only focused on the current state of affairs, but also take into account potential future legislation.

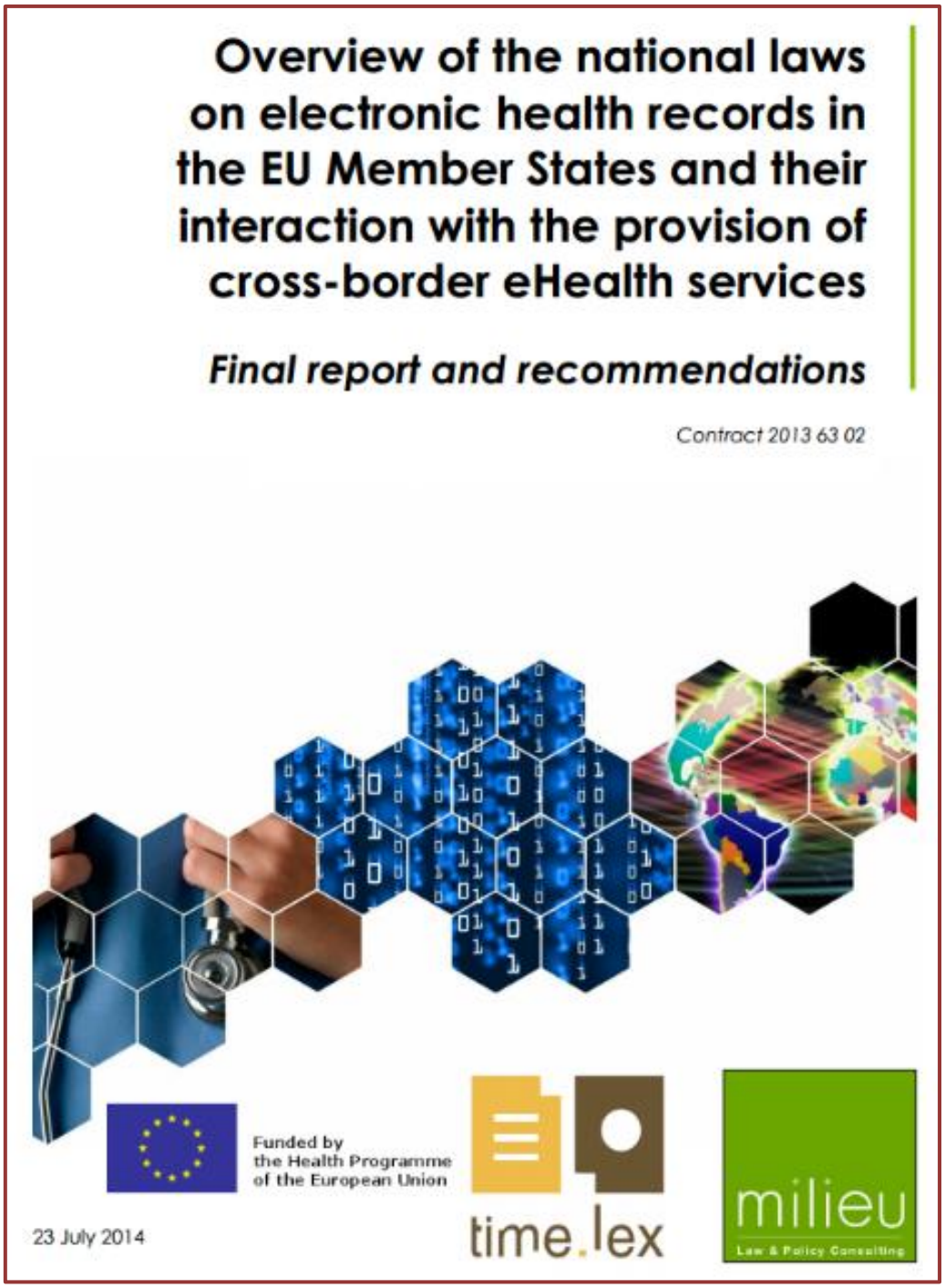


Figure 5.2: EU legal study on electronic health records – Final report and recommendations, 2014.

At the end of 2012, the European Commission adopted a new action plan "eHealth Action Plan 2012-2020 - Innovative healthcare for the 21st century". In this new plan, the European Commission proposes a series of new measures, recognizes that the promises of eHealth remain *"largely unfulfilled"* and expresses its commitment to remove the existing barriers to *"a fully mature and interoperable eHealth system in Europe".* Directive 2011/24/EU on the application of patients' rights in cross-border healthcare reflects the need to balance the deployment of health data and privacy safeguards, by making clear that the objectives of eHealth – namely enhancing continuity of care and ensuring access to safe and high-

quality healthcare – cannot be pursued in violation of EU data protection rules. Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, is the core instrument of the EU legal framework on data protection and covers also health data.

The above-mentioned Study seeks to identify and examine the national laws of the 28 Member States and Norway in order to identify legal barriers for the deployment of shared electronic health records at national level and for their cross-border transfer within the EU. The information provided in the national reports forms the basis of the comparative analysis of the legislation applying to EHRs. This analysis is facilitated by the common templates used by the national experts. On the basis of the national reports, comparative tables have been developed in order to present, in a synthesized manner, the common or different regulatory approaches of the themes in the countries.

The following list puts in evidence the main challenges encountered in the comparative analysis:

- The term EHR is generic and can include many types of patient medical information stored in electronic form. Generally speaking, the data are collected from the individual patients in the context of the provision of care but, once collected, there is a wide variety of EHRs, e.g. with regard to the identification of the patient, the type and format of the data, the place of storage, the use of outsourcing and cloud computing services and more in particular the exchange of the collected data among healthcare practitioners having a therapeutic relationship with the patient.
- Readers of this report should be aware of the fact that the term “creation of an EHR” is ambiguous and take into account that, in some Member States, this concept refers directly to EHRs created to be shared among healthcare professionals. This is typically the case for France (the French report was used as a model for the other country reports).
- Whereas the use of EHR systems at the level of individual healthcare institutions or practitioners is widespread, the exchange among healthcare professionals of data extracted from these EHR systems is in several EU countries still at an early stage of development. As a result, the legal framework tends to evolve rapidly at national level, with new legal developments being proposed as this report was being drafted. This report endeavored to reflect the latest legal developments in the countries covered even at the stage of proposal or draft laws.
- Several stakeholders mentioned that it was difficult to identify legal barriers or good practices for the deployment of EHRs or for the cross-border transfer, since they could not draw conclusions on their national system that was either not implemented or at the pilot phase and/or no EHR legal text was yet adopted.
- In several countries, experts experienced a lack of available information on the policy and legal initiatives developed on EHRs.
- The research focused on one specific aspect of e-Prescription systems – their relationship with EHRs – and therefore it cannot give a complete, final assessment of the state of development of e-Prescriptions or the legal barriers and best practices in this field. Moreover, stakeholders surveyed have given only little evidence on the operation of e-Prescription systems.
- The Study does not enter into the discussion about the “ownership” of EHRs. The term “ownership” is commonly defined as “a legal title coupled with exclusive legal right to possession”. Ownership is therefore closely linked to the notion of “property” (“owner” and “proprietor” are mostly considered as synonyms). Ownership or property can relate to material

goods or immaterial goods. In the latter case the term "intellectual property" is mostly used. Data are immaterial goods but they can never be the object of intellectual property as such. This does not mean that data can never be the object of rights. For example, a person who makes a substantial investment in the obtaining, verification or presentation of data can have certain rights under the Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases. This person will, however, not be considered as the "owner" of the data.

5.2.1.1 Implementation of shared EHR systems and legal approaches

The following table is taken from the above-mentioned Study, and summarizes the stage of implementation of shared EHR systems and legal approaches in each EU Member State and in Norway.

Country	Stage of implementation	Legal context
Austria	Deployment phase of shared EHR system since 2012 (ELGA[19])	Specific legal framework for shared EHR system first phase of implementation measures adopted. Reliance on general health record and data protection for non-specific aspects
Belgium	Deployment of shared EHR systems since 2008	Specific legal framework for shared EHR systems at federal and regional level. Reliance on general health record and data protection for non-specific aspects
Bulgaria	Full implementation of a shared EHR system (PIS records)[20] since 2009	No specific legal provision applicable to PIS records General rules on health records, data protection, liability and secondary use apply to PIS records.

