The new EU IVD Regulations and CE Marking Invitro Diagnostic Medical Devices

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1 Introduction

The new EU IVD Regulations (IVDR 2017/746) was formally published in May 2017 and comes into full force from 26 May 2022. The IVDR consolidates and replaces the IVD Directive (MDD) 93/79/EC and is a significant change for the industry. Currently the majority of IVDs do not require Notified Body involvement but under the new IVDR this will change so that most Invitro Diagnostic Devices will require notified body involvement. BSI and LRQA estimate that the re-classification of IVDs will mean 80-90 % will no longer be able to self-certify conformity.

The IVDR comprises of 157 pages up from 37 pages in the IVD Directive and is far more strictly implemented and complex. For those IVD's that are CE marked under the IVD Directive there is no grandfathering of devices which means all existing devices will need to be assessed against the IVDR and current standards and state of the art.

CE Marking provides access to the European Single Market comprising of 28 Member States, the European Economic Area (Iceland, Liechtenstein, and Norway) and, through bilateral treaties, Switzerland and Turkey. These 33 Markets mostly comprise a wealthy, aging population of over 515 million consumers. In addition to the above markets CE Marking can be leveraged to access other markets adding further to its importance.

The IVDR introduces a risk-based approach to classification and there is no direct correlation between the old and new classification system. The IVDR is similar to the MDR in that it takes a lifecycle approach to IVD regulation. It also incorporates many elements of the current European guidance documents and concepts which were not previously legislated for such as Performance Evaluation, Vigilance and Post Market Performance Follow-Up.

A new regulatory body called the Medical Device Coordination Group (MDCG) has been created to foster harmonization efforts, foster cooperation and increase the Commission's power to act as needed. The MDCG may be assisted by expert panels and EU reference laboratories.

As this goes into publication there are many areas including the appointment of reference laboratories that need to be determined, clarified, developed or enacted as well as updates to guidance documents and standard harmonisation. Manufacturers

will need to use the best information available at the time of CE Marking and then update their records as more information becomes available.

Below is a summary of many of the key aspects as well as reference material. SEHTA also runs courses covering many of these requirements throughout the year.

The purpose of the regulations is to ensure that only safe devices that perform effectively are placed on the European market. To achieve this the regulation provides a framework whereby a manufacture may show compliance to the regulation through the CE Marking of their devices. The starting point is setting out the devices ***Intended Purpose*** from which it can be determined whether it is an Invitro Diagnostic ***Medical Device*** and if it is, what the ***Classification*** is.

Once the ***Classification*** of your device has been determined it becomes clearer what conformity assessment routes are available for the manufacturer. ***Conformity Assessment*** is the process whereby the manufacturer demonstrates that they have fulfilled the requirements of the IVDR. Manufacturers demonstrate conformity through their ***Technical Files*** and records, ***Quality Systems*** and ***Clinical Evidence & Performance***.

Once CE Marking has been achieved your CE certificate will be issued and uploaded onto the ***European Database of Medical Devices*** (EUDAMED).

1.1 Classification

IVD's are classified into **four** risk classes. These classes are determined through the application of 7 classification rules taking into account the potential risks associated with the device. The starting point for any classification is **Intended Purpose**

The four classification categories are class A, B, C and D with "D" being the highest risk devices and "A" the least. In addition to these categories, Class A has one subclasses; A **s**terile.

Risk Based Classification

A	low individual risk and	low public health risk
B	moderate individual risk and/or	low public health risk
C	high individual risk and/or	moderate public health risk
D	high individual risk and	high public health risk.

For devices with multiple intended purposes, all purposes must be classified, and the highest risk class is applicable. For devices that do not fall under any of the 7 rules below they will automatically be a class B device.

