

Pre-analytical processes in medical diagnostics: New regulatory requirements and standards

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ABSTRACT

In May 2017, the European *In Vitro* Diagnostic Regulation (IVDR) entered into force and will apply to *in vitro* diagnostics from May 26th, 2022. This will have a major impact on the *in vitro* diagnostics (IVD) industry as all devices falling under the scope of the IVDR will require new or re-certification. It will also affect health institutions developing and using in-house devices. The IVDR also has implications with respect to product performance validation and verification including the pre-analytics of biological samples used by IVD developers and diagnostic service providers.

In parallel to the IVDR, a series of standards on pre-analytical sample processing has been published by the International Organization for Standardization (ISO) and the European Committee for Standardization (CEN). These standards describe pre-analytical requirements for various types of analyses in various types of biospecimens. They are of relevance for IVD product developers in the context of (re)certification under the IVDR and to some extent also to devices manufactured and used only within health institutions.

This review highlights the background and the rationale for the pre-analytical standards. It describes the procedure that leads to these standards, the major implications of the standards and the requirements on pre-analytical workflows. In addition, it discusses the relationship between the standards and the IVDR.

Introduction

On April 5th, 2017, two new EU regulations on medical devices were adopted: the Regulation (EU) 2017/745 on medical devices (MDR) and the Regulation (EU) 2017/746 [1] on *in vitro* diagnostic medical devices (IVDR). The novel legislation of the European Union

(EU) has to be applied in 2020 for the Regulation on medical devices and in 2022 for the Regulation on *in vitro* diagnostic medical devices. One key objective of the regulatory reforms is to promote higher levels of evidence for safety and quality including performance before *in vitro* medical devices are approved in Europe (Recitals 1 and 4).

The IVDR will replace the existing IVD Directive 98/79/EC in May

Abbreviations: IVDR, regulation on *in vitro* diagnostic medical devices; MDR, regulation on medical devices; IVD, *in vitro* diagnostic; IVDMD, *in vitro* diagnostic medical device; CEN, European Committee for Standardization; TS, technical specification; ISO, International Organization for Standardization

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2022 after a 5 year transition period. Although the IVD Directive requires devices to be CE-IVD marked before being placed on the market, the regulatory requirements were lower for most devices than in the IVDR including self-declaration of conformity by the manufacturers for most such devices. The requirements change significantly with the new IVDR, which established a new risk-based device classification and requirements for broader verification of the analytical performance including definition of pre-analytical parameters. Furthermore, depending on the device, the fulfilment of the specific intended use has to be validated, requiring clinical evidence to demonstrate the claimed benefits and safety of the device, and ongoing post-market surveillance to ensure conformity.

The scope of the IVDR

The Regulation covers *in vitro* diagnostic medical devices as defined in Article 2:

“*in vitro* diagnostic medical device’ means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software 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 on one or more of the following:

- a) concerning a physiological or pathological process or state;
- b) concerning congenital physical or mental impairments;
- c) concerning the predisposition to a medical condition or a disease;
- d) to determine the safety and compatibility with potential recipients;
- e) to predict treatment response or reactions;
- f) to define or monitoring therapeutic measures.”

The term *in vitro* diagnostic medical device (IVDMD) applies amongst many others to devices e.g. for genetic testing, infectious disease testing, cancer diagnosis and specimen receptacles for IVD and also includes “companion diagnostics”, devices which are essential for the safe and effective use of a corresponding medical treatment to:

- a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;

IVDMDs also include software, depending on its intended use (e.g. health apps), and genetic as well as epigenetic and metabolic tests, which examine specimens from the human body to seek to predict or diagnose disease.

The IVDR is also relevant to the dedicated software which makes the diagnosis or predicts disease risk or drug response, as this is likely to count as a medical device and will therefore be regulated to ensure that it provides the claimed benefits and is safe. If genetic test results (specific tests or whole genomes analysis) are used for a medical purpose, these will also be covered by the IVDR, whilst genetic ancestry or paternity tests are not.

