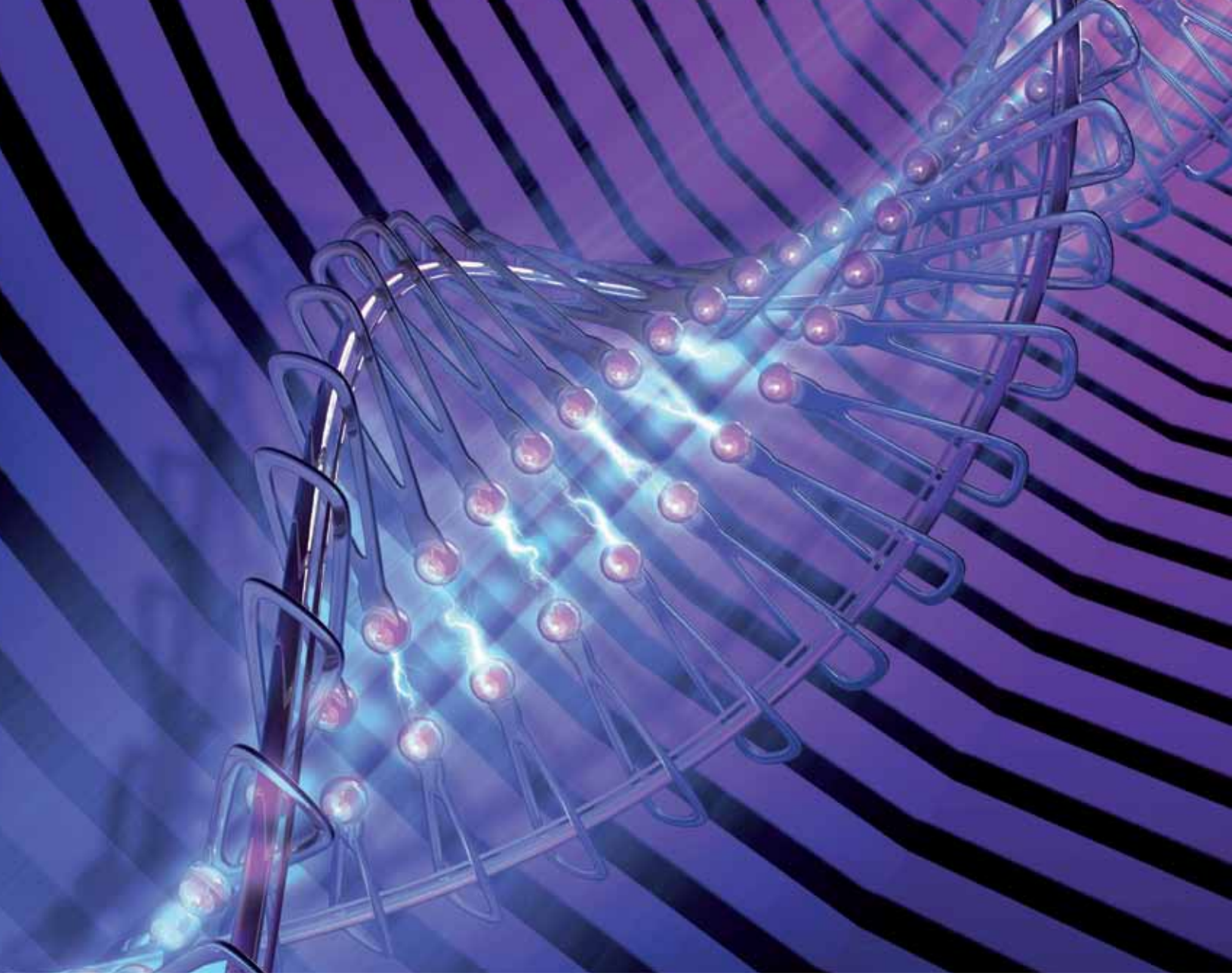

BSI: An In Vitro Diagnostics Notified Body

A guide to the In Vitro Diagnostic Directive

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A BSI guide to the In Vitro Diagnostic Directive

Introduction

In Vitro Diagnostics (IVD) is an essential and fast growing part of the global healthcare system, as they add value to patients, medical professionals and the industry along with enhancing the well-being of the population as a whole.

