Due diligence in the European medical devices industry

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As the medical devices industry is highly regulated, determining a target company's regulatory compliance profile represents a key component of any due diligence undertaking. In Europe there is generally little publicly available information about medical devices which are the subject of the regulatory processes allowing them to be placed lawfully on the market. For this reason it is important that due diligence request lists and warranties are drafted to flush out the information required to properly evaluate the regulatory status of the company's products.

Regulatory due diligence for medical device companies whose products are already on the market typically involves two overlapping components:

- The applicable regulatory framework within which the company operates (since the requirements differ in certain respects for different types of medical devices).
- Identifying any outstanding compliance issues that could become problematic in the future. This enquiry includes not only consideration of actual enforcement actions, but of potential shortcomings or gaps that the competent authorities in member states of the European Union (EU) could challenge in the future.

A third possible area for review is the reimbursement status and pricing for the product and its competitors. This information is important to enable a potential purchaser to make reasonable profit projections. This is a complex area, with many EU member states having quite unique systems for determining reimbursement status and pricing. This third issue is outside the scope of this chapter.

Against this background, this chapter examines:

- Requirements for medical devices to be lawfully placed on the market, including the regulating directives.
- Due diligence documents and issues frequently arising in the medical devices industry.

REQUIREMENTS FOR MEDICAL DEVICES TO BE LAWFULLY PLACED ON THE MARKET

A due diligence inspection of a medical device company begins with the basics: a listing of all medical devices which the company sells, sponsors in clinical trials or intends to sell or sponsor in clinical trials. If only certain product lines are being acquired, the list can be limited to those. The approval or clearance status of each product must be determined and confirmed.

Medical devices are regulated by the following Directives:

- Directive 93/42/EEC concerning medical devices (Medical Devices Directive).
- Directive 90/385/EEC on active implantable medical devices (Active Implantable Medical Devices Directive).
- Directive 98/79/EC on in vitro diagnostic medical devices (IVD Directive).

The first step in determining whether the approval process has been correctly followed is to establish which of these three regimes apply to the products in question. The Medical Devices Directive regulates all medical devices except for active implantable devices or in vitro diagnostic devices, which are regulated by the other directives (*see box, Which regulatory regime?*).

Medical Devices Directive

Devices regulated by the Medical Devices Directive are categorised into four classes, depending on the type of product. The categorisation is based on the perceived risks of the device, according to its use. The following is a general outline, but more detailed rules can be found in Annex IX of the Medical Devices Directive.

- **Class I devices.** Generally those considered to involve the least risk and which are mainly non-invasive devices.
- **Class IIa devices.** This includes non-invasive devices which are connected to an active medical device and invasive devices inserted into the natural cavities in the head.
- **Class IIb devices.** This includes devices used in the short-term or transiently and which are invasive devices which supply energy or radiation, administer medicines or are otherwise potentially hazardous.
- **Class III devices.** This includes invasive devices used in the most complicated procedures, such as to diagnose, monitor or correct heart, central nervous system or circulatory defects.

The different classes determine the rigour of the regulatory requirements to be met before a device can be placed on the market. There are different assessment procedures, set out in the annexes to the Medical Devices Directive. The following table sets out which procedures are relevant for CE (European conformity) marking (except for special purpose devices or devices intended for clinical

WHICH REGULATORY REGIME?

The Medical Devices Directive regulates all medical devices which are not otherwise regulated by the Active Implantable Medical Devices Directive or the IVD Directive. Below are the definitions of medicinal products (which are not regulated by the Medical Devices Directive), in vitro diagnostic medical devices (regulated by the IVD Directive) and active implantable medical devices (regulated by the Active Implantable Medical Devices Directive).

Definitions

Products classified as medicinal products will not be regulated by the medical devices legislation. Directive 2001/83/EC on medicinal products for human use (Human Medicines Directive) defines a medicinal product as:

"Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product".

A medical device is defined as:

"Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software 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".

An in vitro diagnostic medical device is defined as:

"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;
- Concerning a congenital abnormality;
- To determine the safety and compatibility with potential recipients; or
- To monitor therapeutic measures.

Specimen receptacles intended for "primary containment and preservation of specimens from the human body" are included in this definition.

Accessories for in vitro diagnostic medical devices are included in the same regulatory regime.

An active medical device is defined as:

"A medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity".

An active implantable medical device is defined as:

"Any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure".

Where an active implantable medical device is intended to administer a substance defined as a medicinal product by Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, then that substance is itself subject to the system of marketing authorisation provided for in that Directive.

Where an active implantable medical device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product (as defined above), then the Active Implantable Medical Devices Directive will apply.

investigations) (*see box, Medical Devices Directive: routes to CE marking*). In some cases, there are alternatives which can be selected. These are indicated by different numbers (for example those labelled 1 indicate one option and those labelled 2 are another route to CE marking).