Country	Stage of implementation	Legal context
Croatia	Pilot phase of a shared EHR system (CEZIH)[21] since 2006	Specific rules concerning EHRs Reliance on general health data legislation and data protection legislation for certain aspect of EHRs Legal initiative underway (e.g. requirement on patient access)
Cyprus	Deployment phase of shared EHR system (early stage) since 2012	No specific legal framework that regulates EHRs and ePrescriptions Reliance on general health and data protection law
Czech Republic	No shared EHR systems. Several policy initiative underway since 2013	No specific legislation on EHRs reliance on general health record legislation and data protection rules
Denmark	Full implementation of shared EHR systems since 2003	No specific and comprehensive legislation on EHRs Reliance on general legislation on patients' rights and health care professional's duties. Certain provisions of this legislation contain few specific rules targeting EHRs.
Estonia	Full implementation of shared EHR systems (ENHIS)[22] since 2008	Specific and comprehensive legislation on EHR systems
Finland	Deployment phase of a data transmission and archiving service (Kanta) [23] that ensure interoperability of regional EHR systems since 2007	Specific legislation on EHR system Reliance on general health law and data protection law for non-specific aspects Legal initiatives are in place (interoperability, information security, data protection and functionality)
France	Deployment phase of shared EHR system since 2006 (DMP[24])	Specific legislation on EHR system Reliance on general data protection and health legislation for non-specific aspects of EHRs
Germany	No shared EHR systems. Several policy initiative underway	General provision setting the general framework for the development of EHR system Reliance on general data protection and health record legislation
Greece	Pilot phase of a shared EHR system since 2014	Only general legislation on EHRs (requiring further regulation) Reliance on general health records legislation and data protection rules

Country	Stage of implementation	Legal context
Hungary	Shared EHR system in place (health information registry where patient can access certain health information). Policy initiative to develop further shared EHR system	Reliance on general health records legislation and data protection rules
Ireland	No shared EHR system, but some policy initiatives underway	No specific legislation on EHRs but a proposal is under discussion Reliance on general data protection rules
Italy	Deployment phase of EHR system at regions and autonomous provinces	Legal obligation for region and autonomous provinces to develop EHRs Draft law specific on EHR
Latvia	Pilot phase of a shared EHR system since 2014	Only few legal provisions specific on EHRs but a proposal is under discussion Reliance on general health records legislation and data protection rules
Lithuania	Final phase of a shared EHR system to be completed in 2015	Specific legislation on EHRs Reliance on general health record legislation and data protection rules for certain aspects of EHRs
Luxembourg	Deployment phase of shared EHR system (RSC)[25] since 2012	Adoption of several provisions in general healthcare legislation setting the legal framework for the EHR system Implementing measures on the EHR system to be adopted Reliance on data protection law for non-specific aspects of EHRs
Malta	Shared EHR system (myHealth) since 2012	No specific legislation on EHRs Reliance on general health record legislation and data protection rules
Netherlands	Several shared EHR systems being deployed. Deployment of a shared EHR system (LSP)[26] since 2011 that has the potential of being a nationwide system.	No specific legislation on EHRs but a proposal is under discussion Reliance on general health records legislation and data protection rules
Norway	Pilot phase of a shared EHR system (Nasjonal Kjernejournal)[27] since 2013	Specific legislation on shared EHR system Reliance on general health record legislation and data protection rules for non-specific

Country	Stage of implementation	Legal context
		aspects of EHRs
Poland	Shared EHR system under development foreseen by 2017	Specific legislation on shared EHR system Reliance on general health record legislation, patients' rights and data protection rules
Portugal	Deployment phase of a shared EHR system (RCU2)[28] since 2012	No specific legislation on EHRs (but for a ministerial order on content of EHRs) Reliance on general health records' legislation and data protection rules
Romania	Pilot phase of a shared EHR system (DES)[29] since 2013	No specific legislation on EHRs but several legal initiatives under discussion Reliance on general health legislation and data protection rules
Slovakia	Deployment phase of a shared EHR system since 2013(NHIS)[30]	Specific legislation on EHRs Reliance on general health record legislation and data protection and medical rules for non-specific aspects of EHRs
Slovenia	No shared EHR system, but some policy initiatives underway	No specific legislation on EHRs Reliance on general health record legislation and data protection rules
Spain	Shared EHR systems developed at regional level (at different stages of development) Interoperability system in deployment at state level (cross-regional e-patient summary system) since 2006	Specific legislation on shared e-patient summary at state level (a minima requirements possibility for regions to implement further measures) Reliance on general health record legislation and data protection rules (a minima requirements possibility for regions to implement further measures)
Sweden	Full implementation of a shared EHR system (NPO) since 2012[31]	Specific legislation on shared EHR system Reliance on general health record legislation for non-specific aspects of EHRs
UK[32]	Full implementation of a shared EHR system in the UK countries - England (SCR in 2008)[33], Scotland (ECS[34] in 2006, ePCS in 2009[35], KIS in 2013[36]), Wales (IHR in 2005[37]) and Northern Ireland (ECS in 2008[38],NIECR in 2013[39])	Only few legal provisions specific on EHRs Reliance on an information governance framework which includes - general health record legislation, data protection legislation and medical rules Institutional guidelines on EHRs

Table 5.1: summary table on stage of implementation of shared EHR systems and legal approaches in each EU Member State and in Norway.

5.2.1.2 Informed consent

The concept of informed consent is directly related to the principle of the autonomy of the patient, therefore it is understandable that most legislation on EHRs "includes the requirement to seek a patient's consent before collecting, processing, or sharing health related information" to ensure that the right to privacy of health data is respected. Consent is, under Article 8.2(a) of Directive 95/46/EC, one of the exceptions to the general rule of prohibition of the processing of special categories of data, including data concerning health; in accordance with the definition of the same Directive, the consent must be freely given, specific and informed. Only few countries have specific legal rules regulating the patient's consent in relation to EHRs in place. As shown in the table below, less than half of the countries covered by this Study have legal rules on patient consent in relation to EHRs in place.

	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IT	LT	LU	LV	MT	NL	NO	PL	PT	RO	SI	SK	SE	UK
Specific legal rules on consent	√	√				√	√			√	√	√	√			√		√	√									√	√

Table 5.2: countries with legal rules on patient consent.

5.2.1.3 Archiving

Archiving duration of EHRs in the context of this project refers to the period of time during which health data is stored in an electronic health record system. There are no specific rules at the EU level on the archiving of EHRs. However, pursuant to Article 6.1(e) of Directive 95/46/EC, personal data must be kept in a form which permits identification of data subject for no longer than necessary for the purposes for which the data were collected or for which they are further processed.

5.2.1.4 Interoperability

The European Commission has renewed in 2012 its commitment to a fully mature and interoperable eHealth system in Europe. Interoperability in this context means the ability of two or more electronic health record systems to exchange both computer interpretable data and human interpretable information and knowledge. Interoperability issues arise not only at the cross-border level, but also for instance between health institutions, health practitioners, and different geographical areas in a single Member State. In the national development of eHealth, the countries covered may therefore already have experienced different obstacles linked to the issue of interoperability of EHRs and developed various solutions to address those. This section therefore assesses how the interoperability of EHRs is regulated and achieved in the countries covered, including with other eHealth solutions. In the absence of specific EU legislation, only a few Member States have set legal provisions for cross-border interoperability of EHRs. The Table below identifies which countries have adopted legal provisions relating to the interoperability of EHRs in cross-border situations.