The purpose of the BSI IVD Guide is to provide useful information to *In Vitro* Device Manufacturers and other interested parties seeking to place products on to the European Market. This requires a clear understanding of the *In Vitro* Diagnostic Directive (IVDD) 98/79/EC which sets the regulatory requirements for obtaining CE marking. Information is also presented on how to determine if you require a Notified Body to assess conformity prior to affixing a CE mark.

If you think you may need a Notified Body, whether your device ranges from simple to complex, BSI's in-house team of experts are here to assist you. We promise to deliver professional, fast and responsive services with the highest quality and most efficient reviews possible.

The Aim of the *In Vitro* Diagnostic Directive (98/79/EC)

The *In Vitro* Diagnostic Directive (IVDD) 98/79/EC was introduced in the later part of 1998 and compliance became mandatory on December 7, 2003. The Directive provides regulatory requirements that facilitate the free trade within the European Economic Area (EEA), which comprises the 27 European Union (EU) member states and Iceland, Liechtenstein and Norway as members of the European Free Trade Association (EFTA).

The IVDD specifically addresses the safety, quality and performance of *In Vitro* Diagnostic medical devices (IVDs). The aim of the Directive is to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels specified by the manufacturer.

The manufacturer is responsible for ensuring their products comply with the Essential Requirements of the Directive before affixing the CE marking and legally gaining access and free movement within the EEA. However, for some devices the use of a Notified Body may be required for conformity assessments before placing the device on the European market.

What is an *In Vitro* Medical Device?

IVDs are medical devices and accessories used to perform tests on samples, such as blood, urine, tissue, taken away from the human body to help detect infection, diagnose a medical condition, prevent disease or monitor drug therapies.

The first step is to determine if the product is a medical device as defined by the Directive. The *In Vitro* Device Directive Article 1, point 2b defines an IVD as any medical device which is a

- Reagent, Reagent Product
- Calibrator, Control Material
- Kit
- Instrument, Apparatus
- Equipment, System

Whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimen, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological of pathological state of health or disease, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures.

Examples include:

- HIV test kits
- Immunoassay analysers
- Blood gas analysers
- The calibrators and control materials used to verify the performance of the analysers
- Specimen receptacles and blood collection tubes
- Blood glucose meters and strips

Who Does the Directive Apply To?

The Directive applies to all IVDs sold in the EEA regardless of where they are designed and manufactured. If the manufacturer is based outside the EEA you may still be responsible for ensuring your device meets the requirements of the Directive.

If you are a distributor and the device is not already CE marked or you change the intended purpose of a device, for example from point of care to self test or you add your own instructions for use or labelling you could become the manufacturer and therefore responsible for meeting the requirements of the Directive.

If you are not based in the European Union, you will be required to have an Authorised Representative based in the EU.

The Directive lists "Essential Requirements" to which all IVDs must comply before being placed on the market. These requirements address the design, production, labelling and instructions for use. Not all the Essential Requirements will apply to all devices; the manufacturer determines which are appropriate for their device according to the manufacturer's intended purpose.

Manufacturers commonly demonstrate compliance using an Essential Requirement checklist, which considers each Essential Requirement and determines whether it is applicable. One way in which manufacturers can demonstrate that they have met the Essential Requirements is to comply with the relevant standards. Harmonised standards, such as ISO 13485 for Quality Management Systems or ISO 14971 for Risk Management, have been written especially to help demonstrate compliance with the Directive.

If you meet the requirements of these standards in full there is a presumption that you conform to the requirements of the Directive.

The Essential Requirements address the risk of the device including:

- Analytical & diagnostic sensitivity,
- Analytical & diagnostic specificity,
- Accuracy,
- Repeatability,
- Reproducibility.

