I. Introduction
This chapter discusses the European Union (EU) regulation of in vitro diagnostic (IVD) medical devices, covering both pre- and postmarket regulatory requirements. In order to understand these rules and the manner in which they operate, both at the EU level and at the national level, it is first necessary to provide an introduction to general principles of EU law and the manner in which the European legislators have sought to facilitate the free movement of a wide variety of products within the EU using so-called “New Approach” directives. This is followed by a discussion of the premarket regulation of IVD medical devices and then a discussion of postmarket regulation.

II. Key Concepts of EU Law
EU law is a body of law that applies to the current 27 EU member states, plus three European Economic Area (EEA) states (Norway, Iceland and Liechtenstein). These three EEA member states are signatories to the EEA Agreement, under which they agree to implement and apply certain EU laws, including those governing the marketing of medical devices. Any reference to EU law, the EU or the Community in this chapter should therefore be read to include both the 27 EU member states and those three EEA countries.

A. European Union Institutions
The key EU institution for the regulation of medical devices is the European Commission, which acts as the civil service for the EU. The Commission can adopt legislation when that power is delegated to it and is also responsible for proposing legislation and steering it through the primary EU legislative process involving the European Parliament and Council of the European Union. It is the body that ensures that all signatories to the Treaty on the Functioning of the European Union (TFEU) and other international agreements underpinning the EU comply with their treaty obligations. Where necessary, the Commission may commence legal proceedings before the European Court of Justice to ensure compliance, for example where a member state has failed to implement EU law or has done so inappropriately. As discussed below, it also plays a key role in assessing member state actions that may restrict the marketing or supply of medical devices and ensuring that member states deal with
such issues in a consistent manner. The Scientific Committee on Medicinal Products and Medical Devices provides technical and scientific support to the Commission.

**B. Legislation**
The EU medical devices legislation comprises a series of directives. Directives allow the EU legislators to adopt legislation that takes into account the differing national legal systems. They impose on member states an obligation to transpose certain provisions into their national laws and to enforce the resulting measures by specific deadlines. The intention is to harmonize laws, while giving each country some flexibility in terms of the manner in which it implements and enforces the requirements. Failure to implement by the deadline constitutes a breach of EU law, and member states must therefore notify the Commission when they have adopted the implementing measures.

The other forms of binding legal act that are relevant to the medical device sector are regulations and decisions. Regulations have binding legal force throughout the EU and do not need to be transposed into the national laws of member states. The power to adopt decisions is delegated to the Commission in certain areas and these are binding only on those member states, companies and/or individuals to which they are addressed.

There are also a variety of nonbinding instruments, statements or documents such as opinions, communications and guidance documents. Although nonbinding, some European Commission guidance is considered to be the definitive statement of a medical device manufacturer’s obligations in certain areas, including the area of postmarket vigilance.

**C. Freedom of Movement of Goods**
One of the four so-called pillars of the EU is the principle that there should be freedom of movement of goods, services, workers and capital within the EEA. The freedom to move goods within the EU is enshrined in Articles 34 and 36 of the TFEU. These prohibit any quantitative and qualitative restrictions or measures affecting free movement of goods and restrict the ability of member states to adopt national regulations that interfere with this freedom. The concept was first crystallized by the European Court of Justice in the so-called *Cassis de Dijon* case, which established the principle that products legally manufactured or marketed in one country should move freely throughout the EU. Barriers to trade resulting from differences between national laws are only acceptable if they are necessary to protect health, safety, consumers and/or the environment. In addition, they must serve a legitimate purpose and be proportionate. In the absence of EU measures, however, member states are free to legislate within their territories.
The intention of much of EU law, including that governing the marketing of medical devices, is to avoid restrictions on the free movement of goods through technical harmonization of requirements at both the EU and national levels. The vast array of products and product types with highly technical requirements made this harmonization effort all but impossible if the regulators were to adopt product-specific norms, standards or requirements. The European Commission therefore devised a new regulatory mechanism, the “New Approach.”

D. The “New Approach”
Under the so-called new approach, legislators were required only to set out certain essential requirements with which products must comply to benefit from free movement within the EU. To further reduce administrative burden, the approach pre-supposed that premarket review and approval by regulators would be replaced by a variety of conformity assessment techniques, either by the manufacturer itself or by a third-party assessor of conformity. The design, manufacture and release of all products must be in accordance with appropriate quality assurance standards.

The first attempt to define the new approach was a 1985 Council Resolution on the New Approach. This provided that any new approach legislation would be limited to defining key essential requirements for a variety of products and that detailed technical specifications would be set out in harmonized European standards. Compliance with standards would not be mandatory because of concerns that this might hinder innovation. Manufacturers would have discretion to apply these harmonized standards or other technical solutions, but compliance with harmonized standards would raise a presumption of conformity with the essential requirements. The final component of the new approach was to be a safeguard procedure whereby member states could take action to prevent or restrict the marketing of nonconforming products or to address shortcomings in the harmonized standards.

