

## TOWARDS A GUIDED AND PHASED INTRODUCTION OF HIGH-RISK MEDICAL DEVICES IN BELGIUM





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Acknowledgements:	Annabelle Lepière (lawyer), Shuna Mason (lawyer)
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Hans Hellinckx (UNAMEC) A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Yves Taeymans (funding UZ Gent and Ugent) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Hans Hellinckx (consultant as second profession), Stefaan Callens (as a lawyer, gives advice to distributors of medical devices or their professional association) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Yves Taeymans (annual participation TCT), Stefaan Callens (as a lawyer, gives advice to distributors of medical devices or their professional association) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Els Geeraerts (international relations FAGG), Yves Taeymans (UZ Gent), Patrick Galloo (president Commissie Terugbetaling Implantaten en Invasieve Medische Hulpmiddelen), Hans Hellinckx (UNAMEC) Participation in scientific or experimental research as an initiator, principal investigator or researcher: Yves Taeymans (clinical research UZ Gent) Other possible interests that could lead to a potential or actual conflict of interest: Augustin Coppée (cabinet Minister of Public Health)



Layout: Ine Verhulst

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Publication date: 07 July 2015  
Domain: Health Services Research (HSR)  
MeSH: Device Approval ; Equipement and Supplies ; European Union ; Government regulation  
NLM Classification: W82 (Biomedical technology)  
Language: English  
Format: Adobe® PDF™ (A4)  
Legal depot: D/2015/10.273/63  
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<http://kce.fgov.be/content/about-copyrights-for-kce-reports>.



How to refer to this document? Baeyens H, Pouppez C, Slegers P, Vinck I, Hulstaert F, Neyt M. Towards a guided and phased introduction of high-risk medical devices in Belgium. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 249. D/2015/10.273/63.

This document is available on the website of the Belgian Health Care Knowledge Centre.





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## LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
510(k)	Premarket Notification
AAA	abdominal aortic aneurysm
ACMD	Assessment Committee for Medical Devices
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
APS	approved practice setting
CA-AF	Catheter ablation of atrial fibrillation
CE marking	Conformité Européenne
CJEU	Court of Justice of the EU
COPD	Chronic obstructive pulmonary disease
CQC	Care Quality Commission
CTS	Common technical specifications
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FAMHP	Federal Agency for Medicines and Health Products (fagg-afmps)
GMC	General Medical Council
HCO	Healthcare Organisation
HDE	Humanitarian device exemption
HTA	Health technology assessment
HUD	Humanitarian Use Device
IDE	Investigational device exemption
IRB	Institutional review board
IVD	In vitro diagnostic
KCE	Belgian Health Care Knowledge Centre
MDCG	Medical Device Coordination group
NB	Notified Bodies
NHS	National Health Service
NICE	National Institute for Health and Care Excellence



NIHDI	National Institute for Health and Disability Insurance (RIZIV/INAMI)
OJ L	Official Journal of the European Union (series L)
PIP	Poly Implant Prothèse
PMA	Premarket Approval
PTAS	Percutaneous transluminal angioplasty and stenting
RCT	Randomized controlled trial
TAVI	Transcatheter aortic valve implantation
TFEU	Treaty on the Functioning of the European Union
UDI	Unique Device Identification



## ■ SCIENTIFIC REPORT

### 1 INTRODUCTION

#### 1.1 Background

EU Member States may, in principle, not prohibit, restrict or impede the placing on the market or putting into service of CE (Conformité Européenne) marked products that meet the provisions of the applicable European Union harmonisation legislation. Once they bear the CE-marking, medical devices can thus circulate freely within the European Union. However, this study explores the possibilities for a **guided introduction** of certain high-risk medical devices in the Belgian healthcare system. The study focusses on high-risk medical devices, since of all medical devices, safety and patients' health issues are particularly at stake given the devices' risk profile (see examples in 2.5). For the report, the notion high-risk medical devices covers Class III medical devices, active implantable medical devices and any other implantable medical devices (for risk classification devices see 2.2). The aim is to shape, within the limits of the European framework, a coherent set of rules, focussed on patient's health and safety, for a responsible and reasoned use of certain high risks medical devices and implants in Belgium.