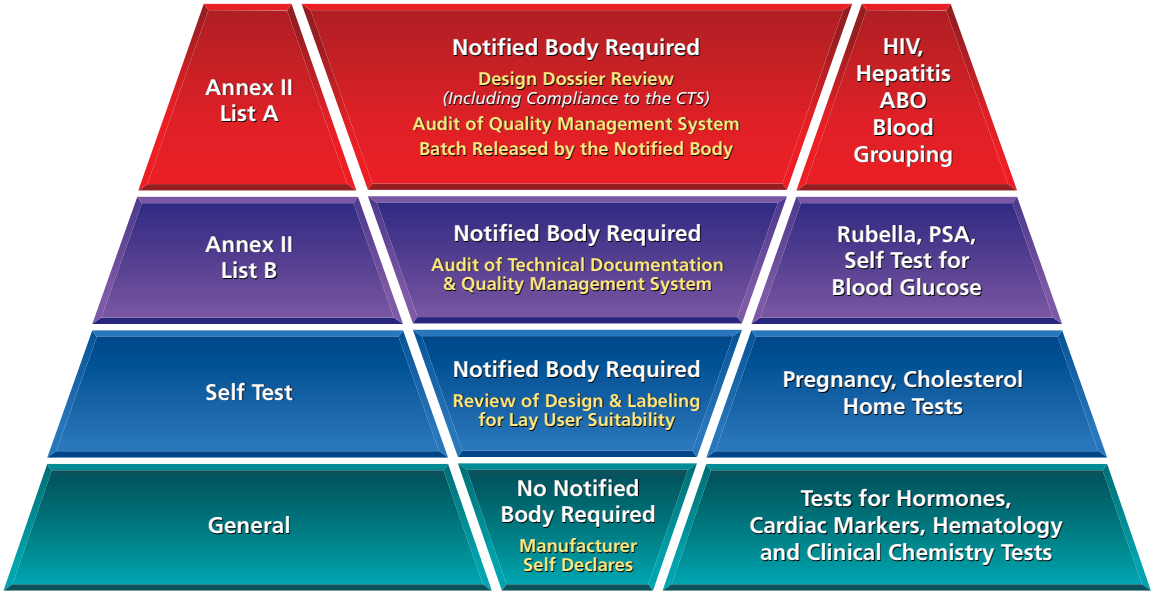
Classification and the Conformity Assessment Routes

There are a number of ways you can demonstrate conformity with the Directive, these involve a choice of testing and quality assurance modules. The choices available depend on the classification of the device. Appendix I describes the different routes available.

The Directive groups IVDs into four categories according to the perceived risk associated with the relative danger to public health and/or patient treatment by an IVD failing to perform as intended. The diagram below shows the classification and indicates where a Notified Body is required.

Annex II of the Directive contains an inclusive list of products which require certification by a third party called a Notified Body. Only the devices specifically listed in Annex II require a Notified Body, for example PSA is the only cancer marker in List B.

Is a Notified Body Required?



General IVDs

General devices include all IVDs other than those covered by Annex II and IVDs for self-testing. For a general IVD the manufacturer "self-declares" conformity with the relevant Essential Requirements of the Directive, and ensures the device fulfils the applicable obligations described in Annex III. These devices do not require the involvement of a Notified Body.

IVDs for Self-Testing

The particular requirements for self-testing set out in the Directive exclude self-test devices covered in Annex II. The manufacturer prepares a declaration of conformity in a similar way to the general devices but a Notified Body review is also required. The Notified Body will ensure that the device design (section 6 of Annex III) and the information provided for its use is suitable for non-professional users. This is essential as the lay user may make important decisions based on the results obtained, without consulting a healthcare professional.

Alternatively the manufacturer may follow the conformity assessment routes for higher risk products as follows.

IVDs in Annex II

The annex is sub-divided into two lists, List A and List B. All Annex II IVDs require the involvement of a Notified Body before the product can be placed on the market.

IVDs in Annex II List B – Moderate Risk

For devices under Annex II List B, the manufacturer must follow the applicable obligations imposed by either Annex IV, or by Annex V and VI, or alternatively by Annexes V and VII and must declare and ensure that the device meets the requirements described in these annexes.

List B includes - Reagents and reagent products, including related calibration and control material for:

- Blood groups Anti-Duffy and Anti-Kidd; irregular and anti-erythrocytic antibodies;
- Rubella and toxoplasmosis;
- Phenylketonuria;
- CMV, Chlamydia,
- HLA tissue groups DR, A and B;
- PSA;
- Self-test blood glucose measuring;
- Devices & software designed specifically for evaluating the risk of trisomy 21.

IVDs in Annex II List A – High Risk

For devices under Annex II List A, manufacturers must follow either Annex IV, or alternatively Annexes V and VII (they cannot follow Annexes V and VI). In addition, the Notified Body must verify the product meets the Common Technical Specification (CTS) and must release each batch of product before it can be placed on the European market. The batch release often requires testing.

