Contract no. 224306

LABONFOIL

Laboratory Skin Patches and SmartCards based on foils and compatible with a Smartbiophone

INSTRUMENT: Large-scale integrating project (IP)

D13.1 Regulatory analysis of the development

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CO	Confidential, only for members of the consortium (including Commission Services)	☒

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BIOEF

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1. ABSTRACT

The objectives of this Work package are to study the regulatory aspects affecting the new products developed within the project. We understand that since the four applications included within the project are so different, in terms of market regulations and needs, that each will need its own regulation: for example the CEA application will be included within the medical devices regulation while Skin patch application will be regulate under workplace drug testing. That is the reason that has led us to dedicate a section for each application.

2. FOOD REGULATORY ANALYSIS: DTU-FOOD

Currently there is no EU standard for PCR detection. The EU standard is based on non-PCR methods. EU Gold standard for microbiology of food and animal feeding stuffs include two methods for the detection of Campylobacter and Salmonella, which are schematically described in Figure 1 and Figure 2 and which juxtapose the time-to-result, the test protocols and total costs for each test method.

- Detection of Campylobacter ISO/TS 102723 for Campylobacter spp. (March 1st 2010).
- Detection of and Salmonella ISO 6597:2002 for Salmonella spp. (January 2002).

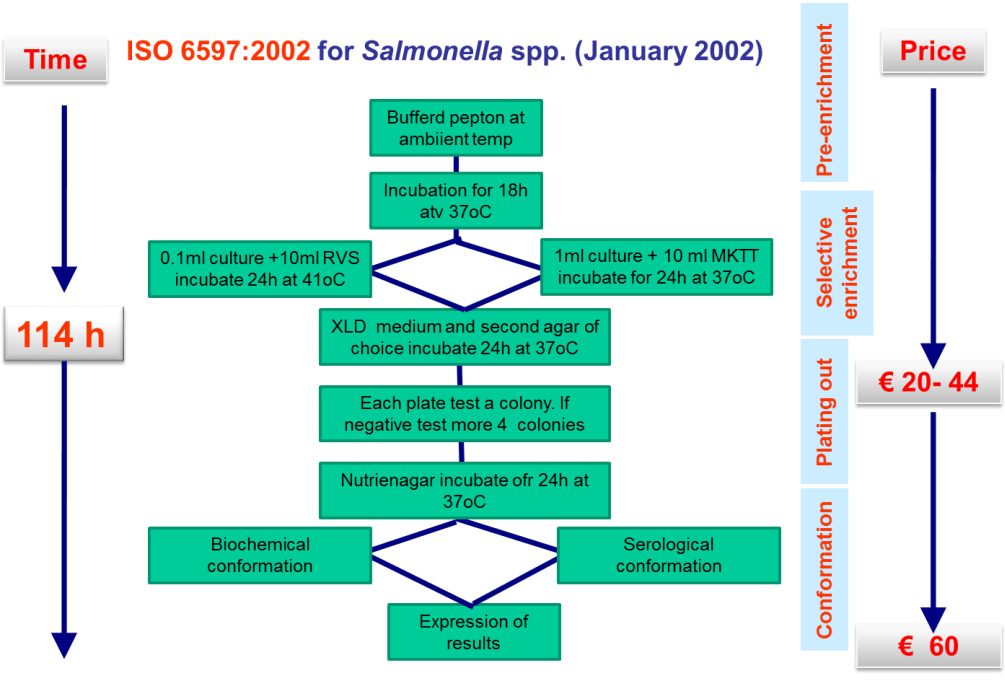

Figure 1. EU standard of Microbiology of food and animal feeding stuffs Methods for the detection of Salmonella spp. ISO 6597:2002. (January 2002).

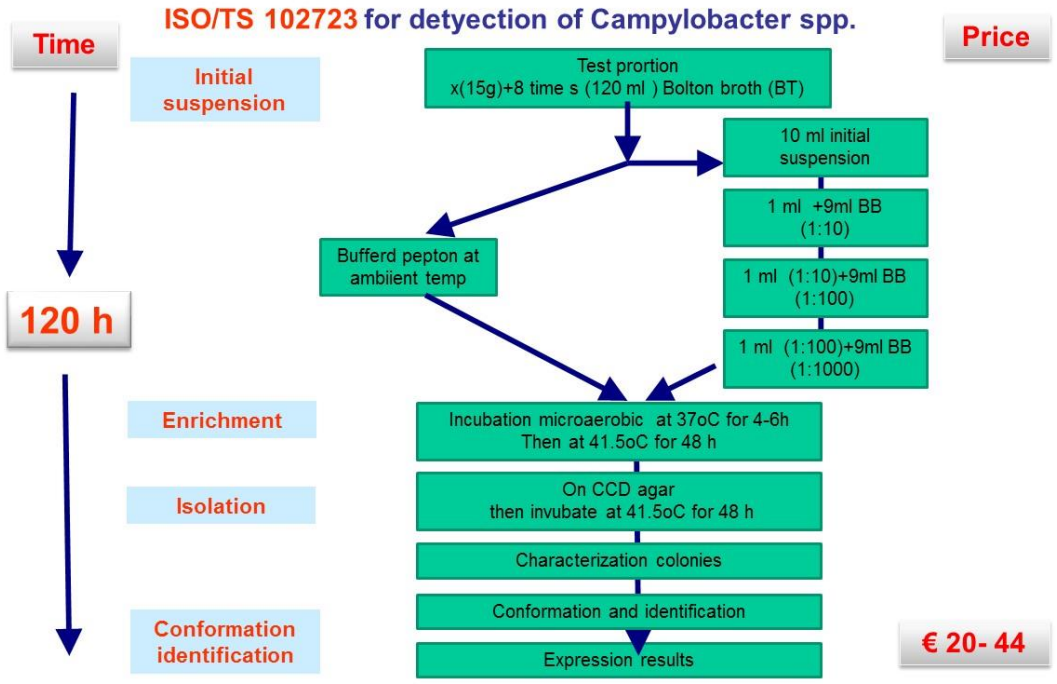

Figure 2. EU Golden standard of Microbiology of food and animal feeding stuffs Methods for the detection of Campylobacter ISO/TS 102723 (March1st 2010).