##### 1.1.1 What is the problem with the CE marking used in Europe?

The supply of new (and sometimes costly) high-risk medical devices and implants increases year after year. These devices are marketed after receiving a CE marking. The pre-market evaluation of a device by a Notified Body is performed only once for the complete European market. It includes the assessment and verification of the clinical evaluation by the Notified Body. In Europe, the clinical evaluation is defined as the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.<sup>1</sup> The European Commission defines clinical safety as the absence of unacceptable clinical risks, when using the device according to the manufacturer's instructions for use.<sup>a</sup> Guidelines issued by the European Commission define clinical performance as the ability of a medical device to

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<sup>a</sup> See i.a. "Guidelines on Medical Devices MEDDEV 2.7/4" (*Guidelines on clinical investigation: a guide for manufacturers and notified bodies*),

December 2010 and MEDDEV. 2.7.1 Rev.3 (*Guidelines on clinical evaluation: a guide for manufacturers and notified bodies*), December 2009.



achieve its intended purpose as claimed by the manufacturer.<sup>b</sup> The acquisition of a CE marking does not require proof of effectiveness and does not automatically qualify the device as eligible for reimbursement by national health care insurances.

A device cannot yet be considered to have an established routine clinical use when introduced on the market. Even after receiving a CE label, **reliable evidence on safety is often lacking and no evidence on efficacy/effectiveness is available.** For the patient, this can mean a more early access to a potentially lifesaving device, but at the risk of unknown efficacy and potential safety issues. Even excess mortality cannot be excluded as the clinical evaluation of the device is often very limited at that stage.<sup>1</sup> This is clearly illustrated in an FDA (US Food and Drug Administration) document entitled “Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US” (May 2012).<sup>2</sup>

### 1.1.2 What is the problem on the Belgian market?

After receiving a CE marking, a new high-risk device or implant requires an additional evaluation by the National Institute for Health and Disability Insurance (NIHDI – RIZIV/INAMI) to obtain reimbursement. If the reimbursement decision is positive, it can be linked to specific conditions, like a limitative list of centres that may perform the reimbursed intervention. **If there is no reimbursement, specialists/hospitals may still choose to use the CE-labelled device. In this case, there are no restrictions which limit the use of this device and technique, for example, to concentrate the expertise and gather further evidence.**

Currently, there is thus a **paradox**. On the one hand, **introduction on the market of a high-risk CE-labelled device can be indirectly limited by reimbursing the device and by linking this reimbursement to specific conditions. On the other hand, if there is no strong evidence for safety, efficacy and effectiveness but if specialists/hospitals choose to use the device, (conditional) reimbursement often comes too early.** In fact, the use of conditional reimbursement to gather evidence on safety and efficacy because of a lack of such data at the market entrance would shift

the responsibility and risks of performing research from industry to government while keeping the gains for the manufacturer.

Without restrictions from conditional reimbursement, the high-risk CE labelled device is often widely spread on the market. The following quote from a Belgian cardiologist (independent from the KCE) illustrates this:

*“The last 10 years, in the cardiovascular world, there has been an explosion of new techniques and implants that received CE marking on the basis of “feasibility” studies. CE marking in Belgium is not equal to reimbursement by the NIHDI. Often, reimbursement is only considered after a couple of years. For some of these techniques or implants, not providing a reimbursement after receiving the CE label has been a blessing since later on they did not pass the test of more comprehensive studies.*

*For many of these new technologies, a high degree of expertise is required and the old rule “practice makes perfect” is still valid.*

*Some of these techniques or implants are very quickly widely spread because of the mediatisation of technical medicine, marketing of the big firms, the competition between institutions and the egos of some doctors. This makes a posteriori regulation or limitation by the government or the NIHDI almost impossible. This is often a financial disaster and the “dilution” of expertise does not benefit patients’ health. In addition, the training and “certification” is done entirely by the involved companies.*

*The examples are numerous: AAA [abdominal aortic aneurysm] prosthesis, carotid stenting, percutaneous aortic valve implantation, “renal ablation” in hypertension, etc.*

*Still there is no clear guideline about how these techniques or implants can be introduced and distributed in a scientifically and clinically responsible manner. There is also no legal framework provided to support this.”*

The last remark in this quote mentions one of the main obstacles: Currently, there is no legal framework for a guided introduction of high-risk medical devices and implants. A **guided introduction** means that for specific

