A Free Regulatory Guide to Bringing your In Vitro Diagnostic to the EU Market

A 'Regulation Made Simple' Series Guide 1.0

Version 1.0

LFH REGULATORY
Regulation Made Simple

Contents

Introduction

You have produced an innovative idea that could change the MedTech market but wonder where you go from there, and what red tape you might encounter to bring your device to market. Worry not, this step-by-step guide will walk you through the regulatory 'hurdles' and make the **regulation simple,** so you can easily understand what happens at each stage and what you need to do.

This guide covers topics that are necessary to understand the main areas of bringing an IVD to EU market and be submission ready.

What is an In Vitro Diagnostic and does my product fall under this definition?

Firstly, we need to ensure that the product we have, is indeed a medical device.

In Article 2 of the EU Medical Device Regulation 2017/745, also referred to as the MDR, a 'medical device' is defined as:

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.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;

The first step is to determine whether your product falls within the definition of an IVD and the easiest way to do that is to break it down into bite-sized chunks. This is how we do this:

Answer the questions in the following steps regarding the target device:

Step 1

Is your product 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?

If so, move onto the next step.

Step 2

It is time to move on to the next part of the definition and it is important to look at whether your product is used solely or principally for the purposes of *information on one or more of the following:*

concerning a physiological or pathological process or state

OR

concerning congenital physical or mental impairments

OR

concerning the predisposition to a medical condition or a disease

OR

to determine the safety and compatibility with potential recipients

OR

to predict treatment response or reactions

OR

to define or monitoring therapeutic measures

OR

Is a specimen receptacle(s)

If you have answered yes, you should have confidence in whether your product falls under the definition of an IVD.

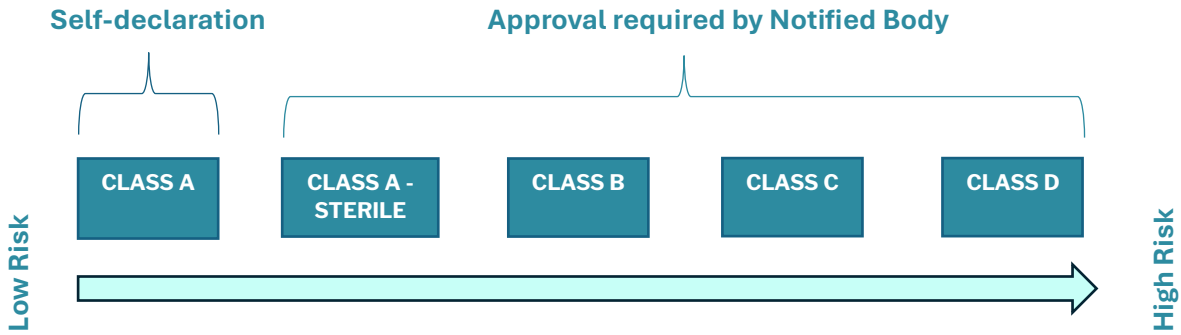
If you are still unclear if your product falls under the definition of an IVD, it is worthwhile engaging with an expert to help. Reach out to our team to see how we can help you with classifying your product.

How to classify your IVD?

When you have determined that your product is an IVD, you will then need to determine the classification of your device.

Classification of IVD's is risk-based that take into account the intended purpose of the device and their inherent risks.

There are four classifications classes under which devices shall be divided considering their intended purpose and associated risks. The 5 classifications are:



Class A is the lowest risk with the risk increasing and class D being the highest risk IVD. The classification rules are set under Annex VIII of the IVDR and there are currently 7 rules set under this Annex.

If you believe your device could fall under 2 different classification rules, you need to apply the highest risk classification rule to your IVD.

Determining the classification of an IVD is vital to your route to market and can have negative consequences if wrongly classified, such as removal from the marketplace with significant loss of revenue.

For a further breakdown and a detailed overview of the classification rules, see Appendix 1 – Classification Rules.

The Medical Device Coordination Group (MDCG), a European Commission Group that provides medical device guidance, published a useful article on the classification rules using product examples; see MDCG 2020-16 - Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746

Quality Management System (QMS)

Once you have established the classification for your medical device, you to need consider the quality requirements that manufacturers adhere to.