At this moment, we have been following the Nordic standards for PCR detection of Campylobacter spp. (Figure 3). Our LABONFOIL Labcard reader for the food application was designed to fit within this protocol.

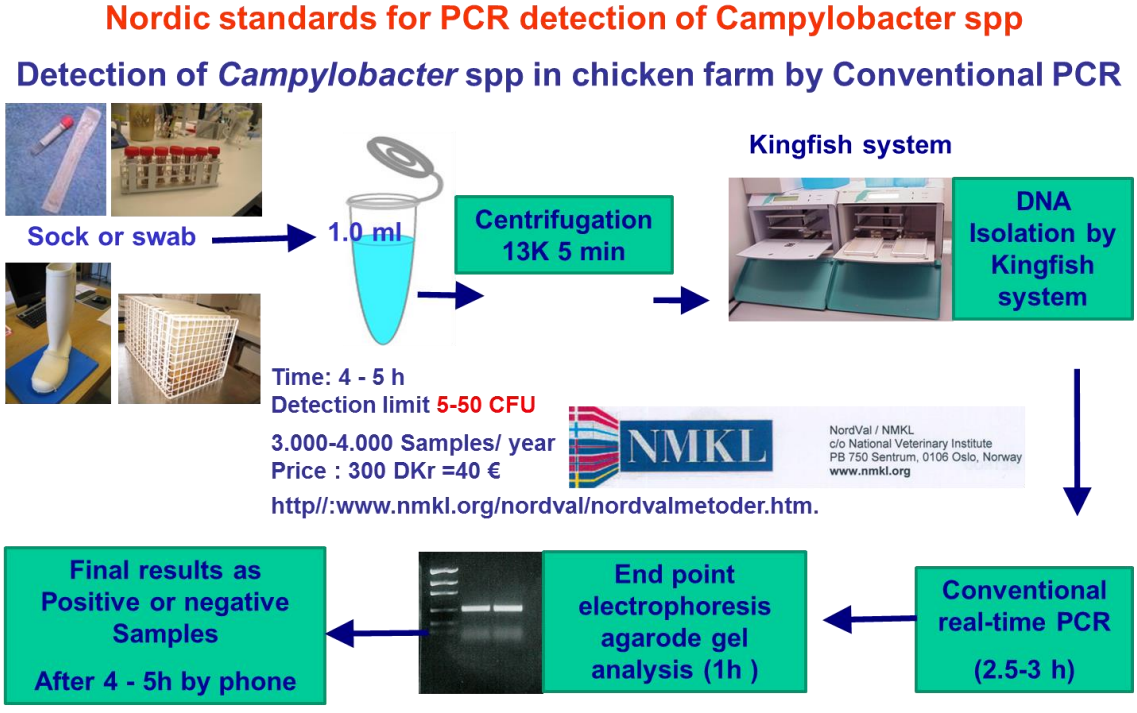

Figure 3. Nordic standards for PCR detection of Campylobacter spp.

3. CEA REGULATORY ANALYSIS

For CEA application we have concluded that the framework to take into account is the related with clinical devices, since is thought to be used within hospitals, smalls clinics or points of care located in outpatient clinics. Given that the main two possible markets are the European Union and U.S.A we have considered timely to detail the regulation and requirements for both markets. Both of them classify all medical devices according to risk, and require approval of riskier devices before they can be marketed. When talking about risk they mean the potential hazards (device safety, potential toxicity) of the device to the patients.

3.1 US Regulatory framework

This regulation requires the acceptance of a notified body. In the United States the agency responsible for regulating firms who manufacture, re-package, re-label, and/or import medical devices sold in their market is the Centre for Devices and Radiological Health (CDRH), a subdivision of FDA. The FDA's regulation process differentiates between three classes of medical devices:

- Class I General Controls: with or without exemptions.
- Class II General Controls and Special Controls: with or without exemptions.
- Class III General Controls and Premarket Approval.

The table in Figure 4 shows risk levels and general regulatory controls for each category:

Classification	Risk Level	Regulatory control	Examples
Class I	Low	General control sufficient, over the counter products	Adhesive bandages, hospital beds, wheel chair
Class II	**Moderate**	**Performance standard and general control, Physician controlled distribution**	**Oxygen marks, blood pressure cuffs, sutures**
Class III	Moderate to high	Require structure type of control, for their safety and efficacy purpose	Pacemaker, Vascular grafts

Figure 4. US classification table. Our Labonfoil Labcard CRC system fells into Class II.

Labonfoil CEA Labcards are classified as Class II in the US market, and if they are not exempt, a 510k application form will be required for their marketing. All devices classified as exempt are subject to the limitations of their exemptions. Device classifications depend on the *intended use* of the device and also upon *indications for use*. A discussion of the meaning of intended use is contained in Premarket Notification Review Program K86-3. Although Labonfoil equipment is a two component system (hardware and labcard) we have considered that our device classification could be:

- Part 862 Clinical Chemistry and Clinical Toxicology devices, subpart C Clinical laboratory instruments, regulation number 862.2570, that defines a device as described as Real Time Nucleic Acid Amplification System (Figure 5).

- We should amend to the previous regulation adding the special feature that is included in Part 866 Immunology and Microbiology Devices, Subpart G-Tumour Associated Antigen immunological Test Systems, Sec. 866.6010 Tumour-associated antigen immunological test system. However we know that the CEA labcard device technology is quite different compared to a regular qPCR, since it includes an immunology part: magnetic beads attached to antibodies, which are supposed to bind to the CEA protein of the patient's serum, which will then join the DNA conjugates. These DNA conjugates will be the templates for the added primers (Figure 6).