A reference to the 7 rules and classification is provided below:

Rule	Text	Class
1	• Detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration; • Detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation; • Determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management. Examples: HIV. Hepatitis C Virus, Hepatitus B virus, HTLV I/II,	D
2	• Devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration; • **Except** when intended to determine any of the following markers: – ABO system [A (ABO1), B (ABO2), AB (ABO3)]; – Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)]; – Kell system [Kel1 (K)]; – Kidd system [JK1 (Jka), JK2 (Jkb)]; – Duffy system [FY1 (Fya), FY2 (Fyb)];	C D
3	a) for detecting the presence of, or exposure to, a sexually transmitted agent; b) for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation; c) for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring; d) for pre-natal screening of women in order to determine their immune status towards transmissible agents; e) for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; f) to be used as companion diagnostics; g) to be used for disease staging, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; h) to be used in screening, diagnosis, or staging of cancer; i) for human genetic testing; j) for monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; k) for management of patients suffering from a life-threatening disease or condition; l) for screening for congenital disorders in the embryo or foetus;	C

	m) for screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities.	
4	• Devices intended for self-testing are classified as class C, • **except** for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine. • Devices intended for near-patient testing are classified in their own right.	C B
5	• Products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended to make them suitable for in vitro diagnostic procedures relating to a specific examination; • Instruments intended for in vitro diagnostic procedures; • Specimen receptacles.	A
6	• Devices not covered by the above-mentioned classification rules	B
7	• Devices which are controls without a quantitative or qualitative assigned value	B

There is no direct correlation between the old and new IVD classifications. Changes to the classification rules mean that a large number of IVD's will need to obtain certification from a Notified body by May 2022 including:

- Devices up-classified to A sterile, B, C or D
- Devices new to the IVDR scope

Furthermore, all Class A devices will need to re self-certify to the MDR by May 2022.

1.2 Technical Documentation & Records

The technical documents required to assess conformity are set out in the following three Annexes:

Annex I - General Safety and Performance Requirements (SPR), previously known as the essential requirements);
Annex II – Technical Documentation;
Annex III – Technical Documentation on Post Market Surveillance.

1.2.1 Annex I – SPR

There are 20 SPR requirements in Annex I grouped in three sections:

1. SPR 1-8 General Requirements
2. SPR 9-19 Design and Manufacture

3. SPR 20 Information supplied with the device

Every IVD Device no matter what class is required to complete and satisfy the General Safety and Performance requirements. SPR 20 on “information supplied with the device” has more than 70 sub-parts covering labelling, instructions for use, information required, UDI, warnings and so on.

1.2.2 Annex II – Technical Documentation

The technical documentation requirements closely resemble the Global Harmonization Task Force Summary of Technical Documentation format for Demonstrating Conformity to the Essential Principles of Safety and Performance often abbreviated to the STED format.

Technical documentation covers the following six areas:

1. Device Description and Specification including Variants and Accessories	Intended purpose, how it works, product specification, materials, components, assays, classification, conformity assessment route, software and similar devices on the market
2. Information Supplied by the Manufacturer	Labels, IFU, promotional material, language requirements
3. Design and Manufacturing Information	Design stages and further detail, manufacturing process, critical ingredients and suppliers, product release process, address of manufacturing sites and certificates
4. General Safety & Performance Requirements (Annex I)	EC Declaration of Conformity, product detail classification, completed General Safety and Performance Requirements document, list of applied standards.
5. Benefit-Risk Analysis and Risk Management	Risk analysis & control: ISO 14971:2012 - Summary of the risks identified, analysis of how the risks have been controlled and reduced, risk management plan. Importantly needs to incorporate PMS
6. Product Verification and Validation	Verification and Validation: Summary of the results of verification and validation activities e.g. analytical performance, accuracy of measurement, sensitivity, specificity, metrological traceability, performance evaluation reports, stability, engineering tests, biocompatibility data, sterilization, software verification and validation.

1.2.3 Annex III – Technical Documentation on Post Market Surveillance (PMS)

This is a new addition in the IVDR and requires that the manufacturer has a documented post-market surveillance (PMS) system which collects and utilises all available information including publicly available information for other comparable devices.

The IVDR requires that the manufacturer shall proactively collect and evaluate clinical data with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence.

The manufacturer needs a proactive and systematic PMS plan, implementation of the plan followed by reporting of the information gathered in a post market surveillance report or periodic safety update report which also feeds into the manufacturer's risk assessment and ongoing clinical evaluation.