The new approach was further refined in 1989 with a Council Resolution on the Global Approach. This created the concept of the CE mark, which manufacturers would apply to their products once they have demonstrated conformity with the essential requirements. Where possible, manufacturers would have some flexibility to choose from a variety of modular conformity assessment procedures. This flexibility would allow manufacturers to adapt to their company’s needs, the nature of the company’s products and their stage of development. The conformity assessment procedures would, however, share certain themes, including the possibility of conformity assessment based on documentary checks, product type approval or quality assurance systems. The procedures would be conducted either by the manufacturer of
lower-risk products or by third-party conformity assessment bodies that have been licensed by the relevant national regulator of the products (the so-called notified bodies).

Decisions 90/683/EEC and 93/465/EEC had set out some general guidelines and procedures for these conformity assessment procedures. These decisions have now been superseded by Decision 768/2008/EC, which establishes a toolbox of measures for use in future legislation, including provisions to support market surveillance and CE marking and a set of simple common definitions. Meanwhile, Regulation (EC) No 764/2008 and Regulation (EC) No 756/2008 set out some additional rules on market surveillance, accreditation of notified bodies and the application of national technical requirements.

The new approach has produced a significant number of “total harmonization” directives. These directives require that member states must repeal all contradictory national requirements. These are replaced by certain specific essential requirements set out in the annexes to the directives, compliance with which is a prerequisite for placing the product on the market or putting the product into service.

III. EU Regulation of IVD Medical Devices

The two key directives for manufacturers of IVD medical devices are the Medical Devices Directive 93/42/EEC (MDD) and the subsequent In Vitro Diagnostic Medical Devices Directive 98/79/EC (IVDD). These each establish essential requirements for their respective products and require manufacturers to carry out an appropriate conformity assessment procedure to demonstrate compliance with those requirements, either by themselves or with the assistance of a notified body. Both directives envisage compliance with nonmandatory European harmonized standards that raise a presumption of compliance with the essential requirements in the directives.

As with all new approach directives, manufacturers must apply the CE mark to medical devices and IVD medical devices once they successfully have completed the conformity assessment procedures and before they can be placed on the market or put into service within the EEA. Device regulators must presume that any product bearing the CE mark complies with the essential requirements and that it has been through the appropriate conformity assessment procedures. They cannot restrict or impede the free movement of CE-marked products unless they consider that the CE mark has been incorrectly applied, or that the device might compromise the safety of patients or users, in which case they can invoke safeguard measures.
A. **Key Definitions**

The MDD defines a medical device as follows:

“medical device” means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process, or
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.14

This definition has a number of key features. First, it suggests that it is the intention of the manufacturer that drives the classification of a product as a medical device. The issue is whether the manufacturer intends a product to be used to diagnose, prevent, monitor, treat or alleviate a disease, injury or handicap, or whether the intention is for the product to be used to investigate, replace or modify the anatomy, a physiological process or to control conception. Second, and in contrast to a medicinal product (medicine), a medical device must not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means. This has led some commentators to suggest that medical devices perform their function by physical means, but this is not always the case. For example, certain software products would be classified as medical devices but would not achieve their intended purposes by physical means as most people would understand that term.

IVD medical devices are a subset of medical devices. The IVDD defines an IVD medical device as follows:

“in vitro diagnostic medical device” means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus,
equipment, 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:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures.\textsuperscript{15}

An IVD medical device is any medical device that is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, again intended by the manufacturer to be used in vitro for the examination of specimens from the human body solely or principally for diagnostic purposes.

**B. Borderline Issues**

These definitions open up a range of borderline issues both relative to medicines and other classes of healthcare products and also relative to other consumer products that may or may not have a laboratory or diagnostic purpose.

1. **Medicines Borderline Issues**

The MDD expressly excludes from its scope medicinal products covered by Directive 2001/83/EC.\textsuperscript{16} The definition of a medicine in that directive is as follows:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.\textsuperscript{17}

There are two separate limbs to this definition. First, the so-called “presentation” limb encompasses products that are presented as being able to treat or prevent disease in humans. The second “administration” limb catches products that are administered with a view to modify, correct or restore physiological functions or to make a medical diagnosis. Medicines may fall within one or both limbs of the definition.
Within the last five years, two provisions of EU law have been adopted to help resolve border-line issues involving medicines and medical devices. First, Article 1.5(c) of the MDD clarifies the definition of the device in that directive to emphasize that, although the manufacturer’s intention is important, it is not a decisive factor in determining whether a product should be classified as a medicine or a device. Rather, it is the product’s principal mode of action that is determinative. Article 2.2 of the Medicines Directive 2001/83/EC also provides that in the event of doubt the definition of a medicinal product will prevail over the definition of any other product. This reflects the desire of regulators to bring borderline products within the scope of the medicines rules and the higher level of consumer protection that these rules afford.

2. IVD Borderline Issues
There are also a number of IVD-specific issues, notably the borderline between IVDs and analytical or research products with no medical purpose. The latter fall into two broad classes: 1) products for the detection of physiological or pathological states or harmful pathogens; and 2) general laboratory products. For example, a kit for the detection of biological warfare agents will not be an IVD medical device because the manufacturer’s intention, evidenced by the product’s labeling, instructions for use and/or promotional material, is that the product should not be used for a medical purpose. Likewise, devices intended for law enforcement, such as breathalyzers that measure alcohol levels in drivers, do not have a medical purpose. Similarly, there are many general laboratory products or reagents that are not regulated as IVD medical devices unless the manufacturer intends them to be used for IVD use.