Device	**Real Time Nucleic Acid Amplification System**
Regulation Description	Instrumentation for clinical multiplex test systems.
Definition	The system is a clinical multiplex instrument intended to measure and sort multiple signals generated my multiple probes, intercalating dyes, or other ligands in an assay from a clinical sample. Signals may be generated by fluorescence or other phenomena and may be measured using filters on a photodiode or other detector. It may integrate sample and/or reagent handling, amplification, dedicated instrument control, data acquisition software, raw data storage mechanisms and other essential hardware components along with the signal reader unit. The system is used with specific assays to comprise an assay test system.
Physical State	Should not include microarray or electrophoresis detection methods or instruments.
Technical Method	A real-time thermo-cycler is intended to identify and/or quantify the presence of specific sequences of double stranded DNA, amplified from a biological source and labelled with fluorescently labelled probes or through the use of intercalating dyes and detect using a high-power light-emitting diode (LED). Fluorescence emission is detected through the use of filters on a photodiode. The emission filters are optimized for use with specific fluorescent dyes.
Target Area	N/A
Regulation Medical Specialty	Clinical Chemistry
Review Panel	Clinical Chemistry
Product Code	OOI
Submission Type	510(k)
Regulation Number	862.25700
Device Class	2
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Third Party Review	Not Third Party Eligible

Figure 5. Part 862 Clinical Chemistry and Clinical Toxicology devices, subpart C Clinical laboratory instruments, regulation number 862.2570.

Device	**System, Test, Tumour Marker, Monitoring, Bladder**
Regulation Description	Tumour-associated antigen immunological test system
Regulation Medical Specialty	Immunology
Review Panel	Immunology
Product Code	MMW
Regulation Number	866.6010
Device Class	2
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Third Party Review	Not Third Party Eligible

Figure 6. Part 866 Tumour-associated antigen immunological test system.

Regarding manufacture, the basic regulatory requirements for manufacturers of medical devices (for distribution inside the U.S.) include:

a) Establishment registration.

b) Medical Device Listing.

c) Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA).

d) Investigational Device Exemption (IDE) for clinical studies.

e) Quality System (QS) regulation.

f) Labeling requirements.

g) Medical Device Reporting (MDR) Establishment Registration - 21 CFR Part 807.

More detailed information can be found in ANNEX I.

3.2 EU Regulatory framework

In order to prepare the classification for a CEA product, the European commission has issued legally non-binding guidance documents MEDDEV, consensus statements and interpretative documents. The main guidelines MEDDEV 2.1/1, MEDDEV 2.1/5, and MEDDEV 2.4/1 v9 specify 18 criteria for medical devices. These criteria are applied to help a manufacturer determine whether the device is Class I (low risk), Class IIA or Class IIB (medium risk), or Class III (high risk) (risk concerning the patient's safety). These 18 criteria are divided, depending on whether the device is non-invasive (criteria 1-4) or invasive (criteria 5-8), depending if device is active or not (criteria 9-12); Criteria 13-18 specify miscellaneous conditions.

We must consider that Labonfoil CEA system is a **Class I device in the EU market** with measuring function, so the framework should be specific for Class I medical devices. (see Annex IV to read the used classification protocol).

At this moment the current classification and the IVD directive 98/79 with the ISO 13485 would allow the LABONFOL Labcard system to avoid the participation of a notified body. However, this is going to change in the next years, which is likely to make the approval process more time consuming.

Regarding manufacturing, any private or legal person responsible for the design, manufacture, packaging and labelling of a medical device with an objective to marketing the product under his own name, regardless of whether these operations are carried out by that person or by a third party on its behalf must obtain the certification 13485. The providers of the company do not require the certification. For more information go to ANNEX III : External links to IVD directive and amendments.

The pre-market review and approval in the EU is principally conducted by independent third-party testing laboratories [Notified bodies (NBs)] accredited by member state health ministries to review and approve medical devices for the EU market. However, most governments retain final authority for approval of medical devices.

The following section describes the steps to place the Labonfoil CEA labcard system as a class I medical devices on the EU market.

4. STEPS TO SET LABONFOIL CEA LABCARD SYSTEM AS A CLASS I MEDICAL DEVICES

Manufacturers or their authorized representatives that intend to market Class I medical devices within the EU should follow the procedures mentioned below.

4.1 Step 1 – Confirm product as a medical device

Confirm that the product comes within the definition of a medical device as defined in Article 1 (2) of the MDD as amended in accordance with its principal intended purpose and mode of action.

Medical device definition: 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:

a) Diagnosis, prevention, monitoring, treatment or alleviation of disease.

b) Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap.

c) Investigation, replacement or modification of the anatomy or of a physiological process.

d) Control of conception.

There will of course be borderline products where such a determination could be difficult, in such cases consult the relevant competent authority for advice.

4.2 Step 2 - Confirm product as a Class I medical device

In order to confirm that the product is correctly classified as Class I, we need to consult Annex IX of the MDD.

The application of the classification rules shall be governed by the intended purpose of the device and the time of use, part of the body, whether it is active or not, whether it is invasive or non-invasive. If the device is not intended to be used solely or principally in a specific part of the body, it must be considered and classified on the basis of the most critical specified use. In other words if a device could be classified using different rules then the final classification will be the highest.

4.3 Step 3 – Procedures before the Placing on the Market

4.3.1 3a – Meet the Essential Requirements

The devices must meet the essential requirements set out in Annex I of the Directive which apply to them, taking account of the intended purpose of all the devices concerned. Devices must be designed and manufactured in such a way that, when used under normal conditions of use and for the purposes intended by the manufacturer, they will not compromise the clinical condition or the safety of patients or the safety and health of users or other persons, provided that any risks, which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. The devices must achieve the performance as intended by the manufacturer.

4.3.2 3b – Prepare technical documentation

The manufacturer or his authorised representative must hold technical documentation that demonstrates the conformity of their products with the requirements of the Directive. This technical documentation must be prepared prior to drawing up the EC declaration of conformity and kept available for review by the competent authority. Manufacturers should also check with the Competent Authority as to the language requirements for such information. The technical documentation should be prepared following review of the essential requirements and other relevant requirements of the Directive and must cover all of the following aspects. See Annex II.

4.3.3 3c – Request Notified Body intervention

In the case of products placed on the market in sterile condition, the manufacturer or his authorised representative must follow the procedure referred to in Annex II or V of the MDD. For devices with a measuring function the manufacturer or his authorised representative must follow one of the procedures referred to in Annex II, IV, V or VI of the MDD. This requires the intervention of a notified body. In all other cases the intervention of a Notified Body is not required for Class I devices. The intervention by the notified body is limited to:

- In the case of products placed on the market in sterile condition, only the aspects of manufacture concerned with securing and maintaining sterile conditions.
- In the case of devices with a measuring function, only the aspects of manufacture concerned with the conformity of the products with the metrological requirements.