Conforming to this Regulation is a major challenge for the industry and in particular for small- and medium-sized enterprises (SMEs) developing biomarkers [2] which make up almost 95% of the medical technology industry [3]. In the Netherlands, for example, a study estimated that 84% of the IVDMDs will need to be IVDR certified by a Notified Body (Conformity Assessment Body). Under the old IVDD it was only 7% [4]. The company or institution has to produce a technical dossier (‘technical documentation’) which, amongst others, includes data on the device analytical performance such as e.g. the predictive value of the test (where relevant), and the device clinical performance, and which ensures compliance with the device general safety and

performance requirements. This dossier will be assessed by a Notified Body which must award the test a CE-IVD mark before it can be placed on the market. To collect the information required for the dossier, companies may need to conduct clinical performance studies. In many cases, these studies will need to be registered in advance within an EU member state. There are also requirements for post-market surveillance, updating of technical information and the reporting of adverse events. This procedure needs to be completed before May 2020 for the medical devices and May 2022 for the IVDMDs, although most Notified Bodies have not yet been accredited according to the new IVDR requirements. Many stakeholders fear that an insufficient number of Notified Bodies will be designated on time to enable them to start managing the wave of submissions for initial certification according to the new legislative framework [5] and that a delay in the certification process might occur.

Requirements of the IVDR

IVDMDs are classified on a risk-based criterion as given in Annex VIII of the IVDR. In brief, Class D (highest risk class) includes devices which test for highly critical parameters such as those relevant for transfusion and transplant medicine and for examining life-threatening and highly infectious diseases endangering patients’ lives. Class C includes a large variety of *in vitro* diagnostic medical devices including human genetic tests, companion diagnostics, screening and diagnosis or staging of cancer as well as infectious diseases testing, pre-natal and most self-testing devices; Class B includes less critical parameters such as glucose and leucocyte testing. Class B is also a “default class” for devices not covered by the other classification rules. Class A (lowest risk class) includes products for general laboratory use including buffers, wash solutions, generic nucleic acid isolation kits, instruments and patient specimen receptacles (e.g. for collection of blood or saliva). The software provided with a device is classified with that device, and independent software is classified based on its purpose. Classes B, C and D will require assessment of the technical documentation by a Notified Body. This technical documentation should include an evaluation of its performance based on the:

- a) Scientific Validity: association of an analyte with a clinical condition or physiological state.
- b) Analytical Performance: ability of an IVDMD to correctly detect and measure the analyte. This includes classical performance parameters such as analytical sensitivity, analytical specificity, trueness, precision, accuracy, limits of detection and quantitation, measuring range, linearity, and cut-off. It also includes the determination of appropriate pre-analytical specimen features, such as sample collection and handling as well as traceability of values assigned to calibrators and/or control materials.
- c) Clinical Performance: ability of the test/device to yield results that relate to a particular clinical condition for the intended use and in accordance with the target population, and to the intended user (if applicable).

Many of the IVDMD will under the IVDR be up classified from a lowest risk class device, where currently less data and documentation are required, to a higher class (e.g. classes D, C or B) where a substantial amount of data has to be provided. It is estimated that due to the re-classification about 80–85% of *in vitro* diagnostics companies’ products need a Notified Body for market approval [4,6].

Developers of new devices, in order to access the market in 2022, need to set up analytical and clinical performance studies to fulfil the above requirements. It is also important to mention that existing devices might need to be requalified to access the market in 2022. IVD developers are also required to submit data that fulfil the above requirements. To some degree so called laboratory developed tests (*i.e.* devices manufactured and used only within health institutions) are now also included in the IVDR requirements. The health institution has to

justify in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market. Developing and implementing such an internal device might require setting up appropriate analytical and clinical performance studies and requires that the tests are manufactured and used under appropriate quality management systems (ISO 15189 where applicable national provisions are in place, including national provisions regarding accreditation). The success of these studies depends on a number of factors such as methodological design, patients' inclusion criteria, and also an appropriate quality of biological samples and data.