3. IVD Medical Device Accessories
The IVDD defines an “accessory” as “an article which, whilst not being an in vitro diagnostic medical device, is intended specifically by its manufacturer to be used together with a device to enable that device to be used in accordance with its intended purpose.” IVD medical device accessories are deemed to be IVD medical devices in their own right and are subject to appropriate conformity assessment and CE marking (see below).

Specimen receptacles are IVD medical devices if they are specifically intended by the manufacturer to be for the primary containment and preservation of specimens derived from the human body for the purpose of IVD examination. Examples include sample tubes, microbial transportation devices or other receptacles or tubes intended primarily to collect or store samples for analysis. On the other hand, receptacles that are used in analytical processes (e.g., tubes, cups, cuvettes) are usually general laboratory equipment and should not be classified as an accessory to an IVD medical device, unless the manufacturer makes claims to that effect.
Invasive sampling devices and specimen receptacles that are applied to the human body are classified as medical devices, not IVD medical devices. Devices incorporating both specimen collection and analytical functions are borderline medical devices and IVD medical devices. Classification of these devices can be difficult, and one must consider the principal intended purpose of the product and the invasiveness and continuity of sampling. For example, a device for vacuum suction of saliva with an integral receptacle containing a human immunodeficiency virus (HIV) detection agent will be an IVD medical device. On the other hand, a blood glucose monitoring system providing a continuous supply of the patient’s specimen for in vitro analysis will be a medical device because there is no “dissociation” of the specimen from the patient.

There is an increasing trend toward the sale of medicinal products along with the IVD medical devices necessary to use those medicines appropriately. A good example of a drug that is indicated for use only once patients are tested is Herceptin® (International Nonproprietary Name: trastuzumab). This product is approved for use in the EC in metastatic breast cancer patients whose tumors over-express HER2. If such products were sold as an integral kit containing both the IVD medical device and the drug, there are arguments that the product must comply with the medicines rules and that the manufacturer of the medicine should supply the relevant medicines regulator with evidence that the IVD medical device component conforms to the relevant essential requirements. If that is the case, one might argue that the IVD medical device component would not need to be CE marked separately, but the European Commission and some medicines regulators have indicated that IVD medical device components must be CE marked.

Internal control and calibration materials for use in conjunction with IVD medical devices are normally IVD medical devices in themselves, except where they are internationally certified as reference materials or materials for external quality assurance.

C. Definition of Manufacturer
The IVDD defines the manufacturer of an IVD medical device as the “person who is responsible for the design, manufacture, packaging and labeling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.” The Directive requires that either the manufacturer or an authorized representative of the manufacturer must be established in the EEA. Manufactures outside the EEA must designate an authorized representative by contract, and that representative becomes responsible for many aspects of compliance with the EU devices rules discussed below. The definition of a manufacturer makes clear that so-called
“own branders” of devices manufactured by a third party will be considered the manufacturer for the purposes of the EU IVD medical device rules. Moreover, re-processors of IVD medical devices may be deemed the manufacturer of the re-processed product, particularly if this involves re-use of single-use devices.

IV. Premarket Requirements
A. Placing on the Market and Putting into Service
The IVD medical device rules apply when a manufacturer wishes to place a medical device on the EEA market or to put the device into service, for example, on its own premises.32 In this context, putting into service would encompass any use of an IVD medical device for diagnostic purposes involving human samples.

The IVDD defines placing on the market as “making available in return for payment or free of charge a new or fully refurbished device other than a device intended for clinical investigation, with a view to distribution, use, or both, on the Community market.”33 The European Commission has provided some guidance on this concept.34 The IVD medical device does not need to be supplied on commercial terms; the supply of free product constitutes placing on the market. The term “making available” incorporates any transfer of a product, whether that involves transfer of legal ownership or the physical handover of product, to an EEA distributor. It also includes passing the product to a final customer or user, either as part of a commercial transaction or free of charge. In either case the product must comply fully with the requirements of the IVD medical device before any transfer.

Making available also includes the offer to transfer product; i.e., where product is made available in its commercial distribution chain with a view to transfer to either a distributor or a user. Again, product must comply with the IVDD before any offer to transfer. This has implications for the pre-CE marking promotion of medical devices in the EEA. Although the IVDD does not contain specific provisions governing the advertising and promotion of IVD medical devices, the definition of placing on the market may render premarket promotion of IVD medical devices in breach of the applicable rules. The Directive does, however, provide for an exemption for the display of medical devices at trade fairs, exhibitions and the like.35 Products displayed at trade fairs, exhibitions, demonstrations, scientific or technical gatherings etc. need not be CE marked, provided that the devices are not used on specimens taken from participants and that a visible sign clearly indicates that the devices cannot be marketed or put into service until they have been bought into compliance with the requirements of the IVDD.
There is also a specific exemption from the need for a full conformity assessment and CE marking where health institutions manufacture devices for use within the same institution or on premises within the immediate vicinity of the institution without having been transferred to another legal entity. This captures so-called “home brew” diagnostic tests that may be prepared within a hospital for use in that hospital. It does not permit the commercial or free supply of products to any other hospital, institution or entity.