4.3.4 3d – Prepare Instructions for Use and Labelling

Each device must be accompanied by the information needed to use it safely and to identify the manufacturer or authorised representative, taking account of the training and knowledge of the potential users. This information comprises the label and the data in the instructions for use. By way of derogation to the general principles no instructions for use are required for Class I devices if they can be used safely without such instruction. Such devices could include bandages, readymade spectacles and walking sticks.

National language requirements must be taken into account in relation to the labelling and instructions for use. Language versions used are to be included in the technical documentation.

In the light of technical progress in information technology and medical devices, a process should be provided to allow information by the manufacturer also to be available by other means.

4.4 Step 4 – Draw-up the EC Declaration of Conformity

The EC declaration of conformity is the procedure whereby the manufacturer or the authorised representative, who fulfils the obligations imposed by Section 2 of Annex VII of the MDD and, in the case of products placed on the market in a sterile condition and devices with a measuring function, the obligations imposed by Section 5 of Annex VII ensures and declares that the products concerned meet the provisions of the directives which apply to them. The declaration of conformity should contain all information to identify the directives to which it is issued, as well as the manufacturer, the authorised representative, the notified

body and the product, and where appropriate a reference to harmonised standards or other relevant documents.

4.5 Step 5 – Affix the CE marking

All Class I medical devices placed on the market must bear the CE marking of conformity, which must be affixed in a visible, legible and indelible form on the device or in its sterile packaging, where practicable and appropriate, and on the instructions for use, as well as on any sales packaging. In the case of Class I medical devices placed on the market in a sterile condition and/or devices with measuring function, the CE marking must be accompanied by the identification number of the relevant Notified Body.

It is prohibited to affix marks which are likely to mislead third parties with regard the meaning of the CE mark. Other additional marks may be affixed to the device, to the packaging or the instructions for use provided the visibility or legibility of the CE mark is not impaired.

The CE marking format should be in compliance with Annex XII of the MDD. Where the device is very small the minimum dimensions of the CE mark may be waived.

4.6 Step 6 – Notify the Competent Authorities

Under Article 14, the manufacturer of a Class I medical device, or his authorised representative, must inform the competent authority of the country in which they have their registered place of business of the address of the registered place of business and provide a description of the device that is sufficient to identify it. Manufacturers or his authorised representative should contact their relevant competent authority with regards the procedures and forms required for such notifications and whether a fee will apply.

4.7 Step 7 – Record, evaluate and notify incidents

The manufacturer or his authorised representative is responsible for activating the vigilance system and must inform the surveillance authority about incidents that invoke it according to Paragraph 4, Annex VII of the MDD. After notification, the manufacturer is obliged to make investigations, compile and send a report to the surveillance authority, and consider, in collaboration with the authority, what action should be taken. Directive 2007/47/EC will make it a requirement to notify all relevant competent authorities of adverse incidents occurring as part of a clinical investigation

4.8 Step 8 – Review experience gained from Post-Market Surveillance

The manufacturer shall put in place and keep updated a procedure to review experience gained from devices on the market and to implement necessary corrective action taking account of the nature and risks in relation to the product. Any clinical evaluation and its documentation must be actively updated with data from post market surveillance (Ref: Directive 2007/47/EC).

5. ENV REGULATORY ANALYSIS

No need for regulation due to research focused application.

6. SKINPATCH REGULATORY ANALYSIS: BIOSENSIA

During year three of the lab on foil project, Biosensia continued to monitor the evolving regulatory landscape as applies to work place drug testing (WDT) globally, focusing in particular on activities and developments in policy and legislation within the EU. The use of WDT in both safety critical and non-safety critical workplaces is increasing and has become somewhat routine in private industry workplaces. Calls continue from both private and public organisations for better regulation, definition and guidance of drug & alcohol WDT. Presented herein is an update with respect to changes or progressions (if any) in the current position with regard to work place drug testing with a particular emphasis on testing in the workplace for safety critical occupations.

US perspective – There were no significant changes in drug work place testing regulation during year 3 of the lab on foil project

Mandatory workplace testing for US federal employees has been in place for greater than two decades. US work place anti-drug programs where first established in 1981 for the US Military. Subsequently, mandatory testing was introduced in 1983 for Utilities & transportation, in 1984 for Oil & Chemical Industries, in 1985 for Fortune 500 companies, in 1986 for Federal Government employees and in 1988 for Government Regulated safety critical industries.

Up until April 2004 drug testing for federal workplace were exclusively conducted using urine samples. In April 2004 the department of Health and Human Services (HHS) proposed to establish scientific and technical guidelines for the testing or hair, sweat and oral fluid specimens in addition to Urine (Federal register Vol. 69, No 71 April 13, 2004).

The establishment of guidelines for alternative testing matrices continues within the Federal Government department of transport. No definitive reporting timeline has been established, however it is expected that the guidelines should be issued within the next two to three years.

European Perceptive

The November 2003 the Council of Ministers approved a Resolution on combating the impact of psychoactive substances use on road accidents (2004/C 97/01) states “in order to prevent accidents involving heavy vehicles, the use of psychoactive substances by professional drivers should be detected” and envisaged a “specific regime for professional drivers” (part 18). The council resolution invites the commission to ensure a timely and effective follow-up to the European Action Program on road safety and in particular “to consider the possibility of proposing measures aimed at ensuring appropriate levels of control on professional drivers”.

The resolution further "underlines the importance of taking any appropriate measures, which may include sanctions, in respect of vehicle drivers who are under the influence of psychoactive substances, which reduce their capacity to drive", and "to ensure issues related to driving under the influence of psychoactive substances are tackled in the context of EU activities in the field of road accidents" (part 29).