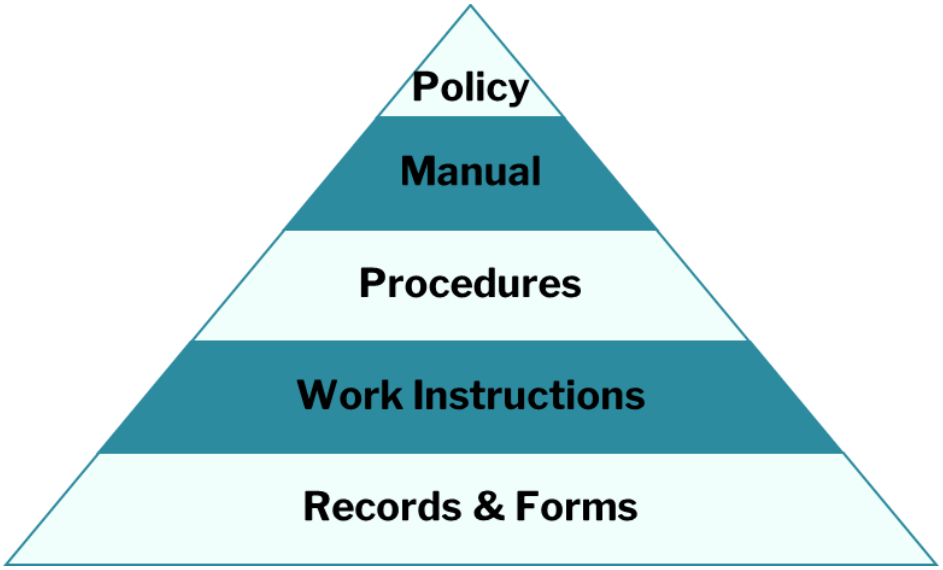
Article 10 – General Obligations of a Manufacturers and Annex IX, chapter 1 of the MDR, it states:

> *The quality management system shall cover all parts and elements of a manufacturer's organisation dealing with the quality of processes, procedures and devices. It shall govern the structure, responsibilities, procedures, processes and management resources required to implement the principles and actions necessary to achieve compliance with the provisions of this Regulation.*

The article outlines the basic requirements that a manufacturer must adhere to. The general rule to demonstrate that you comply with this area of the regulation is to follow standard *ISO 13485 – Medical devices – Quality Management Systems- Requirements for Regulatory Purposes*. Which is an international standard that outlines the requirements for a quality management system (QMS), within the medical device industry. It also covers the entire life cycle of a device from design and development to production, installation, servicing, and post-market activities.

There is also ISO 13485:2016 - Medical Devices - A Practical Guide, which expands the clauses of the standard and gives substance to what is required for each clause.