B. Essential Requirements

Manufacturers may only place an IVD medical device on the market or put the IVD medical device into service within the EEA if the IVD medical device conforms to the applicable essential requirements. These requirements are listed in Annex I to the IVDD. They are very broad and general requirements, for example:

The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons, or the safety of property. Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.

The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in [the definition of an IVD], as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.

There are more detailed and specific requirements, for example, relating to devices that may emit hazardous, visible and/or invisible radiation, devices incorporating an energy source and devices for self-testing, but they all remain fairly broad and general. The essential requirements also provide details of the labeling requirements for IVD medical devices and general requirements for information that must accompany these products.
As indicated above, manufacturers may choose to apply harmonized standards to the design and quality assurance processes for their products. Although compliance is not mandatory, it does raise a presumption of conformity with the essential requirements. Manufacturers that choose not to apply harmonized standards must demonstrate conformity through other means.

European harmonized standards are requested by the European Commission and are developed by European standards bodies, such as CEN and CENELEC. Once adopted, the Commission arranges for the publication of details of each standard in the Official Journal of the European Union.

There are three general classes of standards:

- horizontal standards governing common requirements, e.g. sterilization and safety of medical electrical equipment;
- product standards for specific types of device; and
- quality standards to ensure the quality of design and manufacturing processes.

In many cases these European standards incorporate those agreed upon at the international level. Good examples are the International Standards Organization (ISO) 9000 series of quality standards and the device-specific ISO 13485 standards that apply the ISO 9000 series to the medical device context. These have all been adopted by European standards bodies and bear the designation “ISO EN.”

For certain IVD medical devices—i.e., those listed in List A of Annex II of the IVDD—a European Commission Expert Group has drawn up Common Technical Specifications (CTS) that establish performance evaluation and re-evaluation criteria, batch release criteria and both reference methods and materials for use in the conformity assessments of IVD medical devices. As with harmonized standards, compliance with the CTS is not mandatory but it does result in a presumption of compliance with the essential requirements. Manufacturers of IVD medical devices in List A of Annex II must justify any noncompliance with the CTS and any alternatives must be at least equivalent to those specifications.

C. Classification

Any IVD medical device manufacturer wishing to place a product on the market or put the product into service must first classify the IVD medical device in accordance with certain
predefined risk categories contained in the IVDD. There are four categories of IVD medical devices that are classified in order of increasing perceived risk:

- general IVD medical devices, i.e., all IVD medical devices other than those listed in Annex II of the IVDD and IVD medical devices for self-testing;
- IVD medical devices for self-testing, i.e., those used by lay persons in a home environment, excluding self-test devices covered by Annex II;
- IVD medical devices in Annex II, List B, including reagents and products for testing of rubella, toxoplasmosis and phenylketonuria, as well as devices for self-testing for blood sugar levels; and
- IVD medical devices in Annex II, List A, including reagents and products for HIV I and II, hepatitis B, C and D, and reagents or products for determining ABO systems and anti-kell.

Having determined the risk category for the IVD medical device, the manufacturer must ensure that the device meets the essential requirements of the IVDD by following the appropriate conformity assessment procedure(s) for that device. If appropriate, it must seek notified body input.

**D. Notified Bodies**

Notified bodies are normally private commercial entities that are licensed by national medical device regulators to perform conformity assessment of medical devices, including IVD medical devices. Notified bodies must comply with certain requirements listed in Annex IX of the IVDD. In essence, this requires that notified bodies should have appropriate staff to perform the conformity assessment of IVD medical devices and the associated technical, administrative and inspection tasks. The requirements encourage impartiality and professional integrity. For example, a notified body cannot consult in the development of an IVD medical device and also perform the resulting conformity assessment. However, affiliated companies can do so. Remuneration of the notified body and its staff cannot be linked to the number of conformity assessments performed.

One of the criticisms of the notified body procedure is that notified bodies are in a client relationship with the manufacturer of the medical device and some have suggested that this can lead to conflicts of interest. Manufacturers are free to choose any appropriately qualified notified body within the EEA and, although there are mechanisms to ensure that manufacturers do not simply approach multiple notified bodies until they obtain the desired certificate of
Conformity, some have suggested that notified bodies inevitably are reluctant to lose custom. That said, notified bodies risk losing their license to perform conforming assessment if standards fall below a level that national device regulators deem appropriate or acceptable.

E. Conformity Assessment Processes

The conformity assessment procedures for IVD medical devices are found in Annexes III, IV, V, VI and VII of the IVDD. The specific details of the procedures are beyond the scope of this chapter but it is possible to make a number of generalized comments. For general IVD medical devices—i.e., all IVDs other than devices for self-testing or those listed in Annex II—the manufacturer self-assesses conformity with the essential requirements and prepares a declaration of conformity in accordance with Annex III of the Directive. It can then apply the CE mark and place the product on the EEA market. For all other IVD medical devices, the manufacturer may choose from a variety of conformity assessment procedures, all of which involve some interaction with a notified body. The procedures range from product design examination in accordance with Annex III, through EC type-examination where a notified body reviews a representative sample of production in accordance with Annex IV, through so-called EC verification which ensures compliance with a representative sample of products on a statistical basis, through to either production quality assurance in accordance with Annex VII or a full quality assurance audit in accordance with Annex IV. Many conformity assessment procedures combine two or more of these procedures.