It is quite evident that the clinical performance of a product relies on an appropriate quality of patient samples to be analysed. This includes the documentary proof that the particular requirements for a specific intended use can be consistently fulfilled (validation). In simpler words: validation provides evidence that the right product for a specific intended use has been developed. For example, the data should provide evidence that the appropriate companion test has been developed to identify specific features or diagnose a disease for the effective use of a certain drug. Clearly, in order to achieve this aim, all biological samples used to develop such a test should be well characterised and of appropriate quality.

The IVDR underlines the need to warrant the quality of biological samples in several of its articles. This paper will focus in particular on the requirements necessary to ensure an appropriate quality of the patients samples, as this is one of the major criteria underlying the above requirements, *i.e.* the analytical performance, the clinical performance as well as the entire conformity assessment of the device.

Appropriate quality of patients samples

Indeed, the IVDR explicitly states in the preamble that the benefit of IVDMDs lies in providing accurate medical information on patients (Pt. 64, L117/182). An inappropriate quality of samples might hamper a proper assessment and lead to erroneous diagnosis and medical errors. Errors in medical diagnostics provide major harm to patients by preventing or delaying appropriate treatment, providing unnecessary or harmful treatment and incurring unnecessary costs to the health care system. It is estimated that 5% of US adults who seek outpatient care each year experience a diagnostic error [7]. Post-mortem examination has shown that diagnostic errors contribute to approximately 10% of patient deaths, and medical record reviews suggest that diagnostic errors account for 6–17% of adverse events in hospitals. In this context the role of sample quality is of particular importance since approx. 50% of diagnostic errors can be attributed to the pre-analytical phase [8], which is defined as the phase starting from the consent of the patient and continuing up to the isolation of the analyte. During this phase a number of variables may negatively affect the quality of the samples. In the case of tissue specimens, for example, pre-analytical variables are related to conditions of handling and processing of the sample such as duration of ischemia, and use of fixatives for tissue samples, transport and storage conditions, analyte extraction procedures *etc.*

In order to reduce diagnostic errors due to inappropriate quality of biological samples, the IVDR explicitly requests information related to the sample quality in the context of product verification¹ that relates to assay performance (IVDR Annex II: 6.1.1). The information includes

¹ Verification is the documentary proof that particular specifications have been met, or in other words, that the product has the appropriate analytical performance. For example, the companion test used identifies specific features or diagnoses a disease. There is frequently a misunderstanding using the terms validation and verification. A simple definition to understand the difference is: validation is the process of developing the right product for a specific purpose (*i.e.*, the measured value is relevant for a medical decision), whereas verification refers to the appropriate analytical performance (*i.e.*, the IVDMD measures properly what is claimed).

several key pre-analytical parameters, such as sample types, sample stability during transport and storage including time and temperature limits, and effects of freeze/thaw cycles.

The scientific validity data, the analytical performance data and the clinical performance data, their assessment and the clinical evidence derived therefrom shall be documented in the performance evaluation report submitted for conformity assessment to the Notified Body. The performance evaluation report for classes C and D shall be updated at least annually (Article 56, 6).

The conformity assessment relies on the verification that the performance evaluation is adequate as well as the validation of the intended use. It is expected that the data generated by the performance studies are scientifically valid, reliable and robust (Article 57). Before issuing an EU conformity certificate, the Notified Body shall request an EU reference laboratory to verify the performance of specific devices, or a category or group of devices, or test for specific hazards related to a category or group of devices (Article 100, Annex IX, 4.9).

When appropriate, the regulation requires reference to existing so-called harmonised standards in setting up the performance studies (Section II, Article 9). The new pre-analytical CEN and EN ISO standards pertinent to the pre-analytical phase of *in vitro* diagnostic examination are not harmonized under the IVDR but they can provide guidance for setting up the performance studies of a variety of IVDs for molecular diagnostics (Table 1).