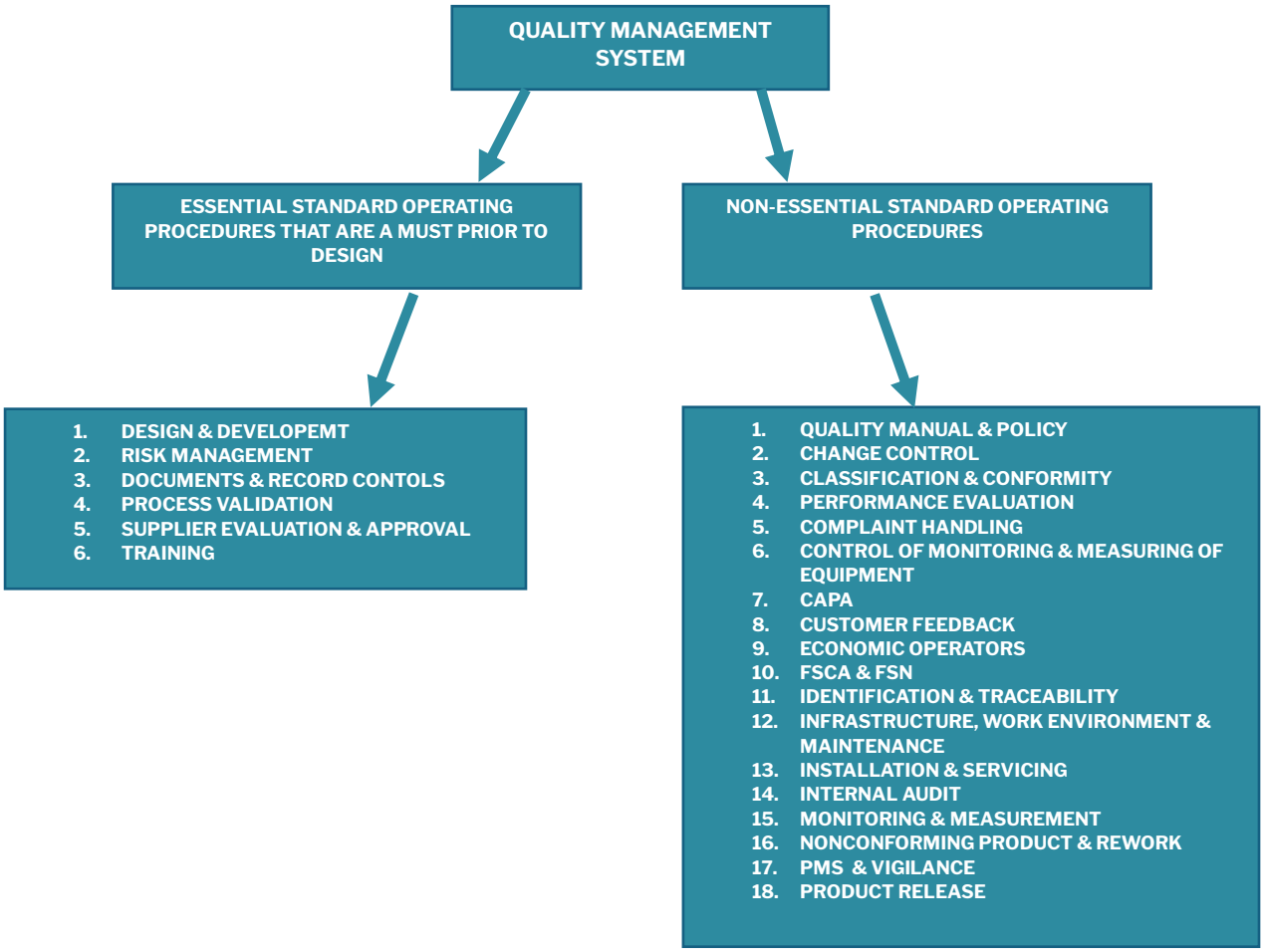
It is worth noting what the QMS documentation structure and hierarchy consists of:



As a consultancy, we work with many start-up companies and appreciate the financial constraints during the initial stages of setup. It is not unusual for a start-up medical device company to have started designing their device and making prototypes before initiating any type of QMS.

Implementing a full, robust, and effective QMS can come at a cost but is essential in future-proofing your device and preventing remediation activities.

The diagram below names the essential procedures required prior to design activities taking place and non-essential procedures which can be implemented late on;



As stated before, the procedures documented above are a starting point. You should implement the required processes as they arise and certainly make sure you have a fully functioning QMS prior to the launch of your device.

At LFH Regulatory, we believe in taking a strategic approach to creating and implementing an effective QMS to suit our client's needs: see our Quality Management System services to see how we can help simplify your QMS implementation.

Technical Documentation

Annex II of the IVDR states that the technical documentation shall be presented in a clear, organised, readily searchable and unambiguous manner and shall include elements listed in the Annex.

The Annex goes on to list what information needs to be presented I technical documentation, this includes:

Technical documentation section	Further information

Device Description and Specification, including Variants and Accessories	Device description and specification including things such as:
	• Product/trade name
	• UDI-DI
	• The intended purpose of the device which may include information on:
	  ○ What is to be detected and/or measured;
	  ○ Its function such as screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic;
	  ○ The specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
	  ○ Whether it is automated or not;
	  ○ Whether it is qualitative, semi-quantitative or quantitative;
	  ○ The type of specimen(s) required;
	  ○ Where applicable, the testing population;
	  ○ Intended user;
	  ○ For companion diagnostics, the relevant target population and associated medicinal product(s).
	• The description of the principle of the assay method or the principles of operation of the instrument;
	• Rationale for qualification as a device
	• Classification of device with classification rule