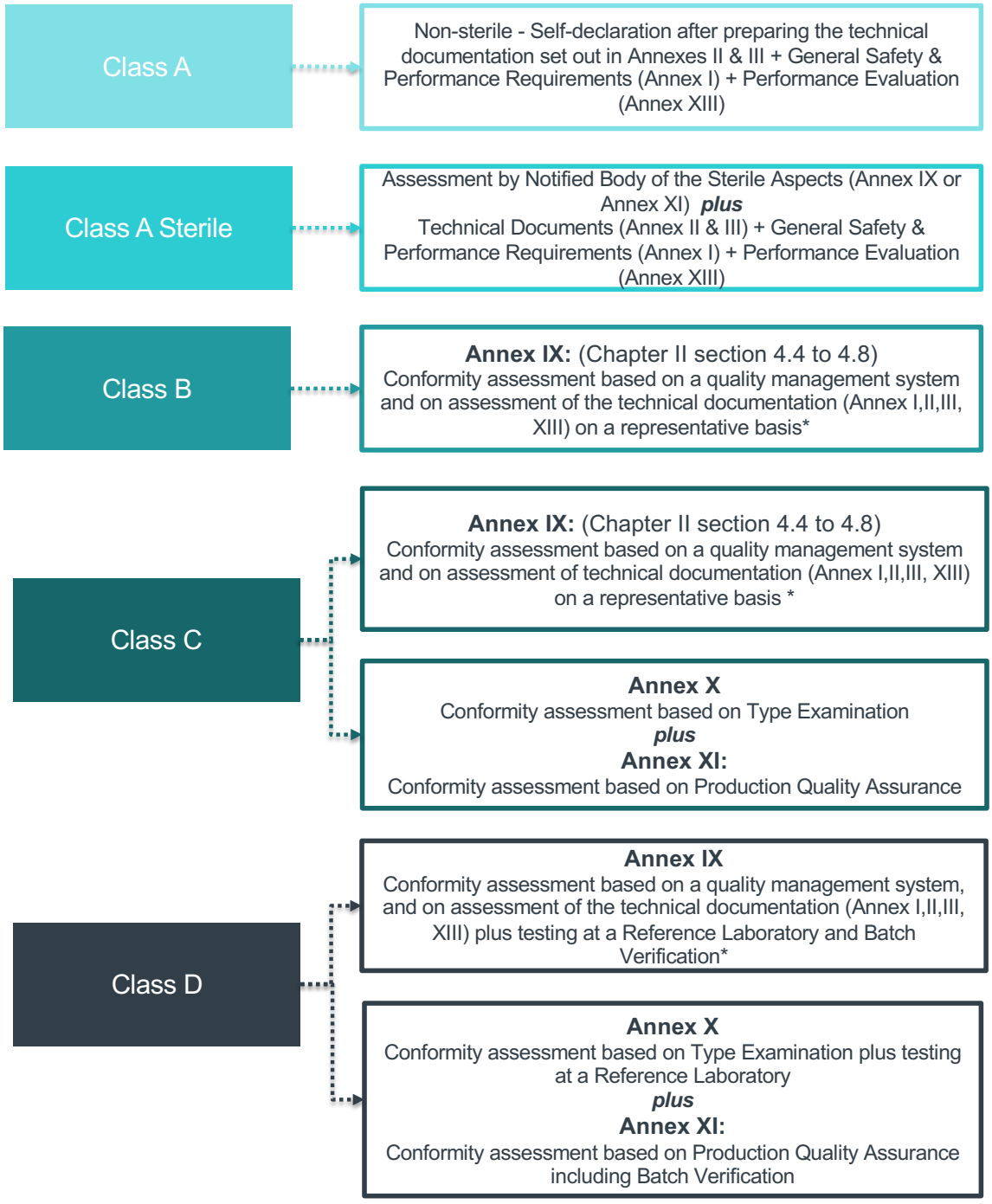
Manufacturers of Class C and Class D devices must create periodic safety update reports and update these reports at least annually (Article 81). Manufacturers of Class D IVDs must also submit these annual updates to Eudamed and have them reviewed by their NBs.