As indicated above, these procedures are modular and there is often some flexibility to select amongst the various conformity assessments procedures. Exactly which route a manufacturer chooses will depend on the circumstances, and selection of the conformity assessment processes is an art. In general terms, however, manufacturers tend to opt for Annex IV full quality assurance audits over more product-focused assessments when they envisage that they will sell a variety of IVD medical devices and/or where they envisage that they may change product specifications and designs from time to time.

Where a notified body is involved in the conformity assessment procedure, it will issue one or more certificates of conformity; for example, it may grant a certificate of conformity following an audit of the company’s quality assurance system in accordance with the ISO 13485 quality assurance standard. Once the manufacturer has received all the appropriate certificates of conformity, it must make a declaration of conformity in accordance with the requirements of Annex III. It may then apply the CE mark and place the product on the EEA market.
Where an IVD medical device has been subjected to notified body conformity assessment, the manufacturer must inform the notified body of any material changes to product ranges and quality systems, plus changes in the design of an IVD medical device or pathogens and markers of infection if the device has undergone type or design examination as part of the conformity assessment procedure.51

F. Technical Documentation and Product Registration
Before and during the marketing of any IVD medical device, a manufacturer must ensure that it or its authorized representative within the EEA maintains all the technical documentation, including certificates and declarations of conformity, necessary to demonstrate that the IVD medical device conforms to the essential requirements at a location within the EEA.52 The technical documentation must be maintained for at least five years after the manufacture of the last device to which the file relates. Either the manufacturer or the authorized representative must ensure that national medical device regulators are able to inspect these documents on request.

The manufacturer or its representative must also register its details and the details of any medical device before the device is launched in any EEA market.53 The registration requirements are not onerous. The information required is purely administrative and ensures simply that the relevant national medical device regulators are aware of which medical devices are being marketed in their jurisdiction. The intention has always been for this registration to occur once for each medical device in a specific European medical device databank (EUDAMED).54 This database is, however, not yet operational and, until then, manufacturers must assess whether separate registrations are required in each member state prior to the products launched in that jurisdiction.

G. IVD Medical Devices for Performance Evaluation
Article 4.2 of the IVDD provides that member states should not create any obstacle to the supply of non-CE marked IVD medical devices for performance evaluation, provided that the manufacturer complies with the requirements with Annex VIII. This annex does not require a formal conformity assessment of a device intended only for performance evaluation. Rather, a manufacturer must draw up a declaration in accordance with the requirements of Annex VIII.55 This includes details of the device and the proposed evaluation, a list of laboratories taking part in the evaluation and details of its start date. In addition, it must include a statement that the device in question conforms to the requirements of the IVDD, apart from aspects subject to the evaluation and any that are specifically itemized in the statement. It must
also indicate that every precaution has been taken to protect the health and safety of patients, users and other persons.

The manufacturer or its authorized representative must also ensure that it registers both its details and those of the IVD medical device for performance evaluation in accordance with the procedures discussed above. Finally, the manufacturer must maintain documentation relating to the device and its performance evaluation for at least five years after the end of the performance evaluation.

V. Postmarket Requirements
A. Advertising and Promotion of IVD Medical Devices

Neither the MDD nor the IVDD contains any provisions that regulate the advertising and promotion of medical devices in the EEA. This means that there is significant variation in terms of the manner in which member states do or do not regulate these practices. Some member states have not implemented any rules that specifically regulate the advertising and promotion of medical devices, including IVD medical devices. An example is the United Kingdom (UK), which subjects most medical devices and IVD medical devices to the same general advertising laws that apply to any other product. These require that advertising is fair, balanced, not misleading and substantiated. The only UK legislation that governs the promotion of an IVD medical device are the HIV Testing Kits and Services Regulations 1992, which makes it an offense to sell, supply, advertise or promote HIV testing kits to the general public.

The laws in other jurisdictions are quite variable. Some member states, like Belgium, have taken the provision in the MDD and IVDD clarifying that display of products at trade shows, exhibitions etc. does not constitute placing on the market as an indication that pre-CE mark advertising of devices is not permitted under any other circumstances. Italy, on the other hand, expressly prohibits the advertising to the public of certain types of medical devices, including custom-made devices, medical devices that are subject to medical prescription and professional use medical devices. The laws in other jurisdictions, such as Spain and Germany, focus less on the advertising of devices as that term is commonly understood, and more on regulating the relationship between medical device manufacturers and healthcare professionals.