Technical documentation section	Further information
	• Description of the components and where appropriate, the description of the reactive ingredients of relevant components such as antibodies, antigen, nucleic acid primers; • Where applicable, the description of the specimen collection and transport materials provided with the device or descriptions of specification recommended for use; • For instruments of automated assays: the description of the appropriate assay characteristics or dedicated assays; • For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation; • Description of any software to be used with the device; • A description or complete list of the various configurations/variants of the device that are intended to be; • A description of the accessories for a device, other devices and other products that are not devices, which are intended to be used in combination with the device. Reference to previous or similar generations of the device.
Information to be Supplied by the Manufacturer	A complete set of labels for the device needs to be available including labels on the device, sales packaging, transport packaging (where applicable). Instructions for use (IFU) also need to be included. Labelling and IFU's will need to be available in the languages accepted in the countries that the device will be sold. The European Commission has published IVDR - Language requirements for manufacturers that documents the language requirements of each state.
Design & Development Information	Information to allow the design stages applied to be understood including: • Critical ingredient of the device such as antibodies, antigens, enzymes and nucleic acid primers provided or recommended for use with the device; • For Instruments- a description of major subsystems, analytical technology such as operating principles and control mechanisms, dedicated computer hardware and software; • For instruments and software, an overview of the entire system;

Technical documentation section	Further information
	• For software, a description of the data interpretation methodology, namely the algorithm; • For devices intended for self-testing or near-patient testing, a description of the design aspects that make them suitable for self-testing or near-patient testing. Information to allow the manufacturing processes such as production, assembly, final product testing, and packaging of the finished device to be understood. More detailed information shall be provided for the audit of the quality management system or other applicable conformity assessment procedures. All sites, including suppliers and sub-contractors, where design and manufacturing activities are performed.
General Safety & Performance Requirements	The General Safety & Performance Requirements (GSPRs) are under Annex I of the Regulation and are used to demonstrate how you meet the requirements of the regulation. You will need to document the GSPRs that are applicable to your device and provide evidence along with any standards that are relevant. For any GSPRs that are not applicable, you will need to justify the reasons why.
Benefit-Risk Analysis & Risk Management	This will be demonstrated by following ISO 14971 Medical Devices – Application of Risk Management to Medical Devices. You should compile a risk management file in line with the requirements of ISO 14971 including Risk Management Plan, Annex A Checklist, Risk Assessment and Risk Management Report.

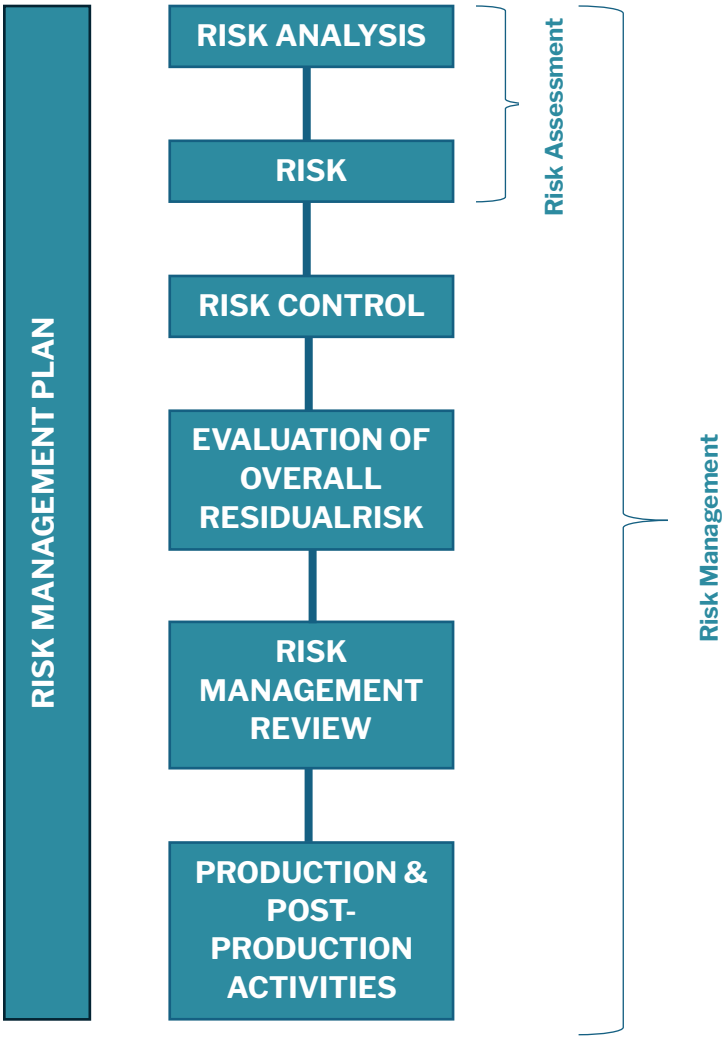
Product Verification & Validation	The documentation shall contain the results and critical analyses of all verifications and validation tests and/or studies undertaken to demonstrate conformity of the device with the requirements of this Regulation and in particular the applicable general safety and performance requirements. This should include;
	• Specimen type
	• Analytical performance characteristics
	  ○ Accuracy of measurement
	  ▪ Trueness of measurement