If a companion diagnostic IVDMD is composed of several components, it is important that the analytical verification and the validation is conducted for the entire test system. The system may include the analytical test components but also instrumentation and software utilized for result generation and analyses, as well as the pre-analytical steps and reagents to prepare the analyte(s) for analytical measurements. Pre-analytical procedures may include specimen collection, stabilization and/or fixation, transport, storage and extraction of nucleic acids, among others. For example, if an IVDMD is a DNA-based assay, designed to assess formalin-fixed, paraffin-embedded clinical specimens, then pre-analytical evaluation would be expected to include assessment of ischemia periods and different fixation conditions, such as duration or temperature of ischemia, and the recipe of formalin and duration of fixation, to show how these pre-analytical variables may affect assay performance, or would apply CEN and ISO standards relevant to sample pre-analytics, such as ISO 20166-3:2018. If an IVDMD is to be utilized on multiple instrumentation platforms (*e.g.* different sample preparation and analysis systems), each of the instrument platforms should be verified for use with the companion diagnostic assay. Thus, verification and validation of a companion diagnostic IVDMD should encompass the whole diagnostic workflow procedure from sample collection to analyte isolation, performing the analytical test up to the reporting of results.

Role of CEN technical specifications and EN ISO standards

The need for common standards for pre-analytical processes has gained major attention both in the US and Europe [9,10]. Major initiatives under the leadership of the US National Cancer Institute (Biospecimen Research Network [11]) and the European framework programme 7 (the SPIDIA [Standardisation and improvement of Pre-analytical procedures for *in vitro* Diagnostics; <http://www.spidia.eu/>] project [12]) have been undertaken to generate the scientific evidence for pre-analytical standards relevant for molecular sciences in research and medical diagnostics. The research grant provided by the European Commission to the SPIDIA consortium requested the participation of standardization organizations and that the work should lead to evidence-based European standards. As a consequence, SPIDIA partners performed experimental work which laid the foundation for nine Technical Specifications (TS) published by the European Committee for Standardization (CEN) that refer to the ISO accreditation norm for diagnostic laboratories ISO 15189:2012 as normative reference. These

Table 1

CEN/TS and ISO standards on the pre-examination process for molecular diagnostics that have emerged from SPIDIA.

Document title:
ISO 20184-1:2018, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 1: Isolated RNA
ISO 20184-2:2018, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for frozen tissue — Part 2: Isolated proteins
ISO 20166-1:2018, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue —Part 1: Isolated RNA
ISO 20166-2:2018, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 2: Isolated proteins
ISO 20166-3:2018, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 3: Isolated DNA
ISO 20186-1:2019, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for venous whole blood— Part 1: Isolated cellular RNA
ISO 20186-2:2019, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for venous whole blood— Part 2: Isolated genomic DNA
CEN/TS 16835-3:2015, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for venous whole blood— Part 3: Isolated circulating cell free DNA from plasma
CEN/TS 16945:2016, Molecular <i>in vitro</i> diagnostic examinations - Specifications for pre-examination processes for metabolomics in urine, venous blood serum and plasma.

CEN/TS are being developed further to EN ISO standards following the Vienna Agreement, which sets out two essential modes for collaborative development of standards: the mode under ISO lead and the mode under CEN lead, in which documents developed within one body are notified for the simultaneous approval by the other. Following the Vienna Agreement, 7 CEN/TS have already been progressed to ISO International Standards under ISO lead in December 2018 / early 2019 and introduced by CEN as EN ISO standards in January / February 2019, thus replacing the former CEN/TS (Table 1).