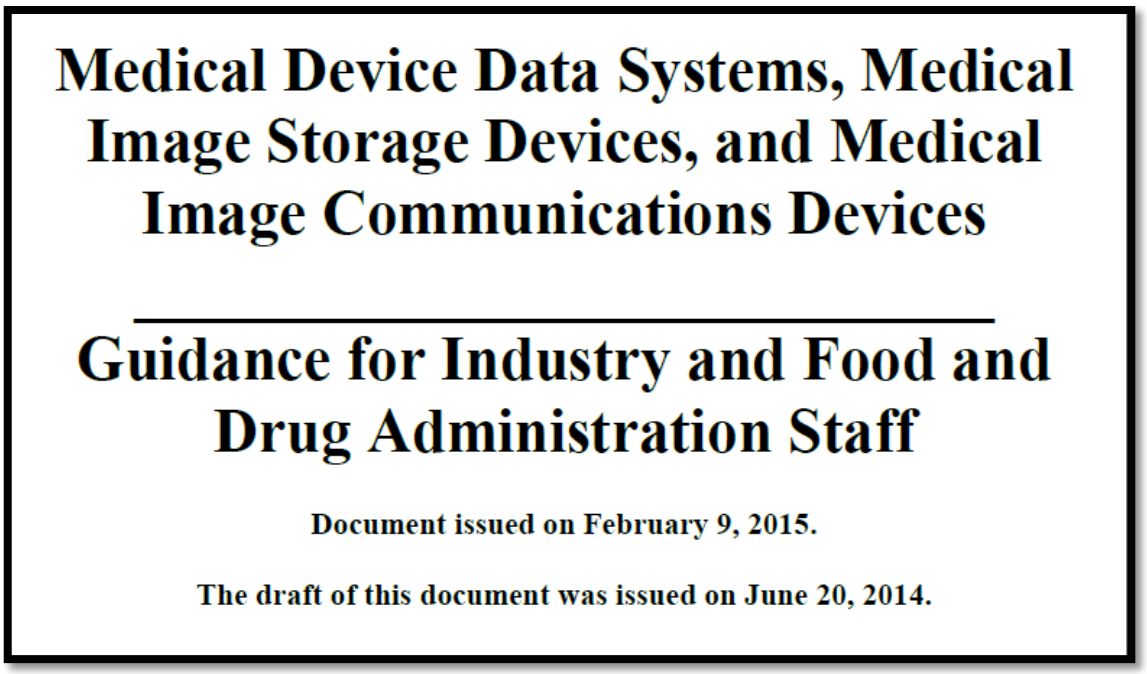
	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IT	LT	LU	LV	MT	NL	NO	PL	PT	RO	SI	SK	SE	UK
Provisions on cross-border interope-rability				√						√						√	√	√							√				

Table 5.3: countries regulating cross-border interoperability.

5.2.2 US regulations on EHRs: classification of back-end plus front-end

The US situation about electronic health records is well defined. Software that performs storage, archiving, communication, simple search or lossless compression of medical data, like the back-end plus front-end of the OraMod network platform, is regulated as a **Class I Medical Device Data System** (commonly referred to as an MDDS device), if the data is obtained electronically from a medical device; in the OraMod scenario, part of the data are in fact obtained automatically from a medical device (Image analysis software by Fraunhofer, for the imaging data) and from an IVD device (qRT-PCR platform by ST, for the genomic data).

This kind of medical devices is described in the guidance document issued by FDA in February 2015 and named "*US - Medical Device Data System - guidance by FDA*". This document also stressed that MDDSs are **exempt from 510(k) premarket notification**.



Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 9, 2015.

The draft of this document was issued on June 20, 2014.

Figure 5.3: FDA guidance on Medical Device Data Systems, 2015.

At the webpage with address:

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDeviceDataSystems/ucm251906.htm

there is a clear explanation on what medical device data systems are, and what they do. The Federal Register notice provides the following definition of a medical device data system:

> ***§ 880.6310 Medical device data system. -- (a) Identification.***
>
> 1. *A medical device data system (MDDS) is a device that is intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected medical devices:*
>   - *i. The electronic transfer of medical device data;*
>   - *ii. The electronic storage of medical device data;*
>   - *iii. The electronic conversion of medical device data from one format to another format in accordance with a preset specification; or*
>   - *iv. The electronic display of medical device data.*
> 2. *An MDDS may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. This identification does not include devices intended to be used in connection with active patient monitoring.*

In practice, a medical device data system (MDDS) is a medical device intended to provide one or more of the following functions:

- The electronic transfer or exchange of medical device data from a medical device, without altering the function or parameters of any connected devices. For example, this would include software that collects output from a ventilator about a patient's CO_2 level and transmits the information to a central patient data repository.
- The electronic storage and retrieval of medical device data, without altering the function or parameters of connected devices. For example, software that stores historical blood pressure information for later review by a healthcare provider.
- The electronic conversion of medical device data from one format to another in accordance with a preset specification. For example, software that converts digital data generated by a pulse oximeter into a digital format that can be printed.
- The electronic display of medical device data, without altering the function or parameters of connected devices. For example, software that displays the previously stored electrocardiogram for a particular patient.

MDDSs include the following, provided the intended use is consistent with the MDDS regulation:

- Any assemblage or arrangement of network components that includes specialized software or hardware expressly created for a purpose consistent with the intended use in the MDDS regulation;
- Products specifically labeled (per 21 CFR 801) by the manufacturer as an MDDS, provided such products do not provide additional functionality.

- Custom software that is written by entities other than the original medical device manufacturer (for example, hospitals, third party vendors) that directly connects to a medical device, to obtain medical device information.
- Modified portions of software or hardware that are part of an IT infrastructure created and/or modified for specific MDDS functionality. For example, when modifying software (writing and compiling software source code), the modified portion is considered MDDS.

What is NOT an MDDS:

- General-purpose IT infrastructure used in health care facilities that is not altered or reconfigured outside of its manufactured specifications. Modifications within the off-the-shelf parameters of operation are still considered general IT infrastructure and not MDDS. For example, components with the following functions by themselves are NOT considered MDDS if they are used as part of general IT infrastructure even though they may transfer, store, display or convert medical device data, in addition to other information:
  - The electronic transfer of medical device data:
    - Network Router
    - Network Hub
    - Wireless access point
  - The electronic storage of medical device data:
    - Network Attached Storage (NAS)
    - Storage area network (SAN)
  - The electronic conversion of medical device data from one format to another in accordance with a preset specification:
    - Virtualization System (ex: VM Ware)
    - PDF software
  - The electronic display of medical device data:
    - Computer Monitor
    - Big screen display
- Networks used to maintain medical devices to see which systems are running or malfunctioning, or other similar uses that do not meet the definition of medical device under 201(h) of the FD&C Act.
- Standard IT software that is not specifically sold by the manufacturer as a MDDS, which may have MDDS functionality such as reading serial numbers, barcodes, UDI or other data from a medical device, but is not used in providing patient care.
- Off the shelf passive network sniffing software that is generally used to monitor any network performance by reading TCP/IP packets on a network, if this software is not intended to connect directly to a medical device.