Technical documentation section	Further information
	▪ Precision of measurement ○ Analytical specificity ○ Metrological traceability of calibrator and control material values ○ Measuring range of the assay ○ Definition of assay cut-off • Analytical performance report • Performance evaluation report including clinical performance and clinical evidence • Claimed shelf life • In-use stability • Shipping stability • Software verification and validation
Additional information required in specific cases	There are special cases where additional information will need to be included, these are; • The device is placed on the market in a sterile or defined microbiological condition • The device contains tissues, cells and substances of animal, human or microbial information on the origin of such material and on the conditions in which it was collected. • Devices placed on the market with a measuring function, a description of the methods used in order to ensure the accuracy as given in the specifications. • Device is to be connected to other equipment in order to operate as intended

Risk Management

There is a strong emphasis on risk management within the MDR regulation. It is mentioned a whopping 243 times!. That is because risk management plays a crucial role in the IVD product development lifecycle. It ensures the reliability of the product, its proper functioning, and the safety of patients, operators, and the environment. The risk management cycle aims to create dependable medical devices by minimising the likelihood of failures.

The General Risk Management Process to follow is ISO 14971, presented in a flowchart below.



The general process of Risk Management under ISO 14971 should ideally be part of the initial stages of any project, but we have seen that it has not always been considered.

To achieve the best practices in IVD development, you should correlate design control with risk management. When identifying hazards or hazardous situations early on, feed them into your design controls, user needs, and design inputs.

By evaluating the risk and putting risk control measures in place e.g. design verification/validation can assist with mitigating the risk to an acceptable level.

Risk management is not only an early-stage requirement but should be reviewed and updated throughout the lifetime of your IVD periodically, or when it becomes available that there is a new risk and/or risk that needs reevaluating.

Conducting risk management activities correctly is crucial for ensuring IVDR compliance of your IVD and following the correct requirements and updating your documentation is crucial for remaining compliant.

We are here to help create or navigate you to implement an effective risk management file.

Performance Evaluation

The IVDR requires that the performance of a device to be evaluated by the manufacturer. The performance evaluation is the assessment and analysis of data to establish or verify the following:

Scientific validity	The association of an analyte with a clinical condition or a physiological state.
Analytical performance	The ability of a device to correctly detect or measure a particular analyte.
Clinical performance	The ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.

The performance evaluation is required to confirm conformity with relevant general safety and performance requirements concerning the performance characteristics, under the normal conditions of the intended use of the device, and the evaluation of the interference(s), cross-reaction(s) and the acceptability of the benefit-risk ratio in accordance with Chapter VI and Article 56 -Clinical Evidence, Performance Evaluation and Performance Studies.

Furthermore, the quality of data and conclusions drawn from these elements shall allow the manufacturer to make a qualified assessment of whether the device is safe and will achieve the intended clinical benefit(s) when used as intended by the manufacturer.

The successful demonstration of a sufficient amount and quality of clinical data and performance evaluation results will constitute the clinical evidence for the device when used as intended by the manufacturer.

The evaluation is performed during development of the IVD, then as an ongoing and continuous process conducted throughout the life cycle of the device.

As the performance evaluation can be a complex and time-consuming set of documents to create, it should be conducted by a suitably qualified individual or team. At LFH Regulatory, we offer a flexible solution option through our Performance Evaluation Services where our experts can deliver your performance documentation needs.

Post Market Surveillance

Post Market Surveillance (PMS) comes under Article 78 to 81 & Annex III of the IVDR which describes what needs to be drawn up as part of the technical documentation. PMS can be defined as:

> *All activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions.*

Manufacturers of class A & B IVD's need to prepare a PMS report from data gathered in accordance with the PMS plan. There is no specified timeframe for updating, with the IVDR stating the report is to be updated when necessary or upon the request of the competent authority.

For Class C & D IVD's:

Article 81 of the IVDR discusses the requirements for Periodic Safety Update Report (PSUR).

For class C & D IVD's, a more detailed PSUR must be produced and will need be updated at least annually. PSUR's for class D devices will be reviewed by the notified body involved.