Manufacturers are expected to comply with the CTS, which are drawn up by an expert group convened by the Commission. The CTS defines performance evaluation criteria and batch release criteria.

List A

Reagent and reagent products, including calibrators and control materials for:

Determining blood groups

- ABO
- Rhesus (C, c, D, E, e)
- Anti Kell

The detection, confirmation and quantification of

- HIV 1 and 2
- HTLV I and II
- Hepatitis B, C and D

Additional Requirements of the Directive

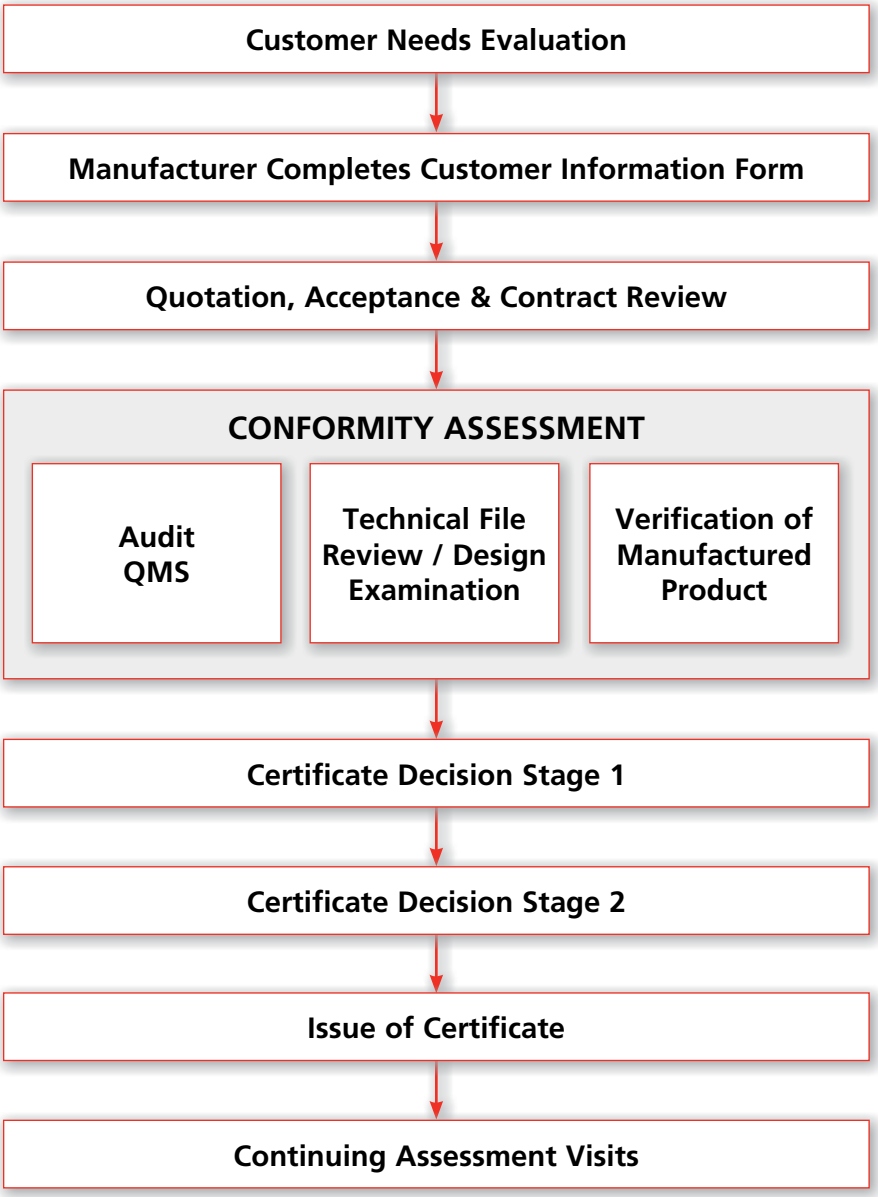
The Directive includes ongoing obligations for the manufacturer with regards to experience gained in the post-production phase, including implementation of any necessary corrective actions. The manufacturer must maintain a 'Vigilance System' and notify the regulatory authorities of any serious incident which could or has put a patient at risk, or requires a product to be systematically recalled. An incident should be reported to the Competent Authority in the country where the incident has occurred.