Eudamed will have specific sections for uploading incidents and post-market surveillance data to facilitate these reporting requirements.

1.3 Conformity Assessment

The conformity assessment routes are set out in Annex IX, X and XI. All of these annexes require a technical file or documentation in compliance with Annex II (Technical Documentation) and Annex III (PMS Technical Documentation) and Annex II requires the completion of Annex I (SPR). The routes available to each device class are set out below.

Conformity Assessment Procedures - IVD



* For self-test devices and near patient tests, manufacturers must also meet the requirements of section 5.1 of Annex IX.
* For companion diagnostics, the requirements of section 5.2 of Annex IX also apply

Conformity assessment routes should be determined in conjunction with a regulatory specialist so that the best choice is made and understood for the required business objectives.

1.4 Clinical Evidence & Performance Evaluation

There is a new requirement for clinical evidence which is clinical data and performance evaluation results. There needs to be a sufficient amount and quality of clinical data to allow a qualified assessment of whether the device achieves the intended clinical benefit and safety, when used as intended by the manufacturer.

Clinical benefit is accurate medical information and is not connected to the final clinical outcome for the patient.

The level of clinical evidence needed to demonstrate the conformity of a device becomes progressively more stringent as the risk class increases. Clinical evidence demonstrates analytical performance, scientific validity, and clinical performance. A Performance Evaluation Plan is developed to capture;

Clinical Performance is the ability to yield results that relate to a particular clinical condition or physiological state for the intended purpose and in accordance with the target population, and where applicable to the intended user. Performance data to support diagnostic accuracy compared to reference tests and information related to expected values is consolidated in a clinical performance report.

Scientific Validity refers to the association of an analyte to a clinical condition or physiological state. For established analytes, this may be from literature; but for novel analytes or companion diagnostics this would need to be established.

Analytical Performance refers to the ability of an IVD medical device to correctly detect and measure a particular analyte.

The above evidence gathering activities are consolidated in a Performance Evaluation Report that supports the intended purpose of the device. The Performance Evaluation Report forms part of the technical file.

For Class C and D IVDs, Performance Evaluation Reports must be updated annually as part of their post market surveillance plans. Reports for Class A and B IVDs are required, but without the requirements to be annually updated. This post market performance follow-up to update the performance evaluation is a new IVD requirement.

1.4.1 European Database of Medical Devices (EUDAMED) & UDI

There is a requirement that devices are traceable by means of a Unique Device Identifier (UDI). Devices shall also be assigned to a “Basic UDI-DI”. The “Basic UDI-DI” is a record key in the UDI database and connects IVD’s with the same intended purpose, risk class and essential design and manufacturing characteristicsis and is separate from the packaging /labelling of the device. The “Basic UDI-DI” is referenced in regulatory documents such as the Technical Documentation, Declaration of Conformity, Notified Body Certificates and Post Market Studies.

The Commission mandated that EUDAMED should include:

- An electronic system for registration of devices referred to in Article 26(2);
- A UDI-database referred to in Article 25;
- An electronic system on registration of economic operators referred to in Article 27;
- An electronic system on registration of manufacturers, authorized representatives and importers referred to in Article 28;
- An electronic system for notified bodies and holding on certificates referred to in Article 52;
- An electronic system on clinical investigations referred to in Article 69;
- An electronic system on vigilance and post-market surveillance referred to in Article 87;
- An electronic system on market surveillance referred to in Article 95.

This is an ambitious project and that will initially be tested with the registration of medical devices per the MDR. The outcome of that launch will inform the timetable and expectation for IVD use of EUDAMED. The existing arrangements will remain in place until EUDAMED becomes fully functional. IVD manufacturers should initially focus on the new labelling requirements and the application of UDI's to IVD's. When available Single Registration Number (SRN) can be obtained from Competent Authorities (MHRA in the UK) and this will allow access to EUDAMED when it is available. Manufacturers should keep a watching brief on EUDAMED progress and the issuance of SRNs.