IVD Directive

The table (*see box, IVD Directive: routes to CE marking*) summarises the regulatory requirements to be permitted to apply a CE mark to in vitro diagnostic medical devices by reference to the Annexes in the IVD Directive.

Active Implantable Medical Devices Directive

Active implantable medical devices are subject to a similar system. There are no separate classes of active implantable medical devices or differing requirements to be met before a CE mark might be applied. In fact, all active implantable medical devices are required to undergo an evaluation by a notified body of the quality system, the design of the product(s), and a representative sample of the production.

MEDICAL DEVICES DIRECTIVE: ROUTES TO CE MARKING

	Classes of medical devices					
Conformity Assessment Procedures (Medical Devices Directive Annexe no.)	**I**	**I sterile**	**I measuring**	**IIa**	**IIb**	**III**
EC Declaration of Conformity (II (+Sec 4)						**1.**
EC Declaration of Conformity (II (-Sec 4)				**2.**	**1.**	
EC Type Examination (III)					**2.+**	**2.+**
EC Verification (IV)		**1.a or**	**1.a or**	**1.a or**	**2.a or**	**2.a or**
EC Declaration of Conformity to type (V)		**1.b or**	**1.b or**	**1.b or**	**2.b or**	**2.b**
Special Purpose Devices (VI)		**1.c**	**1.c**	**1.c**	**2.c**	
Clinical Evaluation (VII)	**1.**	**1.+**	**1.+**	**1.+**		

DUE DILIGENCE DOCUMENTS

Notified bodies

The declaration of conformity for active implantable devices and devices regulated by the Medical Devices Directive in classes II and III requires manufacturers to select a notified body in one of the EU member states (*see box, What is a notified body?*). It is only necessary to obtain the required certification from one notified body in the EU to then be allowed to lawfully apply the CE mark throughout the European Community (EC). The medical device company that is the subject of due diligence should be able to produce certificates from their selected notified body which show that the required conformity assessment procedures have been carried out with acceptable results. The certificates are normally valid for a period of five years, after which an application must be made to extend the certificate.

International standards

Many medical device companies will be able to provide certificates showing compliance with international standards. For the purposes of the directives regulating medical devices, manufacturers generally look to meet the requirements of ISO 13485 (a European harmonised medical device quality system standard). A manufacturer which holds a certificate stating that it meets this standard is deemed to have complied with the requirements of the following annexes of the Medical Devices Directive (and where applicable, in brackets of the IVD Directive): Annex II (Annex III) for quality assurance, Annex V (Annex VII) on production quality assurance and Annex VI for product quality assurance.

General

There is no public register of medical devices entitled to apply the CE mark in the EU. Therefore the target company will have to provide evidence that the correct procedures have been followed and that, where applicable, the notified body has given its approval. It would be wise in a due diligence request to ask to see all correspondence with the notified body. The warranties should also be drafted in a way that produces these documents. Sometimes this correspondence serves to highlight particular issues with the design or production of the product which might at a later date become issues for a regulator.

Once the approval or clearance of a medicinal product has been confirmed, an additional layer of inquiry will be necessary. For medical devices sold in the EU, any substantial change to production quality or any change to the design previously approved by a notified body must be notified to that body. The notified body will determine whether and to what extent it must inspect the products or manufacturing facility. The notified body has to then approve such modifications before they are implemented. If a notified body is not required, the manufacturer will need to ensure that it has made appropriate amendments to its own self-certified documents. Failure to perform the appropriate assessment can lead the competent authorities to view the product as wrongly CE marked. Competent authorities are obliged to end any such infringement, which can include ordering the device to be removed from the market until the regulatory requirements have been met.

The manufacturer placing devices on the market must inform the competent authorities of the member state in which he (or the person designated as responsible for marketing the goods in the EC) has a registered place of business, of the address of that registered place of business and the description of the devices concerned. Under the Medical Devices Directive, if the devices are in class IIb or III, member states can request to be informed of all data allowing for identification of such devices, together with the label and the instructions for use when such devices are put into service within their territory. The due diligence should verify that this notification requirement has been complied with by requesting evidence from the company.

IVD DIRECTIVE: ROUTES TO CE MARKING

Conformity Assessment Procedures (IVD Directive Annexe no.)	All except those in Annex II and for performance evaluation	Devices for self-testing except Annex II and for performance evaluation		Devices in list A of Annex II, but not for performance evaluation	Devices in list B of Annex II, but not for performance evaluation	Devices for performance evaluation
EC Declaration of Conformity (III – point 6)	1.					
EC Declaration of Conformity (III + point 6)		1.+				
EC Declaration of Conformity – full quality assurance (IV)		1.		1.	1.	
EC Type Examination (V)		2.+	3.+	2.+	2.+	
EC Verification (VI)			3a or		2a or	
EC Declaration of Conformity to type (VII)		2.	3b	2.	2b	
Devices for Performance Evaluation (VIII)						1.