Additionally, in the year just past the Pompidou Group a Council of Europe organisation established an ad hoc working group focusing on “the prevention of drug use in the work place” (P-PG/Work(2011)1 who’s terms of reference include a need to “provide benchmarks

for all active partners to strengthen the framework in which any monitoring or checks may be conducted, regulated or prohibited" and to improve exchanges of information between international groups (ILO, US Dept. of Transport & WHO) active in the area. The establishment of the working group further demonstrates the move towards understanding the implications of drug use within the work place and for the need to define and regulate testing for drugs within the work place. The first official meeting of the group will take place in June 2011.

In the terms of reference of the Pompidou working group point to some trends leading to the need for an increase in WDT. They state;

1. 15 to 20% of accidents, absenteeism and personal conflicts at work are said to be linked to the use of alcohol, drugs or psychotropic substances.
2. The problem has grown in recent years.
3. All occupational sectors are affected by the problem.

Movement towards the definition and pan European harmonisation continued during the last 12 months. Private and sector organisations are also moving towards providing guidance on WDT. Organisations such as the European Work Place Drug Testing Society (EWDTS) published draft guidelines in relation to Specimen Collection (July 2009), Oral fluid Testing (July 2010) and hair testing (August 2010). EWDTS will also run a symposium on WDT this June in Edinburgh.

National Legislation Work Place Testing

Presented below is the current status of work place drug testing legislation in selected EU countries. WDT is a complex topic and legislation within the EU member's states is not harmonised, nor is the regulation at European level harmonised. As evidence above there are movements both at a public and private level towards harmonisation. Finland (2003), Ireland (2005), Norway (2005) and Italy (2008) have implemented specific legislation in relation to drug testing in the work place. However, the majority of all other states imply the need to protect the safety of others in the work place including the prevention of drug and alcohol use in the work place. The duty of care typical falls to the employer.

	Legislation on WDT	**Workplace laws related to WDT**
Belgium	There is no specific legislation on workplace drug testing. Pre-employment testing for safety critical roles can be carried out.	Under Art. 14 of Royal Decree 28 Mat 2003, pre-employment drug testing can be done for jobs where drug use presents a safety risk.
CzechRepublic	There is no specific legislation on workplace drug testing. It is regulated generally in The Labour Law No. 65/1965.	It is forbidden to use drugs or to be under their influence at the workplace or in working time. It corresponds to the duty of an employer to ensure safety and health protection at work (The Labour Law No. 65/1965, s. 133, 135). The employee is committing a misdemeanour or a criminal offence, if he/she is under the influence of psychoactive substances and performs a task, by which he/she could endanger others' health or means.
Denmark	There is no specific legislation on workplace drug testing.	The Work Environment Law of 11 October 1999 (LBK 784/99), Chapter 11 allows the Minister of Labour to pass regulations regarding medical examinations of employees in specific sectors whose work is associated with health risks.

Germany	There is no single legislation on drug testing in the workplace, though various laws refer to it, and there is some case law from the Federal Labour Court. Drug testing is reported to be carried out much more during pre-employment than during employment.	The Occupational Safety and Health Act (ArbSchG), ss.3-7, oblige the employer to ban drugs at work if there is a considerable danger. The Accident Prevention Regulations by the Occupational Accident Insurance Funds oblige the employee not to be in a state that endangers himself or others, and the Works Constitution Act (BVG) s.87 permits a ban, and testing, for the influence of drugs during working hours. The Federal Labour Court accepts an obligation to test due to the employee's "general duty of loyalty", provided the employer has a legitimate reason to test (such as suspicion). Routine tests are not allowed except in dangerous or security-sensitive workplaces.
Estonia	There is no binding legislation on testing in the workplace. However, workplace laws allow action to be taken if an employee is intoxicated at work, and a decree might permit doctors to determine the degree of intoxication.	Under s.56 of the Employment Contracts Act, "an employer suspends an employee who is intoxicated by [drugs] from work for that day (shift). The employer is also required to suspend employees with signs of the residual effects of [drugs], and employees who are under the influence of medicines if the job demands particular accuracy, involves control over a major source of danger or working in its immediate vicinity." For civil servants, a similar clause is included in s.109 of the Public Service Act.
Greece	There is no specific legislation on workplace drug testing, though the Data Protection Authority's Code of Conduct refers to it.	Article 7 of the law 2683/1999 (Code for civil servants), regarding health, permits testing individuals at the pre-employment stage. A law of 1997 permits testing of private individuals at the pre-employment stage, for Security Services.
Spain	There is no specific legislation on workplace drug testing.	The Law 13/1995, of 8 Nov on Prevention of Labour Risks declares that "the employer will guarantee to his employees a periodic surveillance of their state of health in function of the inherent risks to the job" (Art 22.1(1)), bearing in mind that the surveillance of the workers´ health will be carried out, as a rule, with their previous consent and "respecting the worker's right to privacy and his dignity, and the confidentiality of all the information related to his state of health" (Art 22.2).
France	Only workers in "traditional" safety-sensitive positions are subjected to testing in any form.	The Labour Code prohibits restriction of workers' rights and individual and collective freedoms unless this is justified by the nature of the task to be accomplished, or proportionate to the desired objective (employers must therefore justify potential restrictions) (Article L120-2, inserted by Law 92-1446 of 31 December 1992 (Aubry Law)); and provides that employees must be made aware of any monitoring that may focus on them (Articles L121-7 and 121-8 inserted by Aubry Law). The Ministry of Transport Act (arrêté) of 30th July 2003 provides for a biological examination conducted by an occupational doctor to detect psychoactive substances for security jobs in the national railway system.
Ireland	The Safety, Health and Welfare at Work Act 2005 requires employees to submit to drug tests if reasonable. These are implemented only in safety-critical sectors.	The Safety, Health and Welfare at Work Act 2005, s.13 requires employees not to be under the influence at work, and to submit to drug tests if reasonable; it is an offence, punishable by fine or prison, to fail to do this (s.77). Employer can ask doctor to check employee's medical fitness to work, s.23.Doctor should tell employer of decision, and employee of reason for decision.s.8 obliges the employer to provide a safe place of work. Regulations in 2006 will implement this Act and define details.
Italy	Specific law on drug-testing at work applies to certain categories of workers to be identified in decree n 131, October 2007	Art. 125 of the DPR 309/90 [the main drug law] states that certain categories of workers, holding "positions which involve a threat to security and the physical safety and health of third parties", must undergo pre-employment and regular testing for drug addiction at the expense of their employer. In the case of a positive result of the drug testing, the employer must relieve the worker from the position which involves a threat to security and the physical safety and health of third parties. The employer may be fined up to €25 000 for non-compliance. Positions specified by the decree include public and private transportation, oil/gas companies