The CEN/TS and EN ISO standards for Molecular *in vitro* diagnostic examinations – Specifications for pre-examination processes consist of several parts with essentially the same structure for the various major diagnostically relevant sample types (*i.e.* tissue, blood and other body fluids) and analytes (*i.e.* genomic DNA, circulating cell free DNA, RNA, proteins, and the metabolome). Starting from sample collection from a patient, they cover the whole pre-analytical workflow and provide requirements and recommendations on the actual sampling process, handling, documentation, storage and processing of specimens to the isolation of the various analytes before one or more molecular assays are performed. The table of contents (see Fig. 1 for an example) and the scope can be consulted on the ISO online browsing platform (<https://www.iso.org/obp/ui/#home>, keywords: words from the title of the standard or CEN/TS or the ISO number in Tables 1 & 2). The standards are applicable to molecular *in vitro* diagnostic examinations including laboratory developed tests performed by medical, molecular pathology and molecular biology laboratories. They are also intended to be used by laboratory customers, *in vitro* diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.

The general principle is that for any procedure applied in the pre-examination process, it has to be shown to be fit-for-purpose either by the manufacturer of an assay or by the user. Every quality-relevant step has to be documented to demonstrate compliance with either the manufacturer's instructions or parameters previously determined by the user to be required for proper performance of an assay. There are only a few parameters where the standards are explicit, such as the definition and recipe for standard buffered formalin solution or the ratio of standard buffered formalin solution and volume of tissue to be fixed.

The work on standards for sample pre-analytics is continued under

Example Table of content of ISO 20166-3:2018(en). Molecular *in vitro* diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 3: Isolated DNA

Introduction	
1	Scope
2	Normative reference
3	Terms and definitions
4	General considerations
5	Outside the laboratory
5.1	Specimen collection
5.1.1	General
5.1.2	Information about the specimen donor/patient
5.1.3	Information about the specimen
5.1.4	Specimen processing
5.2	Transport requirements
6	Inside the laboratory
6.1	Information about the reception of the specimen
6.2	Formalin fixation of the specimen or sample(s)
6.3	Evaluation of the pathology of specimen and selection of the sample(s)
6.4	Post-fixation of frozen samples
6.5	Decalcification
6.6	Processing and paraffin embedding
6.7	Storage requirements
6.8	Isolation of DNA
6.9	Quantity and quality assessment of isolated DNA
6.10	Storage of isolated DNA

Fig. 1. Example Table of content of ISO 20166-3:2018(en). Molecular *in vitro* diagnostic examinations — Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue — Part 3: Isolated DNA.

Table 2

Standards under development or released, supported by SPIDIA4P.

Document title:
FprCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for CTCs in venous whole blood — Part 1: Isolated RNA
FprCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for CTCs in venous whole blood — Part 2: Isolated DNA
FprCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for CTCs in venous whole blood — Part 3: Preparation for analytical CTC staining
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations – Specifications for pre-examination processes for human specimen – Isolated microbiome DNA
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for Fine Needle Aspirates (FNA) — Part 1: Isolated cellular RNA
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for Fine Needle Aspirates (FNA) — Part 2: Isolated proteins
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for Fine Needle Aspirates (FNA) — Part 3: Isolated genomic DNA
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for urine and other body fluids — Isolated cell free DNA
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations — Specifications for pre-examination processes for exosomes and other extracellular vesicles in venous whole blood — Isolated RNA, DNA and proteins
prCEN/TS, Molecular <i>in vitro</i> diagnostic examinations – Specifications for pre-examination processes for venous whole blood – Isolated circulating cell free RNA from plasma
CEN/TS 16826-3:2018, Molecular <i>in vitro</i> diagnostic examinations —Specifications for pre-examination processes for frozen tissue — Part 3: Isolated DNA
CEN/TS 17305:2019, Molecular <i>in vitro</i> diagnostic examinations - Specifications for pre-examination processes for saliva - Isolated DNA
ISO/NP 23118, Molecular <i>in vitro</i> diagnostic examinations – Specifications for pre-examination processes for metabolomics in urine, venous blood serum and plasma
ISO/AWI 20166-4, Molecular <i>in vitro</i> diagnostic examinations – Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue – Part 4: <i>In situ</i> detection techniques

prCEN/TS: CEN technical specification draft; FprCEN/TS: CEN technical specification final draft for formal vote; ISO/NP: ISO New Project; ISO/AWI: ISO Approved Work Item.