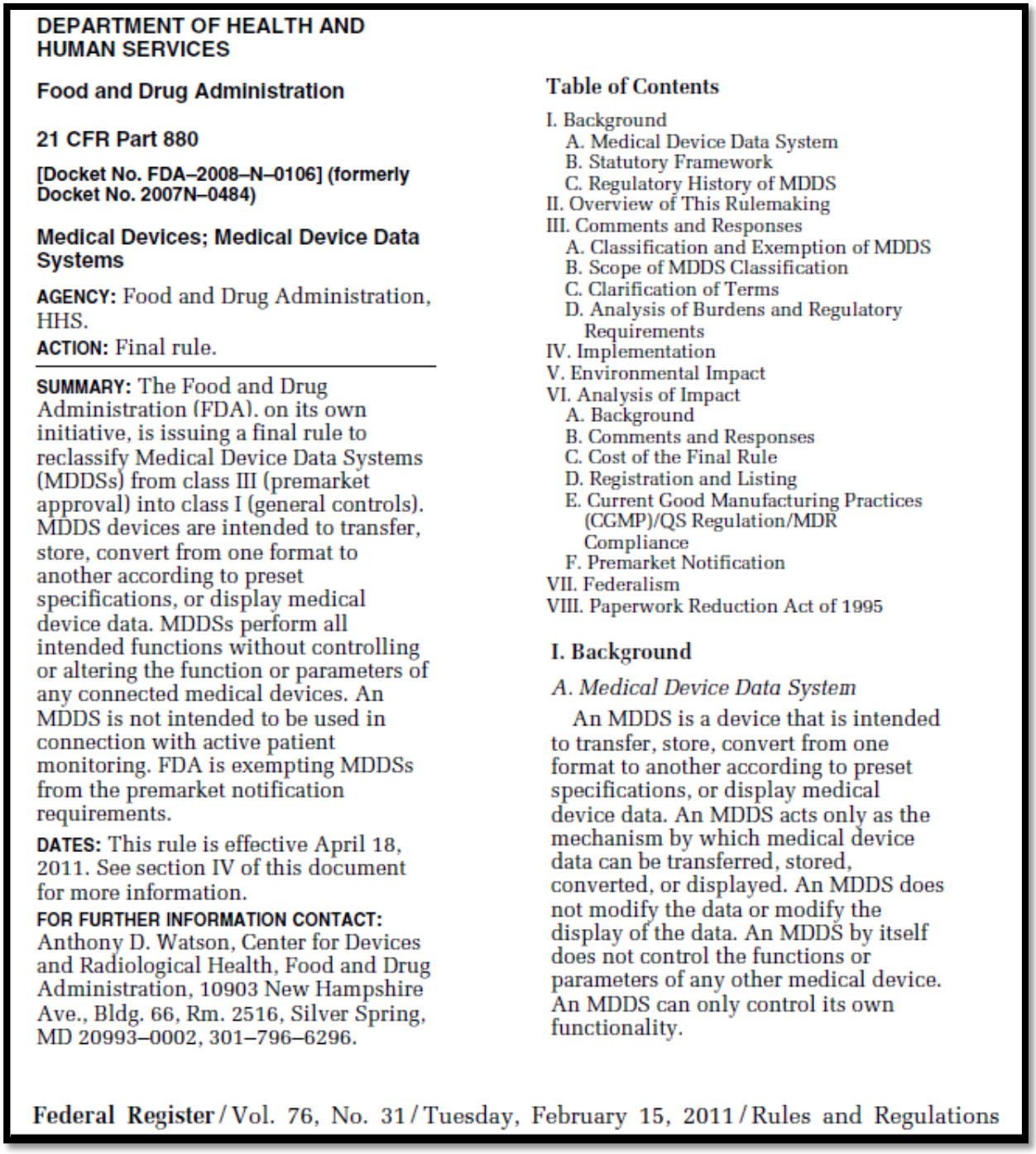
5.2.2.1 Reclassification of MDDSs from Class III to Class I

In the Federal Register of February 15, 2011 (76 FR 8637), the FDA issued a final rule to reclassify MDDSs from Class III (subject to Premarket Approval) to Class I (subject to General Controls). The first part of the text is shown in Figure 5.4.

Devices that were not in commercial distribution prior to May 28, 1976, are generally referred to as “post-amendment devices”, and are classified by operation of law under section 513(f) of the Food Drug and Cosmetic Act (21 U.S.C. 360c(f)) as Class III devices. The FDA’s Center for Device and Radiological

Health (CDRH) evaluates such post-amendment devices to establish the appropriate degree of regulatory controls needed to provide reasonable assurance of their safety and effectiveness. CDRH may decide to re-classify such a device as Class I (requiring General Controls), Class II (requiring also Special Controls), or Class III (requiring Premarket Approval).

Risks associated with MDDSs include the potential for inaccurate, incomplete, or untimely data transfer, storage, conversion, or display of medical device data. In some cases, this can lead to incorrect patient diagnosis or treatment. Based on evaluation of these risks, the FDA has determined that General Controls such as the Quality System Regulation (21 CFR part 820), will provide a reasonable assurance of safety and effectiveness. Therefore, Special Controls and Premarket Approval are not necessary. Moreover, FDA decided to exempt MDDSs from the premarket notification requirements; that is, no 510(k) is required.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 880

[Docket No. FDA–2008–N–0106] (formerly Docket No. 2007N–0484)

Medical Devices; Medical Device Data Systems

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA). on its own initiative, is issuing a final rule to reclassify Medical Device Data Systems (MDDSs) from class III (premarket approval) into class I (general controls). MDDS devices are intended to transfer, store, convert from one format to another according to preset specifications, or display medical device data. MDDSs perform all intended functions without controlling or altering the function or parameters of any connected medical devices. An MDDS is not intended to be used in connection with active patient monitoring. FDA is exempting MDDSs from the premarket notification requirements.

DATES: This rule is effective April 18, 2011. See section IV of this document for more information.

FOR FURTHER INFORMATION CONTACT: Anthony D. Watson, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 2516, Silver Spring, MD 20993–0002, 301–796–6296.

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I. Background

A. Medical Device Data System

An MDDS is a device that is intended to transfer, store, convert from one format to another according to preset specifications, or display medical device data. An MDDS acts only as the mechanism by which medical device data can be transferred, stored, converted, or displayed. An MDDS does not modify the data or modify the display of the data. An MDDS by itself does not control the functions or parameters of any other medical device. An MDDS can only control its own functionality.

Figure 5.4: FDA reclassification of MDDSs, 2011.

5.3 Models: definition of the intended use

The OraMod prediction models are intended for predicting lymph node metastasis, patient overall survival and probability of tumor recurrence for patients diagnosed with HPV-negative Oral Squamous Cell Carcinoma (OSCC). The models use qRT-PCR gene expression data, medical imaging data, clinical data and pathological data as predictors. In addition, the models provide uncertainty bounds for the predictions. Finally, the models provide the markers contributing most to the predictions.

Gene expression data should be produced with the "Q3-Plus OraMod qRT-PCR assay", as described in Section 4.1. In addition, the medical images should be processed with the OraMod image analysis software, as described in Section 3.1. Clinical and pathological data should be obtained according to best practice, in the formats required by the models.

The predictions should be used in combination with the visualization tools in the OraMod platform to allow better interpretation of the predictions, in particular relative to a background patient population.

Intended use is by clinical experts in OSCC. The predictions should support clinical decisions on the treatment of OSCC.

5.3.1 EU regulations on CDS software: classification of models

The predictive **models** included in the OraMod network platform, developed by VUmc, can be considered as a Clinical Decision Support (CDS) software, like the Image analysis software by Fraunhofer. As already said at par. 3.2.1, Annex 1 of MEDDEV 2.1/6 contains some examples of qualification for software used in the healthcare environment. One of such examples is exactly the CDS software: they are computer-based tools which combine medical knowledge databases and algorithms with patient specific data. They are intended to provide healthcare professionals and/or users with recommendations for diagnosis, prognosis, monitoring and treatment of individual patients. Based on decision steps 3, 4, and 5 of Figure 3.4, a CDS software is qualified as **Medical Device**, and therefore needs to be CE marked. More in detail, we believe that the OraMod models can be classified as a **Class I** Medical Device, as most standalone software. Hence, no Notified Body is required for its certification: the legal manufacturer will be able to proceed with a self-declaration.

However, this proposed classification is not in any way definitive: it will be the future legal manufacturer's only responsibility to classify this product, based on the exact intended use he will write down, and to decide the consequent certification route to follow.

The conformity assessment route for Class I Medical Devices is as follows. The manufacturer is responsible for ensuring that his product complies with all the relevant Essential Requirements of the Directive and must draw up a written statement to this effect (self-declaration). Class I Medical Devices without a measuring function and supplied in non-sterile condition, as is the case of the OraMod predictive models, do not require the involvement of a Notified Body. Conformity to the International and European Standard EN ISO 13485 is voluntary. Once the manufacturer is satisfied that his product meets all the relevant Essential Requirements, the manufacturer, or his European Authorized Representative if the manufacturer is located outside of EEA, must register with the Competent Authority. He may then self-affix the CE marking on his product and place it on the EEA market.