Manufacturers who do not have a registered place of business in the EU must designate an Authorised Representative to perform certain obligations. The Authorised Representative will be the first point of contact for Competent Authorities. As an example in a vigilance or compliance case, they may be asked to provide documents to the Competent Authority on behalf of the manufacturer.

What is the BSI CE Marking Process?

The BSI CE marking process starts with a Customer Needs Evaluation which includes a discussion to learn more about your organization, its regulatory requirements, any challenges and timeline demands. Plus we can answer questions you may have regarding BSI and the process.

The next step is the completion of a Customer Information Form which gathers more detailed information about your company and products; this will enable us to prepare a quotation. Once you have accepted the quotation, an application review takes place and the details of the initial assessment and identification of appropriate assessors occurs. If you have an Annex II List A product the criteria for the verification of manufactured product will also be established using three batches of product.



A Scheme Manager, who is part of the in-house IVD Technology Team, will be assigned to handle each customer's account and is responsible for managing all its activities. This enables customers to have one person to contact at BSI that understands their business, as all the Team members have in-depth IVD regulatory and industry experience. The advantage of this structure is that you have a responsive Team who can answer your questions quickly and process your applications, reviews and visits.

BSI conducts post assessment reviews to ensure the quality of our work; the first is a peer review and the second a compliance and quality check to ensure we deliver a consistent service to our clients. All approvals have to be maintained and a program of continuing assessment visits will be established.

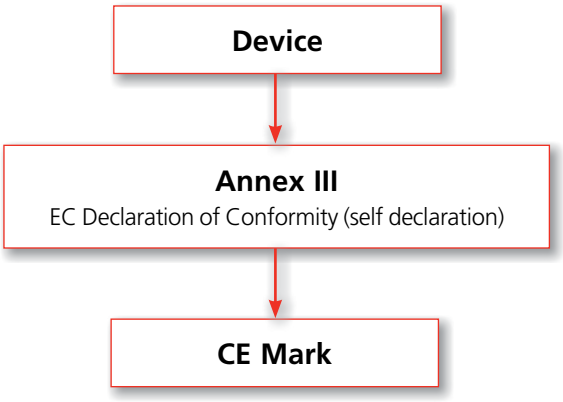
BSI supports you every step of the way. Whether you are a current customer or transferring to BSI, we have a dedicated team of Healthcare Professionals committed to making the process robust, efficient and predictable. In addition BSI is working with two of the leading test laboratories, providing Annex II List A verification of manufactured product testing. Companies using these laboratories that choose to transfer to BSI can keep their same testing facilities which will enable a smooth and more seamless transition.

If you require any further information regarding the IVD Directive, please contact the BSI IVD Team who will be pleased to answer your questions.