Ongoing safety and post-market surveillance

It is important to review how the company deals with complaints and adverse events. There are specific requirements in this area issued by governments and the competent authorities. These requirements are often known as post-marketing surveillance and will generally require that manufacturers and medical practitioners report adverse events that are associated with medicinal products or devices.

Specifically, due diligence should include a review of:

- Adverse event reports and other complaints about a product.
- Investigations conducted by the manufacturer.
- Conclusions reached by the manufacturer.
- Whether and how the events were reported to competent authorities.

Under the Medical Devices Directive, member states are assumed to have their own complaints system in place, which provides for competent authorities to be informed of adverse events relating to the device or the inadequacies of its labelling or instructions. Where competent authorities are notified of incidents which have or potentially might lead to the death or serious deterioration in the health of a patient, they are required to carry out an assessment in co-operation with the manufacturer and to inform the European Commission and other member states. A request should therefore be made for all correspondence entered into with competent authorities in the countries in which the devices in question are being sold. It is also relevant to request details of adverse events in other jurisdictions because these might affect the products sold in the EU.

Notified bodies are required to carry out inspections and evaluations periodically to ensure that the requirements certified by them are continuously met. In addition, unannounced visits may be made by the notified body. The notified body will in both cases supply the company with an evaluation report. These inspection requirements apply to all medical devices regulated by the Medical Devices Directive which are in Class I and which are placed on the market in a sterile condition or which have a measuring function, and those in Class II or III as well as all devices regulated by the IVD Directive and the Active Implantable Medical Devices Directive. All correspondence entered into with the notified body following the issue of the CE marking certificate(s) should therefore also be requested.

As part of the post-market surveillance, manufacturers are expected to review experiences gained from devices post-production and to implement appropriate measures for corrective actions. Notified bodies carrying out post-marketing inspections expect these analyses to be documented and reviewed by the company, with conclusions drawn as to the need for further

action. The company's records of all such experiences should be made available as part of the due diligence process. These records can be very informative because they can identify potential product claims which might require additional warranty or indemnity protection for the purchaser or investor.

In some cases, a manufacturer may have conducted a recall on its products. Recalls are complex, and require consideration of multiple factors, including safety, regulatory compliance and potential product liability concerns. Review of past recalls requires careful consideration of the following factors:

- How the company dealt with the recall process.
- What steps were taken to correct the causes of the recall.
- How to prevent a recurrence of the recall.
- When and how competent authorities acknowledged the manufacturer's completion of the recall.

Advertising and promotion issues

It is important to review a company's advertising and promotion of its products. In the EU, there is no harmonisation of the rules on how, where or to whom medical devices can be advertised, but some countries have their own rules and regulations. There can therefore be very significant differences between jurisdictions as to the permitted amount and nature of advertising and promotion of medical devices, except to the extent that medical claims are made for a medical device which goes beyond the scope of its CE marking authorisation. As far as CE marking is concerned, manufacturers cannot promote their products, explicitly or implicitly for uses other than those for which they were approved. They cannot imply greater effectiveness than has been established through clinical trials, and they must provide a balanced description of the limitations and risks associated with their products.

Reviewing these materials requires an understanding of how individual competent authorities approach advertisements and interpret claims. Competent authorities can require withdrawal of advertisements that fail to comply with the regulatory standards, and even mandate corrective advertising. While these measures generally will not require cessation of operations for the company, they are nonetheless disruptive and can lead to negative publicity. They are therefore worth identifying in advance, and avoiding if possible.

WHAT IS A NOTIFIED BODY?

A notified body is an independent body (normally a company) authorised by the competent authority in the jurisdiction in which the notified body operates to verify and then certify compliance with directives on CE marking requirements. A medical device company seeking CE marking can select a notified body operating in the jurisdiction of any member state. The notified bodies carry out the conformity assessment procedures referred to in the applicable directive. These bodies are authorised for specific types of conformity assessment and specific types of product.

For the latest information on the most appropriate notified body for a particular medical device, see: *http://ec.europa.eu/enterprise/newapproach/nando*.

Clinical trials

Where the target company has devices which are the subject of current clinical trials, the following additional material should be reviewed:

- Clinical trial documentation, including the protocol and investigator's brochure.
- Agreements with investigators, particularly to determine where the liabilities lie.
- Insurance policies covering the clinical trial (verifying that the liabilities of the company are properly covered).
- Results, if these are available. These might show that a product which is fundamental to the business plan needs further development work or is even potentially unlikely to make it to the market.