The following figure schematizes the CE marking routes for Class I Medical Devices, where the specific path for the OraMod models is highlighted:

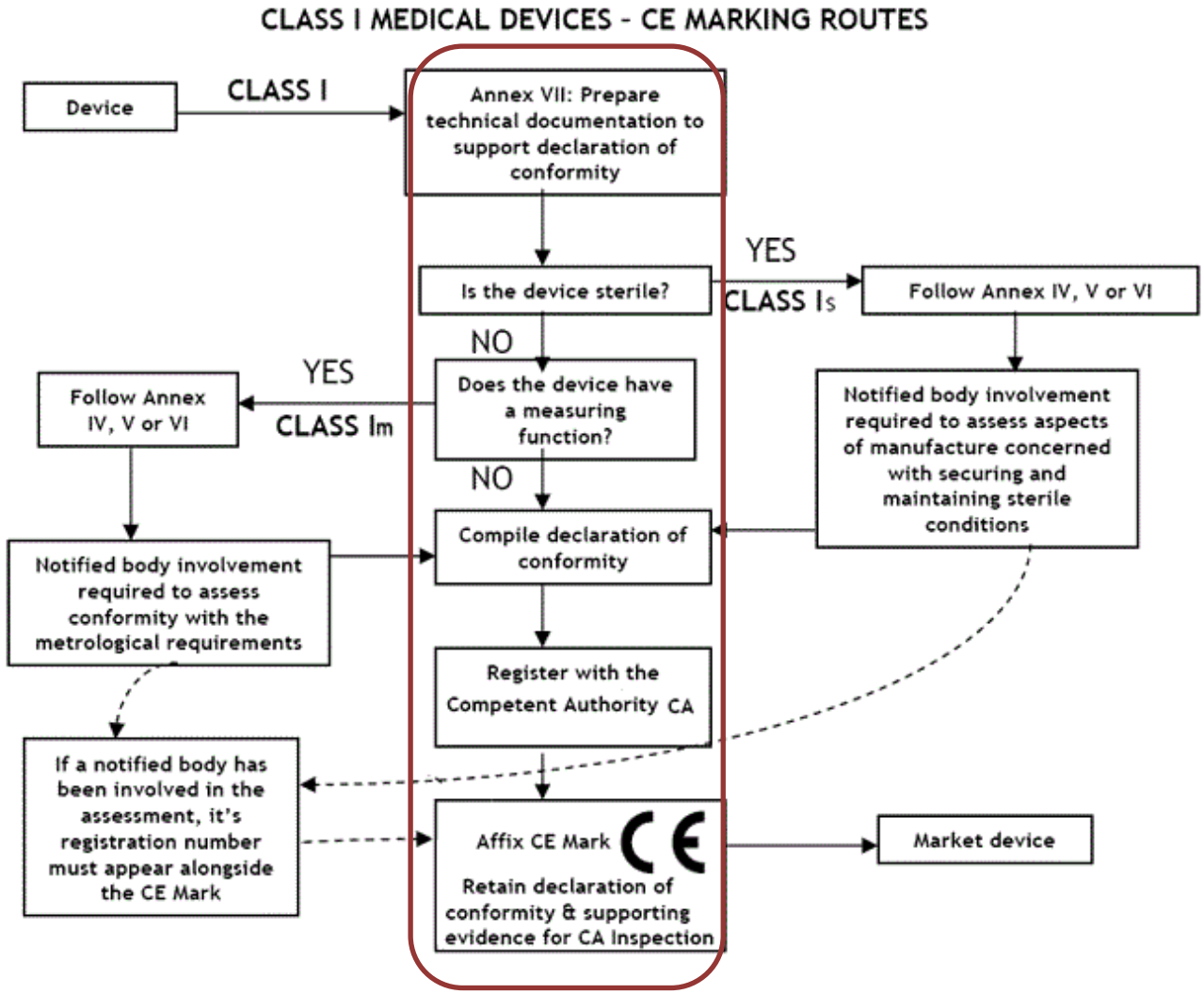

Figure 5.5: CE marking routes for Class I Medical Devices.

5.3.2 US regulations on CDS software: classification of models

The general situation on CDS software regulation is quite complicated in the US. One problem is that CDS software is loosely defined, as any application that analyzes data to help healthcare providers makes clinical decisions. CDS software is meant to enhance health outcomes by providing clinicians and patients with individualized application of medical knowledge, provided by an intelligently organized and filtering data processor. In 2011, FDA announced plans to publish a new guidance document that will define which types of CDS software it will regulate. In fact, FDA already regulates CDS. While the agency has not published yet a guidance document outlining the contours of that regulatory program, over the last 20 years FDA has regulated many different types of CDS. CDS can be divided broadly into two categories: standalone and accessory. Standalone includes that software intended to be run on a computing platform that is not attached to a medical device, but that will directly provide a diagnostic or treatment recommendation. Accessory software, on the other hand, is specifically marketed to support the functionality of a medical device like a blood glucose meter. Understanding this framework is important because it determines the regulatory requirements that apply. If the software is designed,

for example, to analyze data downloaded from a blood glucose meter, the software is an accessory and will be regulated in the same manner as the blood glucose meter. The classification and most of the FDA regulatory requirements will be dictated by how the parent medical device is regulated. Standalone CDS, in contrast, like the model composing the OraMod network platform, is regulated or not on its own merits, without regard to another medical device. Then, the regulatory status of a CDS (or any other kind of) software is typically one of the following three choices:

1. Software that does NOT meet the legal definition of a device and is not FDA regulated;
2. Software that DOES meet the legal definition of a device, but FDA does not expect these products to undergo premarket review; and
3. Software that DOES meet the definition of a device and FDA is actively regulating and would require a premarket review.

Except for a few specific exempt device types identified in the classification regulations like medical device data systems (MDDS devices), that middle category is not today a regulatory classification that can be found defined in any FDA records. Fortunately or unfortunately, depending on the perspective, FDA has been very reluctant over the last 20 years to define with any real precision its policy on which types of software must undergo premarket review and clearance, or even approval. Historically there have been two key features for most unregulated software:

- The data are entered manually; they are not inputted directly from any machine that touches the patient or a patient specimen. That is important to avoid becoming an MDDS device or an accessory to a medical device.
- Depending on how the data are entered, the output amounts simply to providing the stored data back to the patient or professional. The system does not automatically guide the diagnosis or treatment, nor does it guide any medical instrument. In other words, the software does not contain any algorithms that provide clinical-like functions that go beyond what FDA often refers to as library functions. It merely displays the data for the user to read and interpret.

Much software does indeed fit this category of unregulated software. But the model included in the OraMod network platform does clearly guide the diagnosis/treatment, moreover part of the data are not entered manually, but they are automatically acquired by an IVD device (the qRT-PCR platform, for the genomic data) and a medical device (the Image analysis software, for the imaging data). Therefore, since the model is intended to help with any part of "cure, mitigation, treatment, or prevention of disease or a medical condition", FDA may consider it a medical device.

But, does it require premarket review? It is very difficult to say. Again in April 2014 in the "*FDASIA Health IT Report – Proposed strategy and recommendations for a risk-based framework*", the FDA said it would figure out later what to do about CDS. Until FDA publishes its draft guidance on CDS, the best anyone can do is look at a variety of risk factors to figure out which side of the premarket review line a piece of software falls. Based on FDA comments and actions over the last 20 years, the following list of factors has guided the dividing line historically:

1. Whether the software is intended or designed to provide any real time, active, or online patient monitoring functions.

2. Whether the software has the capability to display, create, or detect alarm conditions, or actually sound an alarm, or the capability to create alarms that are not already present from the connected medical device.
3. The seriousness of the particular disease or condition that the CDS is intended to diagnose, cure, mitigate, treat, or prevent.
4. How the software contributes to the user's decision-making for diagnosis or clinical management of the patient. For example, is it software designed to call attention to imminent hazard conditions or does it provide diagnostic support for chronic disease?
5. The amount of time available before using the information provided by the CDS, i.e., the time until a therapeutic or additional diagnostic intervention must be implemented by the health care provider after the results of the software have been provided. For example, is the device an EKG reading and analysis package whose output is "SHOCK NOW" or does it provide a proposed reading with notation that the rhythm itself should be checked?
6. Whether the data output is provided or manipulated in a novel or non-traditional manner. For example, do the system's algorithms, parameters, internal decision trees, or other output manipulations depart from customary use or traditional data presentation?
7. Whether the CDS provides individualized patient care recommendations, e.g., whether the software suggests or recommends specific treatment for a specific patient. For example, how specific is the software output with regard to particular patients? Is the software providing general advice or information, like a library, article, or textbook, or is the software designed to provide a specific recommendation for a specific patient whose individual data have been entered as input?
8. Whether the mechanism by which the CDS arrives at a decision is hidden or transparent, i.e., does the product use undisclosed parameters or internal decision trees or other mechanisms that are not available for review by the health care provider. For example, how transparent is the software manipulation to the intended user community? Included in transparency is the extent to which limitations on the process are made known to the user, such as data compression, deletion, editing, or simplification. Also, how are comparisons made to normative databases and how are normative databases created?
9. Whether the product provide new capabilities or intended uses for the user.