		and explosives/fireworks companies
Cyprus	There is no specific legislation on workplace drug testing.	There is a general duty of the employer to ensure health and safety at work under the Safety and Health at work Law, 89(I)/1996, but no specific reference to this issue, except a general prohibition of the use of controlled substances at the workplace. There is no provision on how this is checked.
Latvia	The issue of drug testing at the workplace has limited regulations applicable.	Labour Law of 1 June 2000, Chapter 26 Section 101 states that the employer has the right to terminate an employment contract on the basis of listed circumstances, including that the employee when performing work is under the influence of drugs. The Cabinet Regulation N 625 adopted 23.08.2005 "Procedure of alcohol, narcotic, psychotropic and toxic substances impact test" provides that if employer is suspicious that employee is under the influence of drugs he can be referred to drug testing.
Lithuania	Workplace laws allow action to be taken if an employee is intoxicated at work, and a decree might permit doctors to determine the degree of intoxication.	Administrative Infringements Code of the Republic of Lithuania (Section ten "Administrative Infringements in transport, traffic economy and communication area") states transport drivers shall be suspended if there is sufficient presumption that they are intoxicated with narcotic substances. Order No 92 of the Government of the Republic of Lithuania (15 January, 1996) on Testing for intoxication of drivers and other persons defines the persons authorised to test (including certain employers of drivers), test procedures and consequences of testing drivers.
Luxembourg	There is no specific legislation on workplace drug testing.	Law of 6 May 1974 Creating Joint Work Committees In Private Sector Enterprises And Organising The Employee Representation In Companies, Ch.I, Section 4 Art. 7: joint works committees in private sector enterprises (with over 150 employees) have co-determination rights on the introduction and application of techniques designed to monitor employees' behaviour and performance at work.
Hungary	There is no specific legislation on workplace drug testing.	The Act on Labour Safety (No. 93/1993) does not authorize the labour safety controllers to make drug tests. The practice of the courts is only standard in the field of alcohol tests: involvement is obligatory for employee because of his labour relations.
Netherlands	There is no legislation which regulates workplace drug testing, so drug tests are not obligatory and the employees have the right to refuse. Pre-employment drug testing of all applicants is prohibited by law; testing of the successful applicant is permitted in certain circumstances.	In March 1990, a cross-Ministerial government report stated that testing is possible only when the type of work justifies it. A WDT programme must be based on an agreed procedure between the employer and the workers council. The Medical Examinations Act s.4, only permits drug tests if there is a justifiable cause connected with the job itself, such as risks to the employee or third parties. A contractual clause giving the employer a right to test the employee is generally not considered to be sufficient, though this may differ in special circumstances (the Court permitted it in a case dealing with a rehabilitation centre for drug addicts).
Austria	There is no specific legislation on workplace drug testing.	According to s.15 (4) of the Employee Protection Act (ArbeitnehmerInnenschutzgesetz, ASchG) employees are obliged not to be in a state caused by the use of alcohol, medicines and drugs that endanger themselves or others.
Portugal	There is no law that regulates drug testing, but the Data Protection Authority has made a pronouncement on it.	The employer shall promote medical exams with the intention to verify the physical and psychic condition of the employees for the exercise of their profession, as well as to verify the impact of the work and the working conditions on the worker's health (Decree-Law 26/94, Art. 16.1).

Slovenia	There is no specific legislation on workplace drug testing.	Drug testing is implemented on the basis of assessment of employee's capability to work (if he/she is fit to work). The occupational physicians are authorized to make such examinations. Some employers include drug testing in preventive and (in the case of suspicion) also periodic medical examinations. There are special regulations on drug testing for risk professions (e.g. transport, army, police etc.).
Slovakia	The issue of workplace drug testing is regulated by the law on safety and health protection at work.	In the act No. 330/1996 Coll. on safety and health protection by work, the employer has a legal duty to test if the employee is under the influence of drugs during the working time. Under s.14 the employee has a duty to be subject to examination by the competent state authority or employer to find out if he is not under the influence of drugs. The criteria and other details of the testing procedure should be set out in internal regulations issued by each employer, following their approval by the trade union involved.
Finland	The 2004 Act on Workplace Drug Testing defines the details for workplace testing.	The Act on Workplace Drug Testing (759/2004) ss.7-8 permits workplace drug testing paid for by the employer, for successful job applicants, or current employees. This is in certain defined circumstances, where intoxication or addiction may endanger life, health, national or traffic safety, security of information in the public interest, or business or professional confidentiality. The State Council Decree on Good Practice in Workplace Drug Testing outlines the details of the testing procedures.
Sweden	There is no specific legislation on workplace drug testing.	The 1994 Public Employment Act, s. 30 permits the employer to conduct regular health tests, following a special request, if health problems of the employee at work could entail a risk of human life, personal security or health, or of substantial damage to the environment or property. Employers and employees may stipulate conditions for WDT in the collective bargaining agreement. Case law from the Swedish Labour Court stipulates that certain conditions, such as security reasons, could justify an employer to oblige an employee to undergo a drug test.
Norway	Testing is regulated by the 2005 Act relating to Working Environment, Working Hours and Employment Protection. Subjection to medical examinations (eg drug testing) is a serious interference with the personal integrity of the employee/ job applicant and should only be executed when strictly necessary	The Act No. 62 of 17 June 2005 relating to Working Environment, Working Hours and Employment Protection s.9-4 states that the employer can only demand medical examinations (eg drug testing): when pursuant to law or regulation - for positions which are associated with special risk - when the employer finds it necessary to protect the life or health of employees or a third party.

Figure 7. National Legislation Work Place Testing.

7. CONCLUSIONS

In terms of food, there are no current EU regulations for pathogens based on PCR. This can be used as an advantage for future commercialisation.