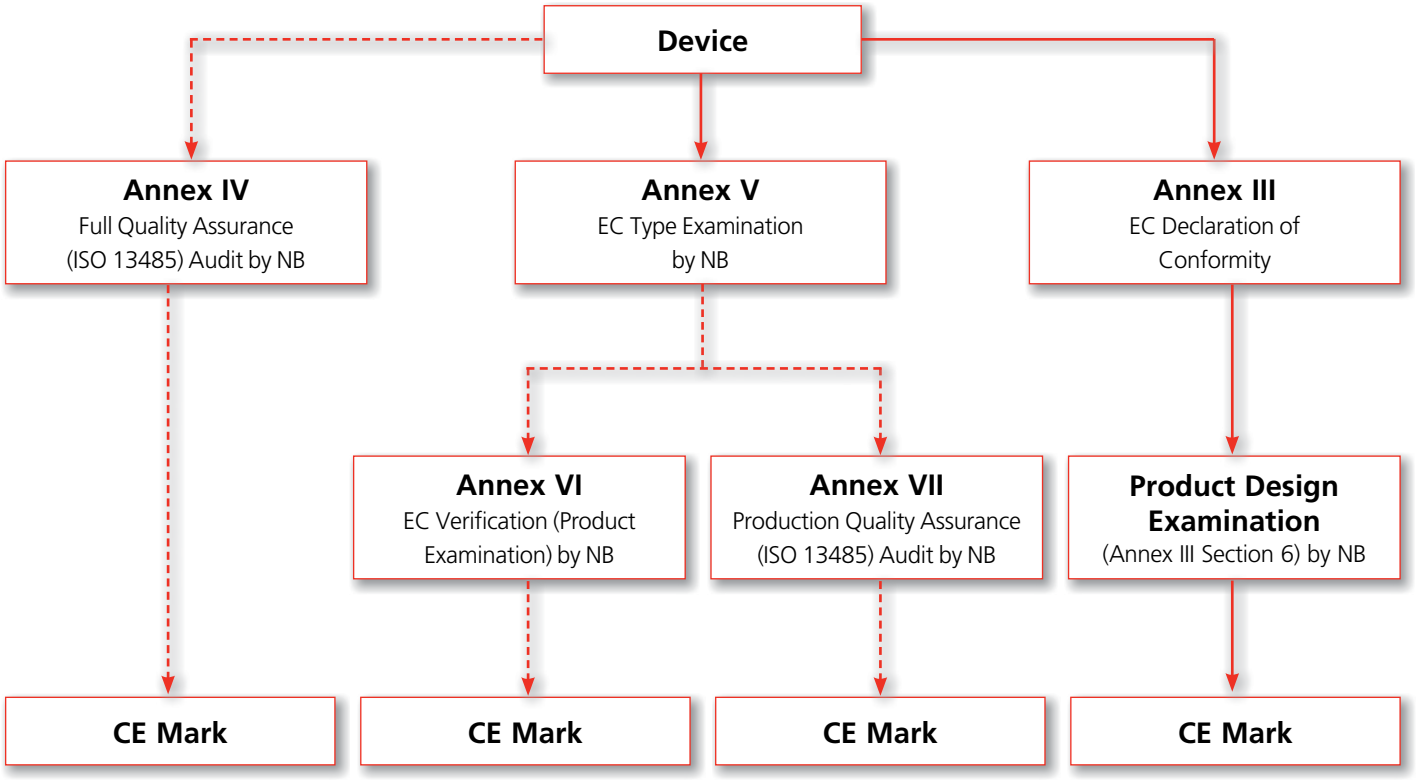
Appendix A

General IVD Device

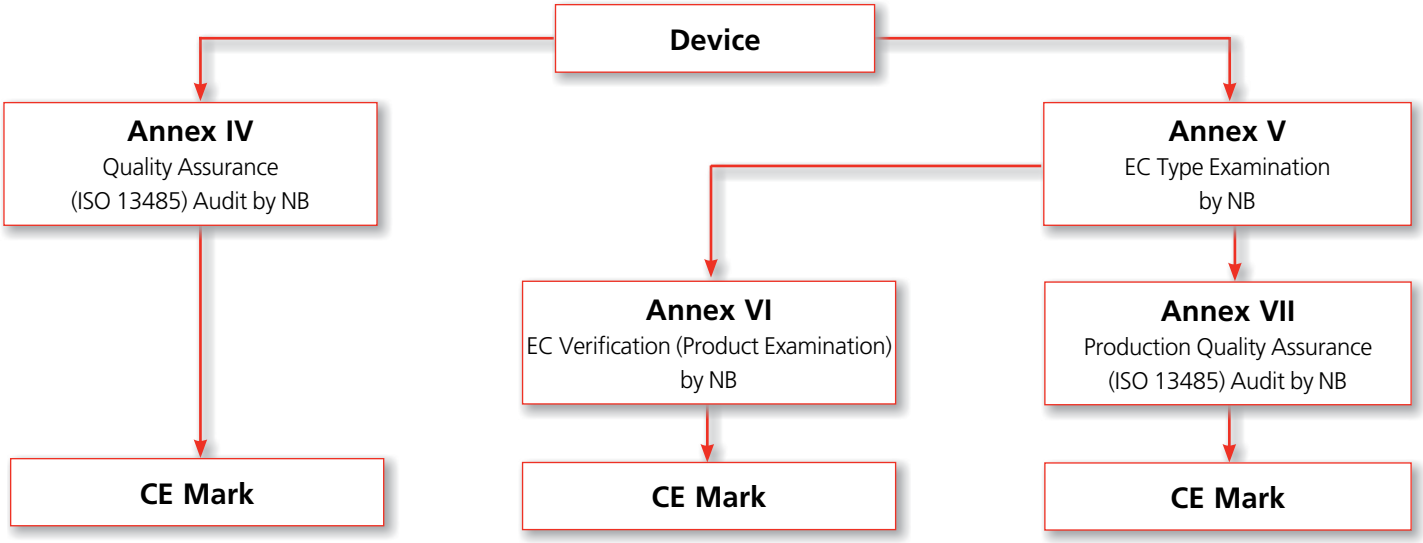
i.e. all devices other than self-testing devices or devices appearing in Annex II