Most countries also have anti-bribery laws that may regulate interactions between a company and physicians who are either government officials or employees of government health service providers.
B. Device Vigilance

One of the features of the EU IVD medical device regime is that national medical device regulators are not involved in premarket review or approval of those products. Indeed, the only medical devices that are subject to any premarket scrutiny by a regulatory body are medical devices incorporating ancillary medicinal products. The only notification that regulators receive that devices are to be marketed in their jurisdiction involves the administrative registration process discussed above. The national medical device regulators are nevertheless legally responsible for ensuring that devices marketed in their jurisdictions conform to the essential requirements and that they do not compromise the health of patients, users and other third parties. They rely on manufacturers to report adverse incidents involving medical devices to them and will exercise their safeguard powers to remove nonconforming or harmful devices from the market.

Since EEA device regulators rely almost exclusively on manufacturers fulfilling their device vigilance obligations, it is perhaps surprising that the main text of the IVDD does not impose any direct safety reporting obligations on manufacturers of those products. Rather, manufacturers are obliged when preparing an EC Declaration of Conformity under Annex III of the IVDD to put in place and maintain a systematic procedure for review of postmarket experience and to implement any necessary corrective actions. Manufacturers must notify the national authorities of the following incidents immediately on learning of them:

The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the competent authorities of the following incidents immediately on learning of them:

(i) any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to, or might have led to, the death of a patient or user or other persons or to a serious deterioration in his or their state of health;

(ii) any technical or medical reason connected with the characteristics or the performance of a device for the reasons referred to in subparagraph i) leading to systematic recall of devices of the same type by the manufacturer.
These safety reporting requirements have been supplemented by European Commission device vigilance guidance, which was most recently updated in December 2009. In many ways this guidance differs from the safety reporting requirements in the IVDD, but is not legally binding. In addition, a number of member states have implemented the requirements of the IVDD differently, which leads to further ambiguities.

1. **Incidents**

Under both the IVDD and the Commission Vigilance Guidance, manufacturers must report any adverse incident related to a medical device that leads or might lead, directly or indirectly, to the death of a patient, user or other person or to a serious deterioration in their state of health.

The Commission Vigilance Guidance acknowledges that IVD medical devices do not act directly on an individual, but harm may occur as a consequence of the medical decision or action taken or not taken on the basis of information or result(s) provided by the IVD medical device. Thus, examples of indirect harm include misdiagnosis, delayed diagnosis, delayed treatment, inappropriate treatment and transfusion of inappropriate materials.

Under the IVDD, only incidents that result in death or a serious deterioration in health need to be reported. The Commission Vigilance Guidance specifies that a serious deterioration in health includes, as well as a life-threatening illness, permanent impairment of a bodily function, any condition necessitating medical or surgical intervention to prevent such illness or impairment and any indirect harm suffered as a result of an incorrect test result of an IVD medical device when used in accordance with the manufacturer’s instruction for use. This means that almost any incident involving an IVD medical device will be regarded as resulting in a serious deterioration in health.

The IVDD suggests that all reportable incidents should be reported immediately. The Commission Vigilance Guidance, on the other hand, states that such incidents must be reported immediately (without any delay that could not be justified), but then sets out maximum reporting time lines that reflect the seriousness of the incident. Where incidents present a serious threat to the public health, they must be reported within two days. In the event that there is a death or unanticipated serious deterioration in health, the reporting time line is ten days and for all other incidents the time line is 30 days.

There is further ambiguity between the directive and guidance in a number of other areas. For example, the IVDD suggests that incidents should be reported to all competent authorities,
whereas the guidance suggests that they should be reported to the national device regulator in the country where the incident occurred. The Directive suggests that only incidents that are directly causally related to the device must be reported. The Guidance explicitly deals with this point, requiring that manufacturers report incidents only if the device is suspected to be a contributory cause, but suggests that manufacturers should assume that the device may have caused or contributed to the incident and should err on the side of caution when deciding whether to report. The IVDD draws no distinction between incidents occurring within the EEA and incidents occurring elsewhere, but the Guidance requires reporting of incidents outside the EEA only if they have resulted in a field safety correction action (FSCA). The Directive does not require reporting of safety trends and signals, whereas the guidance does require such reports. Finally, the Directive does not provide any exemptions to the obligation to report, whereas the guidance provides for a significant number of exemptions from the need to report serious adverse incidents. Examples include side effects or incidents that are expected and foreseeable, i.e., are listed in the information accompanying the device; deficiencies of a device found by a user prior to its use; and events caused by pre-existing patient conditions.

2. Field Safety Corrective Actions
The IVDD requires the reporting of systematic recalls of IVD medical devices, while the Commission Vigilance Guidance requires the reporting of any FSCA. The Guidance defines an FSCA as “an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market.” This would, for example, include on-site modification of a device to reduce or eliminate a risk or the circulation of amended instructions for use for those reasons.

3. National Device Vigilance Requirements
Perhaps because the MDD and the IVDD do not impose clear, safe reporting obligations on manufacturers of medical devices, the member states differ in the manner in which they have implemented these safety reporting requirements. A detailed discussion of these national rules is beyond the scope of this chapter but member states can be split into two broad categories: those that have implemented specific device vigilance reporting obligations and those that have incorporated the obligations from the Annexes to the MDD and IVDD by reference. Germany and France fall within the first category. For example, Article L5212-2 of the French Code de la Santé Publique (Public Health Code) imposes a direct reporting obligation not only on manufacturers of a device, but also on users and any third parties having knowledge of an incident or hazard involving a device. They are all obliged to report these issues to the
French regulator, AFSSAPS. The obligation to report “without delay” is at odds with the reporting time lines in the Commission’s Guidance. It also seems that the AFSSAPS requires reporting of all reportable serious adverse incidents to the AFSSAPS, whether they occur inside or outside France.