Until FDA publishes its CDS guidance, consideration of these practical factors should help decide whether in FDA's eyes the software is risky enough to require premarket clearance. Based on answers to the above questions 3, 4, 6, 7, 8, and 9, we believe that the **models** included in the OraMod network platform are a **Medical Device** that would probably need to undergo a **510(k) premarket notification**, in order to obtain FDA clearance.

Nevertheless, this proposed classification does not want to be definitive at all: it will be the future legal manufacturer’s only responsibility to classify this product, based on the exact intended use he will write down, and to decide the consequent certification route to undertake.

5.4 Timing and costs to obtain certification

The back-end plus front-end of the OraMod network platform, defined as an electronic health record (EHR), does not have to be certified in the EU, since it is not a medical device according to Directive 93/42/EEC (see par. 5.2.1).

In the US, the back-end plus front-end is classified as a Class I Medical Device Data System, exempt from 510(k) premarket notification (par. 5.2.2). Proper Technical File and software testing need to be done before marketing the device in the US. We can estimate around 3 months for these activities.
No additional time for FDA review of the 510(k) Premarket Notification submission has to be considered in this case, since MDDSs are exempt, as already said.

Regarding the costs for certification of a MDDS in the US: no 510(k) is required, and thus no 510(k) review fee has to be paid. While the annual establishment registration fee has to be paid by the manufacturer, amounting to USD 3845 in 2016.
Besides this cost, one has to consider the personnel cost as well, for about 3 months.

In order to obtain the CE certification as a Class I Medical Device for the predictive models (par. 5.3.1), the main activity to be performed is a documental one, that is, preparing a proper Technical File. Software testing according to ISO 62304 must be carried out as well. We estimate that around 3 months are needed to perform these activities, from the moment when the software has reached the necessary maturity and reliability (even if, ideally, the technical file should be set up properly since the very beginning of the development process of a medical device), as for the Image analysis software (par. 3.4).
No Notified Body has to be involved in this case, that is, the manufacturer can proceed with a self-declaration. Hence, no further time has to be considered: the manufacturer will be able to sell the product in Europe within one week of submitting the necessary paperwork to the Competent Authority in which its European Authorized Representative is based, once the requirements of the Directive have been met.

Regarding the costs for CE marking of a Class I Medical Device, they mostly consist in 3 months of personnel cost, since no Notified Body has to be involved.

The predictive models are considered a Medical Device in the US, most probably needing a 510(k) premarket notification (par. 5.3.2). We estimate that around 3 months are needed to conduct preparation of the Technical File and execution of software testing.
Moreover, one has to consider also the time employed by FDA to review the 510(k) submission, which is typically 3 months.
Thus, the total time to obtain FDA clearance to US market is estimated at around 6 months here.

Regarding the costs in the US, besides the same personnel cost as for the EU scenario, there are some fees to be paid: the fee for FDA review of the 510(k) submission (standard fee of USD 5228, or small business fee of USD 2614 if the manufacturer has no more than 500 employees, including affiliates), plus the annual establishment registration fee (USD 3845 in 2016).

6 Certification roadmap for the whole OraMod system

6.1 Intended use of the whole OraMod system

The OraMod system is intended as an integrated environment for clinical decision support on the management and treatment of Oral Squamous Cell Carcinoma (Oral Cavity Cancer) patients.

The system is composed of a suite of tools that allow the collection of patient's data:

1. The image analysis software (see section 3 above);
2. The "Q3-Plus OraMod qRT-PCR assay" (see section 4 above);
3. The back-end plus front-end of the OraMod network platform (see section 5.2 above);
4. The prognostic models (see section 5.3 above).

The OraMod system is fully integrated into the hospital legacy systems, thus constituting a building block of the patient's IT integrated care delivery system and a Departmental Clinical Information with some features of a Decision Support System for the maxillo-facial and ENT (Ear, Nose and Throat) units of hospitals.

With this software suite a clinician can enter, store and modify patient clinical data in the daily clinical practice for the management of OSCC patients from the first visit down to the last follow-up, visualize all the data as he likes, simulate prognosis at baseline and after treatment, analyze data and prognostic factors, use automatic functionalities to determine anatomical features from diagnostic images, establish collaborative decision making procedures, and agree on treatment decisions by means of an IT-supported Tumor Board Meeting.

As such, the OraMod system facilitates collaborative clinical care delivery and treatment decisions, as it facilitates the shared communication of patient's information and clinical expertise among the multidisciplinary team of clinicians concerned with OSCC patient's management.

6.2 Product classification according to EU and US legislation

The whole OraMod system, being composed of the three regulatory elements identified at chapter 2, and described at chapters 3 to 5, can be classified as the sum of its elements with regard to the regulatory requirements. Thus, since the strictest classification has to be considered, we believe that the whole OraMod system can be classified as a **Class IIa Medical Device + General IVD Device** according to **EU legislation**. That is, it has to meet the requirements of both the Medical Device Directives 93/42/EEC and 2007/47/EC, and the IVD Directive 98/79/EC; a Notified Body will have to be involved for its certification.

While it can be classified as a **Class II Medical Device + Class II IVD Device** according to **US legislation**, requiring 510(k) Premarket Notification and GMP compliance.

Nevertheless, this proposed classification does not aim to be definitive at all: it will be the future legal manufacturer's only responsibility to classify this product, based on the exact intended use he will write down, and to decide the consequent certification path to follow.

6.3 Clinical evaluation of medical information systems

Clinical evaluation involves analysis and evaluation of clinical data about a medical device, to verify the clinical safety and performance of a device. Clinical evaluation is a continuous process that shall be carried out during the entire life cycle of a device. It starts during the design phase, before the device is placed on the market, and is thereafter continuously updated at regular intervals with new clinical experiences about the device's safety from daily use. This information is fed back to the manufacturer's risk management process where it is used.

All medical devices, irrespectively of class, must have a clinical evaluation (see also par. 3.2.1), unless the manufacturer can demonstrate that it is not necessary or appropriate. The clinical evaluation shall verify the clinical purpose and capabilities that are being claimed for a medical device. The clinical evaluation must be based on one or more questions that shall be answered by the evaluation. These questions are identified in the manufacturer's risk management process and usability analysis (Usability Engineering Process according to IEC 62366), and checked against the essential requirements in the directives.

A clinical evaluation must be based on relevant clinical data. Relevant clinical data can be found in the records of own previous experiences, scientific or other trustworthy documentation for the same or similar devices that can confirm the performance of the actual device. If such relevant information is deemed necessary, but does not exist, the manufacturer must conduct a clinical trial. Clinical data is needed to fulfill some of the essential requirements in the directives. In reality, this means that the specific questions in the risk management process must be answered and hopefully the issues can be solved. In that respect, a clinical evaluation for medical information systems does therefore not differ from a clinical evaluation of other medical devices. The risk management process and usability analysis, based on the essential requirements, determines which questions need to be answered.

Medical devices are normally used in a context, in a method, established and applied by the healthcare provider. Extensive medical information systems have a tendency to control the medical methods. Although the methods need to be adapted to the technical tools that are available, it is in this context important to make clear who shall be responsible for the device and who shall be responsible for the method. A great deal of the reported incidents is due to misunderstandings and vague roles of responsibility in this respect. The problem applies to all medical devices but has proven to be especially important to clarify when it concerns medical information systems. The model in Figure 6.1 illustrates this concept: both grey ovals together represent the device as a whole. The light green oval in the middle represents what the manufacturer specifies as intended use for a device, according to the description in the instructions for use, and for which the manufacturer is responsible for, here referred to as normal use. The top light green oval demonstrates use errors, partly what the manufacturer has already assessed in the risk analysis and has evaluated as reasonably foreseeable misuse, and partly abnormal use such as severe use errors and abuse that the manufacturer cannot always prevent in the risk management process. The green oval on the right describes the situation, the method used in health care where the device is a tool for reaching the medical purpose. The responsibility for the method lies with the healthcare sector.