Post market can be classified as reactive or proactive and both approaches should be taken. The following table gives examples of the types of post-market activities that should be carried out but are not limited to:

Reactive Post Market Data	Customer complaints Vigilance including adverse events, serious incidents & Field safety corrective actions (FSCA)
Proactive Post Market Data	Customer Surveys and Feedback Literature Searches: Systematic literature searches and/or review for a particular product, material used in a product or clinical procedure which may be conducted. Post-market Performance Follow Up

Post Market Performance Follow-up

Post-market performance follow-up (PMPF) is a continuing activity that ensures the performance evaluation of a medical device remains up to date throughout its entire lifetime.

Annex XIII, Part B of the IVDR sates that what activities should be conducted to fulfil these requirements. The aim of the PMPF plan is:

- Confirming the safety and performance of the device throughout its expected lifetime.
- Identifying previously unknown risk or limits to performance and contra-indications.
- Identifying and analysing emergent risks based on factual evidence.
- Ensuring the continued acceptability of the benefit-risk ratio.
- Identifying possible systematic misuse of the device.

A PMPF plan shall specify the methods and procedures to proactively collect and evaluate clinical experience gained, feedback from user, screening of scientific literature and other sources of performance or scientific data.

Analysis of the findings of the PMPF is required and the results documented within the Performance Evaluation Report.

It is not surprising that you might find post-market activities confusing. At LFH Regulatory, we can help you navigate the complexities of post-market activities including PMCF.

Route to Market & Approval

So, you've carried out the above, but where do you go next? You will need to understand whether your IVD is a self-declared product or whether you will need to go through a review and approval process.

Class A

Class A IVD's are self-declared products which means they will not be required to go through a review and approval process by a Notified Body. Although there is no review process, you will still be required to demonstrate that you mean the requirements of the IVDR and sign off on your technical documentation with your Declaration of Conformity (DoC).

Once you have signed off on the technical documentation with your DoC, you will be able to register with your competent authority e.g. Medicines Healthcare Product Regulatory Agency (MHRA) in the UK. If you are based outside the EU, you will need to appoint an EU Authroised Representative to do this on your behalf.

You will also need to have a QMS implemented and for good practice audited. This will consist of a 2-stage approach with the 1st stage reviewing procedures to make sure they meet the requirements of the standard and any regulatory requirements. The 2nd stage will review that you are adhering to your procedures and will want to witness evidence.

Class A sterile, B, C & D

Class A sterile, B, C & D IVD's will be required to go through a review and approval process with a Notified Body. Generally, they will review your technical documentation and QMS to ISO 13485 for the purposes of CE marking.

There are different stages/audit involved which consist of but are not limited;

1. Technical documentation – review of the complete full technical file including performance data. If you have more than 1 technical file, the notified body made carry out a sampling plan of your technical documentation.
2. QMS audit – This consist of a 2-stage approach with the 1st stage reviewing procedures to make sure they meet the requirements of the standard and any regulatory requirements. The 2nd stage will review that you are adhering to your procedures and will want to witness evidence.

Should you require your IVD to be certified, it is advisable that you communicate with your preferred notified body early on to understand they have the required approval codes and the timeframes for certification (this may vary between notified bodies).

Conclusion

This step-by-step guide has taken you through the main requirements of CE marking your IVD under the IVDR.

Any new product must be determined whether it is defined as a IVD and if so, this needs identification is followed by the product risk classification to understand your route to market and to streamline this process to make it as efficient as possible.

The QMS is not a checkbox exercise and is instrumental in facilitating design control practices throughout the development of your device.

Although we have discussed the PMS, Risk Management, and Clinical Evaluation as separate points, it should be noted that these all encompass important inputs into the Technical Documentation and in demonstrating compliance with the IVDR.

To discuss any requirements you may have around CE marking your device or the EU IVDR, please feel free to contact us for an informal chat.

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Appendix 1 – Classification Rules

Classification Rule	Device Types Covered
Rule 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, 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.
Rule 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, are classified as class C, 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) In which case they are classified as class D.
Rule 3	Devices are classified as class C if they are intended: (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

Classification Rule	Device Types Covered
	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. (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.
Rule 4	(a) 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, which are classified as class B. (b) Devices intended for near-patient testing are classified in their own right.
Rule 5	The following devices are classified as class A: (a) products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination. (b) instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures. (c) specimen receptacles.
Rule 6	Devices not covered by the above-mentioned classification rules are classified as class B.
Rule 7	Devices which are controls without a quantitative or qualitative assigned value are classified as class B.