The UK is an example of a member state that has not implemented specific device vigilance obligations. The Medical Devices Regulations 2002\textsuperscript{75} simply incorporate the reporting obligations set out in the annexes to the IVDD by reference.\textsuperscript{76} Manufacturers of IVD medical devices should therefore exercise some caution when determining whether adverse incidents or FSCAs are reportable within the EEA. Most regulators expect them to comply with the reporting obligations in the Commission Guidance whatever the national laws and the directives may or may not say, but there are some national variations, including those in France.

Manufacturers should also take into account international variations in adverse incident reporting requirements. A discussion of these variations is again outside the scope of this chapter but it is noteworthy that the reporting obligations in the United States differ significantly, with a lower reporting threshold and an absence of exemptions to the need to report, such as those that exist in the EEA.

C. Safeguard Measures

In the event that a national medical device regulator considers that a device should be withdrawn from the market or that marketing should be suspended or restricted, the EC devices rules give the regulator the power to take so-called safeguard measures. It is a requirement of Article 114(10) of the TFEU\textsuperscript{77} that all harmonization legislation or measures must include a safeguard clause. This allows member states to restrict the free movement of products for the non-economic reasons set out in Article 36 of the TFEU, including the protection of health and life of humans.

All the medical devices directives, including both the MDD and IVDD, allow member states to restrict or prohibit the marketing of medical devices or to withdraw devices from the market where a device, although correctly marketed and used, may compromise the health and safety of patients, users or others.\textsuperscript{78} The scope of these powers differs depending on the directive in question. In the IVDD it applies only to CE-marked devices,\textsuperscript{79} whereas the safeguard provisions of the MDD cover both CE-marked and custom-made devices, as well as those that are undergoing clinical investigation.\textsuperscript{80} The IVDD also allows member states to take safeguard measures against devices not only when there is a risk to the health and safety of
patients, users or others, but also when the safety of property may be compromised. Both the MDD and the IVDD require that member states must “ascertain” a danger, and Commission guidance requires that the danger must be “substantial.”

The safeguard provision in the IVDD provides that any measures to suspend or withdraw a device from the market must be “interim.” The requirement that safeguard measures be “interim” reflects the fact that any member state invoking a safeguard measure formally must notify the European Commission, indicating the reasons for its action. The Commission is then required to assess the appropriateness of the measure and to confirm that it is not an inappropriate restriction on the free movement of goods within the EEA. First, it assesses whether the measure has been taken for one of the following reasons:

- failure to meet the essential requirements;
- incorrect application of harmonized standards; and
- shortcomings in the harmonized standards.

This list is exhaustive so that member states can take safeguard measures for other reasons—for example, poor manufacturing or quality control—only if they are directly linked to one of these specified reasons; e.g., the device no longer fulfills the essential requirements.

Once the Commission has analyzed the reasons for the measure, it consults with all parties concerned and comes to a view on whether the measure is appropriate. If the measure is justified, the Commission must immediately inform all the member states and bring any shortcomings in standards before the Committee on Standards and Technical Regulations within two months in order to assess whether amendments to the harmonized standards are necessary. If the measures are unjustified, the Commission must immediately inform the member states and the manufacturer, and the member state would be expected to reverse the suspension or withdraw actions. If the device is CE marked, the member state in the jurisdiction where the manufacturer or its authorized representative is established must “take appropriate action” against the entity that has applied the CE mark, and inform the Commission and other member states of the measure that has been taken. The Commission must ensure that the other member states are informed of the procedure and its outcome.

There are a number of clear issues with these safeguard measures, including that action is only possible against individual products and then only on certain specified grounds. It is for these reasons that Article 13 of the IVDD included a new form of safeguard measure and the IVDD
also amended the MDD to include a new Article 14b. These provisions allow member states to prohibit, restrict or subject to particular requirements a given product or group of products to ensure the protection of health and safety or for public health reasons. These measures may only be temporary, again because the Commission is required to assess their validity. A member state must notify the Commission and the other member states if it takes any action under Article 13 of the IVDD along with justifications for its action. The Commission must consult with interested parties and the member states. If the Commission concludes that the measures are justified, it must adopt Community measures to give effect to those measures which could include adopting legislation to correct deficiencies in the existing framework.

The safeguard measures under Article 13 are also much more broadly worded than those under Article 8 of the IVDD. There is no requirement that devices be used in accordance with their intended purposes and no list of instances that justify restrictive measures. There is flexibility to subject devices to “particular requirements,” which could include additional national processes or procedures. However, any nonconformity must involve a systematic failure in a whole series of products.