the successor program of SPIDIA, SPIDIA4P (Standardisation of generic Pre-analytical procedures for *In vitro* DIAgnostics for Personalized Medicine), which performs dissemination and support for

implementation of published standards and contributes to a series of new CEN/TS and ISO/International Standards addressing pre-analytical standardization needs of a variety of classical as well as highly innovative analytes, such as exosomes and Circulating Tumor Cells (CTC), or focussing on the microbiome. In addition, pre-analytical workflow requirements for *in situ* detection techniques ranging from classical haematoxylin-eosin-stained, formalin-fixed and paraffin-embedded (FFPE) tissue sections to immunohistochemistry, *in situ* hybridization, MALDI-imaging to *in situ* sequencing are covered (for an overview on standards to which SPIDIA4P contributes see Table 2).

Discussion

The European IVDR will have major impact on the IVD industry as essentially all devices falling under the scope of the IVDR will require new or re-certification of devices. It will also affect health institutions developing and using in-house devices. In order to demonstrate conformity with the IVDR, data have to be provided on acceptable sample pre-analytical parameters (e.g. ischemia duration, transport duration, fixation condition etc.) for which the performance of an IVDMD has been shown. This can only be achieved by using samples collected and processed under standardized pre-analytical conditions, as defined for example in the described pre-analytical ISO and CEN standards, and stored in certified or accredited biobanks according to the ISO 20387 standard. CEN/TS and ISO/International Standards provide guidance on pre-analytical workflows, which parameters shall or should be standardized, and which parameters shall or should be documented. The ISO 20387 standard for "biobanking and bioresources" is a conformity assessment standard providing general requirements for the collection, transformation, storage and distribution of biological samples and data in order to guarantee an appropriate quality for the intended use.

There are regulatory requirements in the IVDR for a quality management system at the laboratory of a health institution with specific reference to ISO 15189, particularly for laboratory developed tests. However, there is currently no regulatory requirement to comply with the CEN/TS or EN ISO standards on pre-analytical processes. Nevertheless, providing conformity data that have been generated with biological samples fulfilling the requirements of these CEN/TS and ISO standards is expected to markedly reduce the risk that these conformity data are not accepted by Notified Bodies. This risk reduction in the approval of molecular IVDs is of particular relevance e.g. in the context of companion diagnostics where any delay in the approval of a companion diagnostic relates to the delay of market entry of an expensive drug.

In order to comply with the new IVDR, most future class B, C and D IVDMDs that are currently on the market in Europe under the old IVDD have to provide additional conformity data to Notified Bodies at the latest by 2022, otherwise the device has to be taken off the market. The need to generate these conformity data creates a major demand on access to quality-defined samples with proper documentation of pre-analytical parameters. Since such samples are currently not available in sufficient amounts, biobanks should take actions to provide this material to cover the upcoming need. This will be critical not only to support biotech, diagnostic and pharma industries but also to ensure reliable diagnostics, particularly in the context of precision medicine. The European research infrastructure BBMRI-ERIC [13] has identified

biomedical scientists in biobanks, medical universities, hospitals and laboratories, involved in the research and development of IVDMDs, as important providers of biological material and related data to address this need. BBMRI-ERIC also provides education and training on appropriate quality management as well as tools to monitor compliance with pre-analytical workflows. This will enhance collaboration between industry and academia with the aim of developing new medical diagnostic equipment and medical treatment options. Furthermore, some of the work linked to SPIDIA4P is to develop control and reference materials alongside the appropriate reference measurement procedures for traceable value assignment in accordance with ISO 17511:2003.

The new European IVDR brings the EU closer to the USA with respect to legal requirements for *in vitro* diagnostic medical devices including their clinical validation. Despite differences in the application and approval procedures [14], scientific validity, analytical and clinical performance data providing sufficient clinical evidence are required to support the safety and performance including robustness and effectiveness of the medical device, for the benefit of patients.

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