Related to the CEA detection, the classification gives Class II in the US regulation protocol with the intervention of a Notified Body. Whereas, in EU the Class is I and there is no need of Notified Body intervention. However, in the EU new regulation coming will force the intervention of the Notified body.

The Environmental application is dedicated for research purposes only. Therefore there is no need of certification.

The Skinpatch regulation falls into the drug testing. Therefore, it is very dependent on the country as it can be seen.

8. REFERENCES

- US Food and Drug Administration web site.
- European Commission Public Health Medical Devices Regulatory framework web site.
- How are medical devices regulated in the European Union? French-Mowat E, Burnett J. J R Soc Med. 2012 Apr;105 Suppl 1:S22-8.
- Heneghan C, Thompson M. Rethinking medical device regulation. J R Soc Med. 2012 May;105(5):186-8.

9. ANNEX I: US REGULATORY REQUIREMENTS FOR MANUFACTURERS OF MEDICAL DEVICES

a) Establishment registration

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA. All registration information must be verified annually between October 1st and December 31st of each year. In addition to registration, foreign manufacturers must also designate a U.S. Agent. Beginning October 1, 2007, most establishments are required to pay an establishment registration fee.

b) Medical Device Listing

Manufacturers must list their devices with the FDA. Establishments required to list their devices include:

- Manufacturers.
- Contract manufacturers that commercially distribute the device.
- Contract sterilizers that commercially distribute the device.
- Re-packagers and re-labelers.
- Specification developers.
- Re-processors single-use devices.
- Re-manufacturer.
- Manufacturers of accessories and components sold directly to the end user.
- U.S. manufacturers of "export only" devices.

c1) Premarket Notification 510(k) - 21 CFR Part 807 Subpart E

If your device requires the submission of a Premarket Notification 510(k), you cannot commercially distribute the device until you receive a letter of substantial equivalence from FDA authorizing you to do so. A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent.

- Premarket Notification 510(k)

On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 became law. It authorizes FDA to charge a fee for medical device Premarket Notification 510(k) reviews. A small business may pay a reduced fee. The application fee applies to Traditional, Abbreviated, and Special 510(k)s. The payment of a premarket review fee is not related in any way to FDA's final decision on a submission.

- 510(k) Review Fees

Most Class I devices and some Class II devices are exempt from the Premarket Notification 510(k) submission. A list of exempt devices is located at:

- 510(k) Exempt Devices

If it is planned to send a 510(k) application to FDA for a Class I or Class II device, it is recommended to have the 510(k) application independently reviewed by an accredited persons. FDA accredited 12 organizations to conduct a pre-review of 670 types of devices. By law, FDA must issue a final determination within 30 days after receiving a recommendation from an accredited person. 510(k) reviews by an accredited person is exempt from any FDA fee; however, the third-party may charge a fee for its review.

c2) Premarket Approval (PMA) - 21 CFR Part 814

Product requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device.

Beginning fiscal year 2003 (October 1, 2002 through September 30, 2003), medical device user fees apply to original PMAs and certain types of PMA supplements. Small businesses are eligible for reduced or waived fees.

d) Investigational Device Exemption (IDE) - 21CFR Part 812

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA. Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of non-significant risk must be approved by the IRB only before the study can begin.

e) Quality System Regulation (QS)/Good Manufacturing Practices (GMP) - 21 CFR Part 820

The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labelling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.

f) Labelling - 21 CFR Part 801

Labelling includes labels on the device as well as descriptive and informational literature that accompanies the product.

g) Medical Device Reporting - 21 CFR Part 803

Incidents in which a device may have caused or contributed to a death or serious injury must to be reported to FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported. The MDR regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner.

10. ANNEX II: UE TECHNICAL DOCUMENTATION

DESCRIPTION

A general description of the product, including any variants (for example names, model numbers addition of medicinal substances and sizes).

RAW MATERIALS AND COMPONENT DOCUMENTATION

Specifications including, as applicable details of raw materials, drawings of components and/or master patterns and any quality control procedures.

INTERMEDIATE PRODUCT AND SUB-ASSEMBLY DOCUMENTATION

Specifications, including appropriate drawings and/or master patterns, circuits, and formulation specifications; relevant manufacturing methods; and any quality control procedures.

FINAL PRODUCT DOCUMENTATION

Specifications, including appropriate drawings, and/or master patterns, circuits, and formulation specification; relevant manufacturing methods; justification for choice of materials and any quality control procedures.

PACKAGING AND LABELLING DOCUMENTATION

Packaging specifications and copies of all labels and any instructions for use.

DESIGN VERIFICATION

The results of qualifications tests and design calculations relevant to the intended use of the product, including connections to other devices in order for it to operate as intended. If the manufacturer can provide information showing that a safe design has been established for a number of years and that product has been performing as intended during that time such information is likely to be sufficient to cover this requirements.

RISK MANAGEMENT

The results of risks analysis to review whether any risk associated with the use of the product are compatible with high level of protection of health and safety and are acceptable when weighed against the benefits to the patient or user. If biocompatibility is relevant, for example for skin contact and invasive devices, a compilation and review of existing data or test reports based on the relevant standards is required.

COMPLIANCE WITH THE ESSENTIAL REQUIREMENTS AND HARMONISED

STANDARDS. A list of relevant harmonised standards (for example sterilisation, labelling and information, biocompatibility, electrical safety, risk analysis, product group

standards) which have been applied in full or in part of the products. If relevant harmonised standards have not been applied in full, then additional data will be required detailing the solutions adopted to meet the relevant essential requirements of the Directive. In addition any sterilisation descriptions should be listed.

CLINICAL DATA

Many class I devices will not require a special clinical investigation to establish data on performance and safety or side effects. For products which have been established for a number of years and those which are modifications for such products, it is likely that a compilation and review of existing clinical experience would be sufficient to cover this requirement. However all manufacturers should review the intended use of the product and any medical claims that are being made to ensure that they have both adequate supporting test results and records of relevant experience. However as a general rule confirmation of conformity with the requirements concerning characteristics and performance of the device under the normal conditions of use including undesirable side effects should be based on clinical data. Only in a minority of cases will a specifically designed clinical investigation be necessary in order to demonstrate device safety and performance as required by the Directive. Note that if a clinical investigation is required to justify the use of a device, then the Competent Authority requires advance notification of the proposal.