2 Key Dates

March 2020	Scheduled date for the European Database on Medical Devices (EUDAMED) to go live. There are provisions allowing for a delay.
26 May 2022	IVDR comes into force: • All Class A, self-certified devices must be compliant to the IVDR • All devices up classed to A Sterile through to Class D must be compliant with IVDR and require the involvement of a Notified Body • Clinical investigations/Performance evaluations must comply with the IVDR • All PMS and PMCF requirements of the IVDR apply
26 May 2024	All product certificates under the IVDD expire
26 May 2025	Last possible date for putting devices into service according the IVDR

3 Structure of the IVDR

When looking for key articles and sections it is useful to understand the structure of the IVDR as there is no index.

Chapter I	Art 1 - 4	Introductory Provisions
Chapter II	Art 5 - 21	Making Available on the Market
Chapter III	Art 22 - 30	Identification and Traceability of Devices
Chapter IV	Art 31 - 46	Notified Bodies
Chapter V	Art 47 - 55	Classification and Conformity Assessment
Chapter VI	Art 56 - 77	Clinical Evidence, Performance
Chapter VII	Art 78 - 95	Post Market Surveillance, Vigilance & Market Surveillance
Chapter VIII	Art 96 - 101	Cooperation between Members & Bodies
Chapter IX	Art 102 - 106	Confidentiality and Data Protection
Chapter X	Art 107 - 113	Final Provisions

Annex I	General Safety & Performance Requirements - SPR
Annex II	Technical Documentation
Annex III	Technical Documentation on Post Market Surveillance - PMS
Annex IV	EU Declaration of Conformity - DoC
Annex V	CE Marking of Conformity – CE Mark
Annex VI	Information to be Submitted – UDI+
Annex VII	Requirements to be met by Notified Bodies
Annex VIII	Classification Rules
Annex IX	Conformity Assessment – QMS & Tech Docs
Annex X	Conformity Assessment – Type Examination
Annex XI	Conformity Assessment – Production Quality Assurance
Annex XII	Certificates to be Issued by a Notified Body
Annex XIII	Performance Evaluation, Performance Studies & Post Market Follow-Up
Annex XIV	Interventional Clinical Performance Studies and other Performance Studies
Annex XV	Correlation Table

4 Key Standards & Guidance

There are hundreds of standards covering the many thousands of devices. It is important to search for and apply the standards most applicable for your device. However, there are a core set of standards that are applicable to many devices which are listed below and would be in addition to any specific standards applicable to your device.

Quality Management	ISO 13485
Risk	ISO 14971
IVD Performance Evaluation	ISO 13612
Clinical Investigation	ISO 14155
Biocompatibility	ISO 10993
Software	EN 62304
Medical Equipment	EN 60601

Usability	EN 62366 and FDA Human Factor Analysis
IVD Performance Evaluation	ISO 13612
IVD Information Supplied	ISO 18113
IVD Evaluation of Reagent Stability	ISO 23640
IVD Clinical Performance studies	ISO 20916 (Draft)*
IVD Metrological Traceability of Values	ISO 17511 (Draft)*
IVD Measurement of Quantities in Samples	ISO 21151 (Draft)*
Symbols	ISO 15223

* Draft document may change substantially following public consultation

5 Next Steps

The new IVD regulations are a big change with many additional requirements and the implementation date is fast approaching. Many IVD manufacturers may not have had any Notified Body interaction or scrutiny.

Plans need to be put in place to; determine your IVD classification, understand the IVDR conformity assessment routes available, determine the gaps in technical documentation, clinical data and performance evaluation and quality systems.

Once the current position and future requirements are understood the manufacturer is in a position to generate a plan and actions to close the gap based on overall business objectives.

6 Reference Sites

MHRA: https://www.gov.uk/government/latest?departments%5B%5D=medicines-and-healthcare-products-regulatory-agency

EU Commission: http://ec.europa.eu/growth/sectors/medical-devices_en

Copies of the IVDR: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1542301249315&uri=CELEX:32017R0746

About Psephos

Psephos Biomedica was founded in 2001 and works with clients from around the world to help them bring medical technologies to market. A highly focused, experienced team Psephos only works with Medical Devices and Clients range from innovative start-ups to entrepreneurial corporations. The team has together more than 100 years Medical Device and IVD experience.

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