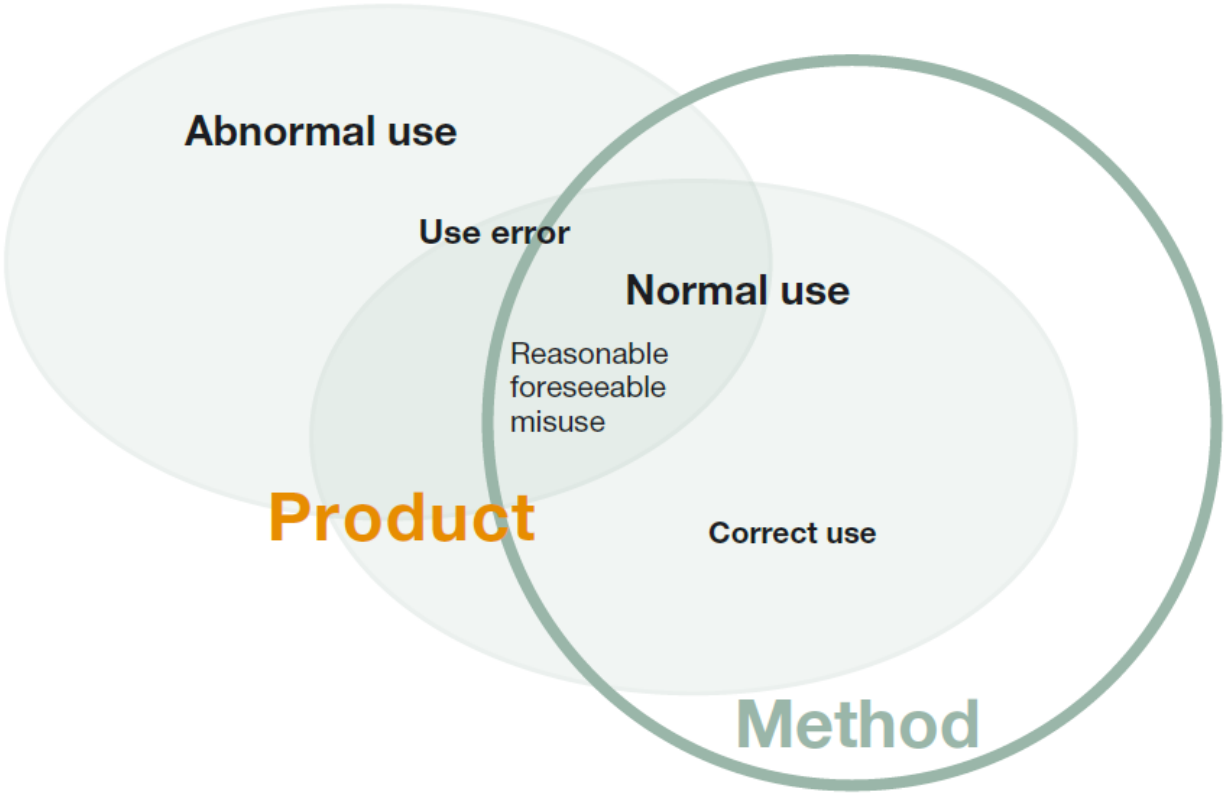

Figure 6.1: concept of usability of a medical device in the context established by the healthcare provider.

A medical information system is provided with a specification for its intended use, as expressed by the manufacturer. Its Normal use must be identified in the risk management process and documented in the instructions for use or other information intended for the user. A user problem could still occur, so called reasonable foreseeable misuse. Use errors may happen even though the user has followed the instructions for use and used the device according to Normal use. This is due to human errors, forgetfulness, pushing the wrong button, etc. It is the responsibility of the manufacturer to foresee, monitor and minimize the consequences of such actions as far as reasonably possible.

Furthermore, there are also use errors that could not have been foreseen or where the manufacturer has limited possibilities to be prepared for, so called abnormal use. This means anticipated risks, taking shortcuts, using the device for the wrong purpose and so on. The liability here rests fully on the user, but does not automatically free the manufacturer from updating the risk evaluation, monitoring and minimizing the consequences for possible use error if it is reasonable.

Additionally, the manufacturer should have been able to foresee in which Method the device is likely to be used. The term method can in this context include routines, other devices, staff, competence, facilities, etc. Methods could for instance be “Record keeping at anesthesia”, “Patient monitoring” and likewise. A device shall not be equipped with functions that are directly inappropriate for the intended method. It is also the responsibility of the user to check that any devices and systems that are going to be used are really specified for the actual method.

This is often where it fails. The health care provider uses the system in their operations, either without taking into account the specification from the manufacturer or due to missing specifications. A manufacturer that resists seeing its system as a device with defined specifications has limited possibilities to meet and assess any specific requests that the health care provider may have. If the manufacturer has little understanding of the methods used in health care, then certain functions or configurations could lead to harmful situations. Different guidelines such as standards for instance, may be useful tools to address the issues in the correct manner. The standard IEC 62366 about Usability Engineering is helpful to analyze and design a customized system. Figure 6.2 illustrates the application of relevant international standards in the context shown in Figure 6.1.

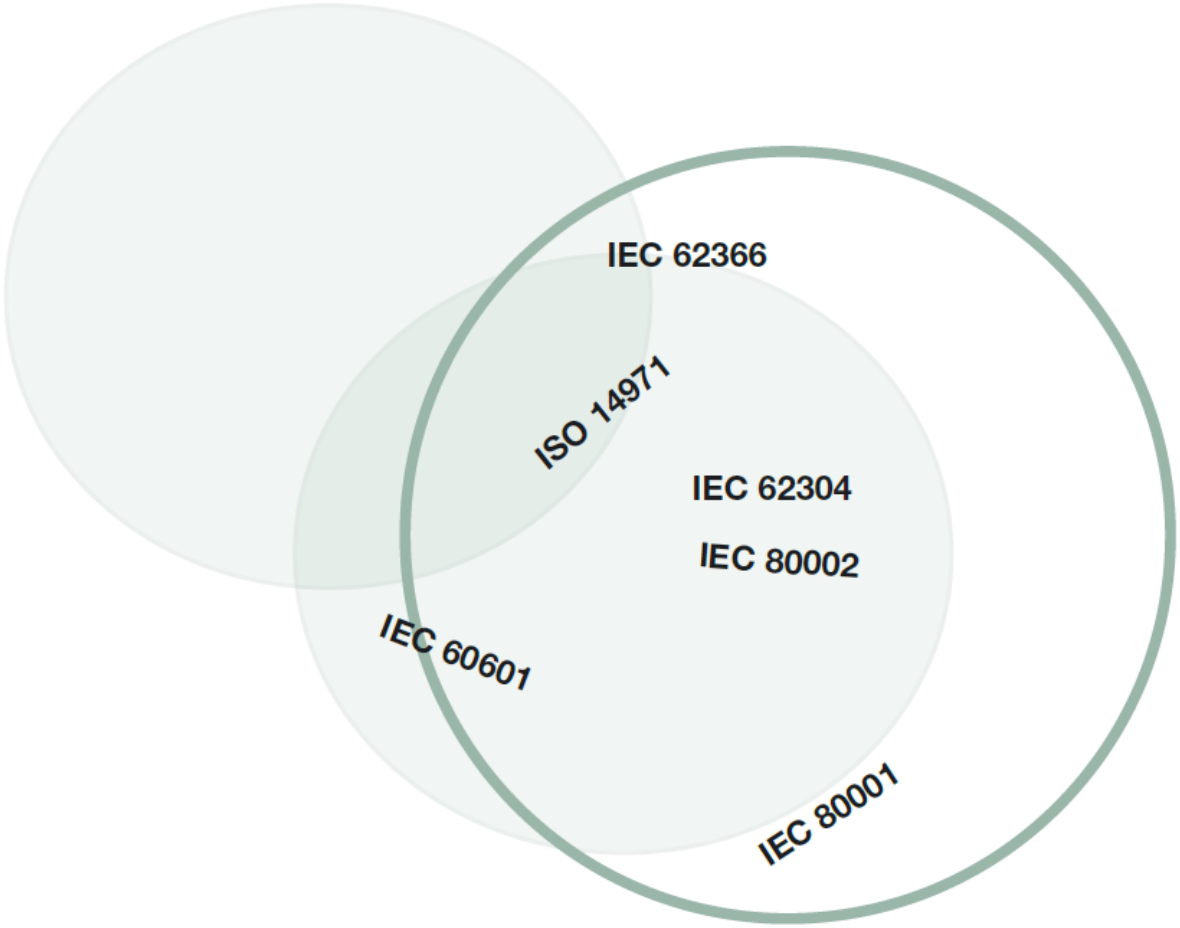

Figure 6.2: international standards on usability of a medical device in the context established by the healthcare provider.