After 21 March 2010 the Directive will include a requirement that evaluation of clinical data must follow a defined and methodologically sound procedure based on (Ref MDD Annex X):

- Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:
    - There is demonstration of equivalence of the device to the device to which the data relates.
    - The data adequately demonstrate compliance with the relevant essential requirements.
        - Or a critical evaluation of the results of all clinical investigations made.
        - Or a critical evaluation of the combined clinical data provided in 1.1.1 and 1.1.2

OVERLAP WITH PPE DIRECTIVE (comes into force 21 March 2010)

Article 1 (6) of the Directive requires that products which are placed on the market by the manufacturers as dual purpose products being PPE as well as a medical device shall also fulfil the relevant basic health and safety requirements of directive 89/686/EEC. A manufacturer who wishes to place his product on the market with the “dual purpose” must verify compliance with both those directives. Further guidance is available at the Commission homepage: “INTERPRETATION OF THE RELATION BETWEEN THE REVISED DIRECTIVE 93/42/EEC CONCERNING MEDICAL DEVICES AND DIRECTIVE 89/686/EEC ON PERSONAL PROTECTIVE EQUIPMENT”.

OVERLAP WITH MACHINERY DIRECTIVE (comes into force 21 March 2010/ 29 December 2009)

Article 3 of the Directive states that where relevant hazards exist medical devices which are also machinery, as defined in the Machinery Directive, should also meet the requirements of the Machinery Directive where its health and safety requirements are more specific than those in the essential requirement of the Medical Devices Directive. Again the Commission have provided detailed guidance on their website on this overlap: "INTERPRETATION OF THE RELATION BETWEEN THE REVISED DIRECTIVE 93/42/EECCONCERNING MEDICAL DEVICES AND DIRECTIVE 2006/42/EC ON MACHINERY".

Specific transitional guidance (See also: INTERPRETATIVE DOCUMENT OF THE COMMISSION'S SERVICES IMPLEMENTATION OF DIRECTIVE 2007/47/EC AMENDING DIRECTIVES 90/385/EEC, 93/42/EEC AND 98/8/EC):

The new Machinery Directive does not exclude medical devices and shall apply where the hazards referred to in its essential requirements are not covered by more specific requirements in other Community directives. During the period between the date of application of the Machinery Directive (29 December 2009) and of the revised Medical Devices Directives (21 March 2010), manufacturers can choose:

- To fully comply with the Machinery Directive and with the relevant Medical Device Directive,
- To comply with all new requirements of the revised Medical Devices Directives or
- To anticipate only compliance with the relevant EHSR of the Machinery Directive while otherwise complying with the requirements of the current relevant Medical Device Directive, including the usual regime regarding change control As of 21 March 2010, the Machinery Directive will cease to apply and the device will be subject to the revised Medical Devices Directives.

RECORDS

Manufacturing and test records to show compliance with the defined procedures and specifications. The manufacturer or his authorised representative must hold the documentation for at least five years after the product has been manufactured (Ref: MDD Article 12 (4), Annex II (6.1), Annex VII (2)).

11. ANNEX III: EXTERNAL LINKS TO IVD DIRECTIVE AND AMENDMENTS

The core legal regarding in vitro diagnostic medical devices is Directive 98/79/EC. They aim at ensuring a high level of protection of human health and safety and the good functioning of the Single Market. These 3 main directives have been supplemented over time by several modifying and implementing directives, including the last technical revision brought about by Directive 2007/47/EC, as you can check in next table.

	Active implantable medical devices	In vitro diagnostic medical devices	(Other) Medical devices
Original directive	Directive 90/385	Directive 98/79 [347 KB]	Directive 93/42
Amendment 1	Directive 93/42	Regulation 1882/2003	Directive 98/79 [347 KB]
Amendment 2	Directive 93/68	Regulation 596/2009	Directive 2000/70
Amendment 3	Regulation 1882/2003 [218 KB]		Directive 2001/104
Amendment 4	Directive 2007/47		Regulation 1882/2003 [218 KB]
Amendment 5			Directive 2007/47 [185 KB]
Latest but one consolidated version	20.11.2003 including amendment No. 3	20.11.2003 [188 KB] including amendment No. 1	20.11.2003 including amendment No. 4
Latest consolidated version	11.10.2007 [158 KB] including amendment No. 4	07.08.2009 [210 KB] including amendment No. 2	11.10.2007 [265 KB] including amendment No. 5

12. ANNEX IV: EU CLASSIFICATION PROTOCOL FOLLOWED

So first we have to know if our system is invasive:

A device is considered invasive if "(…) in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body", so in our case Labonfoil system should be considered non-invasive.

The first Rule establish: "All non-invasive devices are in Class I, unless one of the rules set out hereinafter applies".

To discard that any other rules is applied, first we should know if rules from 9 to 12(active device) are applicable to our Labonfoil system. The definition says that an active device is: "Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities". So we conclude that Labonfoil system is an active one device, but its characteristics do not allow applying none of these rules (9-12). Rule 10 does not affect us since CEA measuring is not "intended for monitoring of vital physiological parameters". Within the last four rules, rule 13 (All devices incorporating, as an integral part, a human blood derivative are in Class III) could be problematic, but the sample (serum) is not an integral part.

Last consideration to make is to check if our system is a Class I medical device with measuring function, because these characteristic forces the manufacturer to additionally "follow one of the procedures referred to in annex Iv, v or VI, for the aspects of manufacture concerned with the conformity of the products with the metrological requirements".

There are three criteria to fulfill:

a) The device is intended by the manufacturer to measure quantitatively a physiological parameter. In our case CEA level.

b) The result of the measurements is displayed in legal units. In our case, although a qPCR just gives a Ct (Cq) result (Cycle threshold) the final validation process is thought to yield a tool to translate from Ct result to ng/ml, the legal unit.

c) The intended purpose implies accuracy, where a non-compliance with the implied accuracy could result in a significant adverse effect on the patient's health and safety.