Despite these powers, there have been very few formal invocations of safeguard measures. This is largely because member states are keen to avoid procedural delays and complications associated with these procedures. Action is therefore normally the result of negotiation with the manufacturer of a device leading to either voluntary modification of devices or withdrawal by the manufacturer. Alternatively, some notified bodies may reassess whether a device conforms to the essential requirements in the IVDD and hence whether the notified body’s certificate of conformity should remain in effect. These measures do not have binding legal effects and a referral to the European Commission following safeguard action is therefore not required. There are many examples where action has been taken either by manufacturers on request or by notified bodies when faced with regulatory scrutiny of a product.

There are a couple of examples of procedures under Article 14b of the MDD. Both of these procedures were initiated by France and resulted, for example, from restrictions by the French government of devices for bone marrow replacement and other medical devices containing animal tissues and a requirement that certain high-risk devices, such as breast implants, be subject to premarket approval. Two of these safeguard measures have led to the adoption of European Commission Directives: i) Directive 2003/12/EC,\textsuperscript{85} which reclassified breast implants from Class 2b to Class 3; and ii) Directive 2003/32/EC,\textsuperscript{86} which imposed specific requirements for medical devices manufactured using tissues or substances of animal origin.
Endnotes


2. On December 1, 2009, when the Treaty of Lisbon came into force, the European Community ceased to exist and was succeeded by the European Union. All relevant guidance documents and legislation still refer to the European Community (EC).


7. Council Decision 90/683/EEC of 13 December 1990 concerning the modules for the various phases of the conformity assessment procedures which are intended to be used in the technical harmonization directives, 1990 OJ (L 380), 13.

8. Council Decision 93/465/EEC of 22 July 1993 concerning the modules for the various phases of the conformity assessment procedures and the rules for the affixing and use of the CE conformity marking, which are intended to be used in the technical harmonization directives, 1993 OJ (L 220), 23, as amended.


14. MDD, art. 1.2.

15. IVDD, art. 1.2(b).


21. IVDD, art 1.2(b) and Commission Borderline Guidance, Section 4.

22. IVDD, art 1.2(c).

23. IVDD, art 1.2(b) and Commission Borderline Guidance, Section 3.

24. IVDD, art 1.2(c).


27. MDD, art. 1.3.

29. IVDD, Recital 9 and Commission Borderline Guidance, Section 8.
30. IVDD, art. 1.2(f).
31. IVDD, art. 10.3.
32. IVDD, art. 2.
33. IVDD, art. 1.2(i).
35. IVDD, art. 4.3.
36. IVDD, art. 1.5.
38. IVDD, Annex I, Part A, para. 3.
39. IVDD, Annex I, Part B, para. 8. Article 4.4 of the IVDD permits member states to require that an IVD medical device’s labeling and instructions for use be translated into their official language(s), while paragraph 8.1 of Annex I, Part B states that, for devices for self-testing, the labeling and instructions for use must include a translation into the official language(s) of the member state in which the device for self-testing reaches its final user.
40. IVDD, art. 5.1.
41. European Committee for Standardization.
42. European Committee for Electrotechnical Standardization.
44. IVDD, art. 5.3.
45. IVDD, art. 9.
46. Article 1.2(d) of the IVDD defines a device for self-testing as “any device intended by the manufacturer to be able to be used by lay persons in a home environment.”
47. IVDD, art. 15.1.
48. IVDD, art. 15.2.
49. Article 15.5 of the IVDD requires notified bodies, on request, to inform other notified bodies and the relevant competent authority of any certificates that the notified body has refused to issue.
50. IVDD, art. 9.1.
51. IVDD, Annex III, para. 6.3; Annex IV, para. 3.4, 4.4 and 4.5; Annex V, para. 6 and 6.1; and Annex VII, para. 3.4.
52. IVDD, art. 9.7.
53. IVDD, art. 10.1.
54. IVDD, art. 12.1(a).
55. IVDD, Annex VIII, para. 1.
56. IVDD, Annex VIII, para. 4.
57. IVDD, Annex VIII, para. 3.
59. Law on Medicinal Products, as amended, Article 9, applied to medical devices by Royal Decree on Medical Devices of March 18, 1999.
61. MDD, art. 1.4.
62. IVDD, Annex III, para. 5.
64. Commission Vigilance Guidance, Section 4.11.
65. Commission Vigilance Guidance, Section 5.1.1(c).
66. Commission Vigilance Guidance, Section 5.1.7.
67. Commission Vigilance Guidance, Section 5.1.8.
68. Commission Vigilance Guidance, Section 5.1.1(b).
69. Commission Vigilance Guidance, Sections 3 and 5.4.4.
70. Commission Vigilance Guidance, Section 5.1.4.
71. Commission Vigilance Guidance, Section 5.1.3.5.
72. Commission Vigilance Guidance, Section 5.1.3.1.
73. Commission Vigilance Guidance, Section 5.1.3.2.
74. Commission Vigilance Guidance, Section 4.6.
76. Medical Devices Regulations 2002, Reg. 32(2).
77. Supra note 3.
78. MDD, art. 8 and IVDD, art. 8.
79. IVDD, art. 8.1.
80. MDD, art. 8.1.
81. Supra note 34, Section 8.3.
82. IVDD, art. 8.1.
83. IVDD, art. 8.2.
84. IVDD, art. 8.3.