The manufacturer of medical information systems can use several different standards, which are useful tools to meet the essential requirements in the medical device directive. ISO 14971 is the general risk management standard for medical devices. IEC/TR 80002 is a guidance on how to apply the standard ISO 14971 when designing medical device software. IEC 60601 is a general safety standard for medical electrical equipment, and the relevant annex H includes overall guidance for Programmable Electrical Medical Systems, description of structure, development life cycle plan and documentation. The most

relevant standard to be used for designing software is IEC 62304 "*Medical device software – Software life cycle processes*". These standards also relate to the awareness of applying risk management according to ISO 14971. The user of medical information systems can apply the standard IEC 80001 "*Application of risk management for IT-networks incorporating medical devices*". IEC 62366 describes the process of usability engineering, which is important in the design phase to assure that medical devices fulfill usability. It is also relevant for the user to have some insights in this process.

6.4 Installation and maintenance of medical information systems in networks

6.4.1 Infrastructure systems and buildings

It is important that systems for infrastructure and support functions are as robust as it would be expected. These support and infrastructure systems, when they function properly, allow for the operation of IT systems by providing electrical power, networks, heating, ventilation, etc. If such infrastructure systems are not planned carefully and properly implemented, including risk management, other systems may fail, which can lead to severe safety risks for both patients and staff. The bigger structures that are dependent on support and infrastructure systems, the bigger losses will be suffered when they fail. The trend to achieve effectiveness by coordinating different systems, leads to a situation where society and health care will become more vulnerable. For infrastructure systems, we see a convergence towards other non-medical IT systems with unclear borderlines. Electronic access control systems are linked to other password-protected systems and can create barriers, for instance allocating resources for treating patients with acute illness.

6.4.2 Medical information systems communication with other systems

One problem with medical information systems is that they often rely to a large extent on the environment in which they are installed. It is normal that these systems share information with other systems, and therefore depend also on the interaction with other systems. In a complicated user network, it will be more or less impossible for a single manufacturer to understand the overall picture. It is therefore an obligation of an individual manufacturer to design a system which is as robust as possible, by applying all existing knowledge. In the risk management process the manufacturer identifies possible weaknesses, establishes acceptance criteria and makes his best attempt to verify the requirements in a controlled environment where no patients are facing any risks from possible problems.

6.4.3 Managing residual risks, verification of installation

The validation of a system and how to use the devices is of significance for the function. The manufacturer shall perform the validation in a controlled environment, as similar as possible to the intended environment of the user. Any residual risks that the manufacturer cannot control and where the result depends on a final installation in the client's network shall be explained to the user. The manufacturer should then be able to expect that the installation in the client's network is done in a

structured way and that the information about any residual risks that have been expressed has been taken into account. The installation and "verification" should be carried out according to a standardized method that is known to both manufacturer and user. This also means that the health care provider shall have a risk management process in order to be able to do a validation based on proper information about the device, including the intended environment where it is often linked to other devices in a network and is depending on other systems or software to check the correct function. Function and safety for patients and staff can then be guaranteed in a better way. The purpose of the verification is to identify problems that could occur due to combinations that are unpredictable. The verification shall have a higher level of attention in the initial phase and focus on the mitigation of the consequences from an error. Emphasis shall be put on the residual risks identified by the manufacturer.

The client's organization is responsible for any additional installation or configurations in the network to be done with the same level of attention and monitoring regarding any residual risks as those expressed by each system manufacturer. This verification process shall not be seen as a clinical evaluation or clinical investigation as described and intended in the medical devices directives. After the procurement of a medical information system, that is a medical device, and after verifying the installation in its environment including an approved delivery, the system shall be maintained. The applicable prerequisites for the original installation and verification constantly change. These changes can affect the system properties negatively and may impair the performance or cause operational disturbances and thereby jeopardize patient safety. When appropriate management routines are missing, then both the health care provider and the manufacturer might not be aware of any ongoing changes in the network or if, for example, more systems have been added. There are appropriate guidelines and terminology for verifying changes in the installation environment, as described in the standard IEC 80001 "*Application of risk management for IT-networks incorporating medical devices*".

6.5 Steps required to obtain the certification for the system as a whole

6.5.1 Procurement

When procuring information systems that are qualified as medical devices intended to be used in either the public or private sector, the requirements in the medical device directives must be considered. In order to avoid ambiguities and appeals in the procurement process and possibly improve the requests for proposals, especially regarding the patient perspective and considering the medical device directives, it is important that both parties are clear about:

- Which parts of an information system should be CE marked;
- Who is the contractor (seller) and procuring entity (buyer). Is it the manufacturer, distributor, subcontractor or other?
- Who will be registered at the Medical Products Agency (if applicable);
- Who is the subcontractor;
- Who will be responsible for complaints;
- Who will be responsible for the overall system or parts of the system;
- How will the contract agreement be followed up during the contract period.

6.5.2 Preparation for tenders

One important aspect is how the relevant manufacturers have described their systems in the offer and that they match the expressed need of the health care provider. To avoid that tenders are ambiguous i.e. where the request for proposal and tender describes different or imprecise system properties, it is important that the health care provider has prepared a proper requirement specification. The health care provider that describes a device must put thought into whether one desires a product with a medical function that clearly benefits the patient or not.

6.5.3 Decision of the manufacturer

It is the specification from the manufacturer that decides whether the product is a medical device or not. The manufacturer may have expressed this as an explicit statement or by a device description in a way that it meets the definition in the law. However, a manufacturer can for some reasons avoid mentioning this, even though it is obvious that the device will be used for a purpose in accordance with the definition. The device then will not be under the supervision by the Medical Product Agency and no requirements for medical devices will be applicable. In a possible procurement situation, a vendor can claim in the tender that the information system, e.g. an electronic patient record system, is not classified as a medical device. A user then cannot expect that the manufacturer has taken patient risks and patient benefits into account when designing the system. There is no guarantee that either the risk management process or post market follow up, which are required to mitigate patient risks, can be fulfilled. Therefore, it will be the responsibility of the health care provider and the clinic to avoid patients or staff getting harmed when the system is used.

6.5.4 Definition of contractual party

In some requests for proposals, it is apparent that the requirements are aimed for a party without mandate to affect the requirements. It is important to differ between vendor, distributor or manufacturer (unless they are the same) in the respect of who will be accountable for product safety. The requirements in the medical device directives are primarily aimed for the manufacturers. It is expected that the requirements are fulfilled in all aspects. It is however necessary that requirements dealing with the manufacturer's customer relations and feedback of experiences are known to distributors and representatives, if they are the contractual party. This applies especially for vigilance reporting. Distributors and representatives must also have knowledge of which demands they can impose on manufacturers. There are often misunderstandings about the requirement for registration.

6.5.5 Managing complaints and adverse events

One important requirement on a manufacturer of medical devices is that there has to be a system for monitoring experiences from the market, i.e. attend to complaints and adverse events such as side effects, accidents and incidents. The request for proposal should include a request to describe how complaints and adverse events will be followed up and who will be responsible for this task. One can also demand that the manufacturer states in the information to the user (e.g. in the instructions for use) how and who to contact in the case of complaints and adverse events. A distributor/representative

indicating in an offer that there has been a number of accidents and incidents does not necessarily mean that the manufacturer has bad products, but rather a functioning system for monitoring experiences from the market.

6.5.6 Documentation

It is of great value that tenders show the documentation from the quality management process in respect to process control, materials, traceability, subcontractor reviews and their competence. Likewise, one shall demand access to instructions for use and safety information to users/patients with information on how to use the device and information on how to contact the manufacturer. The request for proposal may contain a demand to include the "Declaration of conformity" of the CE-marked device together with the tender documentation. The aim is to get assurance from the manufacturer that the medical device fulfills the essential requirements in the medical device directives.

6.5.7 Follow up of contracts

By following up contracts, it is possible to contribute to further improvements which help both the distributor and the client to sustain a safe device with the anticipated patient benefit. It is also of great importance to continuously follow up that the distributor fulfills the requirements as decided in the procurement process, since an agreed contract may not be altered, by either party. The methods for following up a contract by doing supplier vendor evaluations, e.g. using questionnaires during the contract period, can however be further improved.