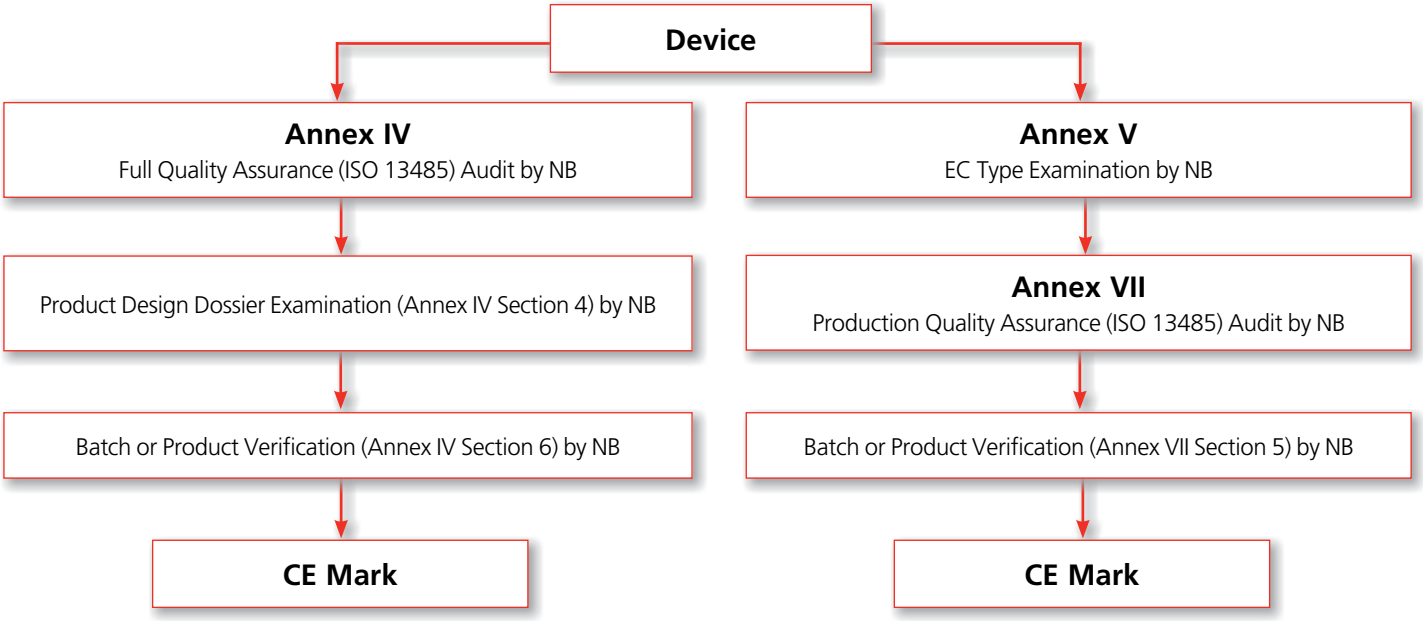
Self Testing IVD excluding those which appear in Annex II



IVDs Appearing in Annex II List B



IVDs Appearing in Annex II List A



If you require any further information regarding the IVD Directive, please contact the BSI IVD team who will be pleased to answer your questions.

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CE marking

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Japan PAL

FDA 510k Third-Party Review Programme

FDA Accredited Persons Inspections

Australia EU CAB

Hong Kong CAB

Russian Registration Certification

Taiwan TCP

Training courses

IVD/Technical File

CE marking and the Medical Device Directives

13485 Auditing

Clinical Data Requirements, PMS and Vigilance

Device Drug Combinations

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BSI is a trusted partner to industry and government with a focus to support their business objectives through the transfer of knowledge of best practices, assurance services to identify and measure performance indicators, training services to aid the building of organizational competency and enable continuous improvement, and the tools to monitor, enhance and report on compliance against the organization's management system objectives.

The BSI certification mark may be used on your stationery, literature and vehicles when you have successfully achieved certification and conform with applicable guidelines. The mark shall never be applied directly on the product or service.

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