<sup>b</sup> See i.a. “Guidelines on Medical Devices MEDDEV 2.7/4” (*Guidelines on clinical investigation: a guide for manufacturers and notified bodies*),

December 2010 and MEDDEV. 2.7.1 Rev.3 (*Guidelines on clinical evaluation: a guide for manufacturers and notified bodies*), December 2009.



reasons the use of a high risk medical device and/or associated care is limited to e.g. a selection of centres of expertise and/or a specific research design to be able to answer important issues (e.g. is this intervention safe and beneficial for a specific indication of patients?) and see whether further spreading of the device and/or associated care or reimbursement is justified. The reasons for such a guided introduction can be e.g. the lack of evidence on the device's safety and efficacy, the need to centralise the medical experience required to use or implant the device, the desirability to collect data or to limit the number of procedure-related events, etc.. There may be many more reasons. In general, the aim of a guided introduction is to regulate and monitor the use of certain high-risk medical devices introduced on the Belgian market when their use or implantation involve a possible threat for the patients' health and safety.

## 1.2 Research questions and scope of the study

The study focuses on the **legally acceptable possibilities for a guided introduction** of high-risk medical devices (class III and implantable devices) after their CE-marking in Belgium.

The research questions are as follows:

- What are the existing legal opportunities in a selection of European countries, including Belgium, to introduce a high-risk device on the market in a guided manner (e.g. concentrate expertise, collect relevant data, etc.)?
- Which legislative initiatives in Belgium are necessary to apply one or more (if any) of the above identified possibilities and new possibilities to have a guided introduction of CE-labelled devices (which are not in conflict with European law)?

<sup>c</sup> For an overview of the reimbursement in Belgium of implants and invasive medical devices, we refer to KCE report 229,<sup>3</sup> chapter 8.2. A.o., this chapter describes the procedure and terms for a reimbursement request, the restricted clinical application and the possibility for the applicant to close a contract with RIZIV/INAMI. In the latter two cases, the reimbursement decision can be linked to specific research conditions.

<sup>d</sup> However, one should take notice of a recent judgment issued by the Court of Justice in that field. This judgment raises potentially the level of liability of medical devices manufacturers: The CJEU said that where it is found that a

The study focuses on the legal possibilities and opportunities to implement a higher protection of the patients **in the phase after the high-risk device or implant received a CE marking and before policy makers decide on reimbursement**. With this aim, the study focuses on the regulation of the “devices” themselves and the “medical care/use” associated with the products. The financial barriers such as conditional reimbursement and/or research funding are thus out of the scope of this report.<sup>c</sup> The study also excludes the liability for defective products that may apply to medical devices manufacturers.<sup>d</sup> The post-market surveillance system is also of importance but falls outside of the scope since this is rather an a posteriori control while this report focusses on an a priori control on patients' safety and benefit before the product is widely spread on the market.

## 1.3 Methodology

Beyond the questions raised in the previous section, the **ultimate objective of this study is to investigate the possibility of a higher protection of the patients when certain CE marked high-risk medical devices are used** (class III and implantable devices). In order to reach that objective, we took a global approach by considering not only the risks linked to the medical devices themselves but also the risks associated with their use or implantation (medical and technical skills of the team using or implanting the device, knowledge of the product by the team, appropriate equipment of the health care facility, etc.).

The **first part** of the study (chapter 2) provides some background information on medical devices and implants and briefly describes the classification and pre-market approval system for high-risk medical devices in the European Union. It provides an overview of the current minimum requirements for a high-risk device to be allowed on the Belgian market. The

medical device has a potential defect; it is possible to classify as defective all products of the same model, without there being any need to show that the product is defective in each individual case. Moreover, the Court also found that with regard to pacemakers replaced following the producer's own recommendations, the costs relating to such replacement constitute damage for which the producer is liable under the directive.” ECJ, 5 March 2015, joined cases C-503/13 and C-504/13.



comparison with the system in the United States helps to identify the current problems with efficacy requirements for these devices.

In the **second part** (chapter 3), we summarize the overall aim of EU health policies and their relationship with national policies. Moreover, we describe the European legal framework applicable to the circulation of medical devices in the EU.

Finally, beyond the reflection on the products - in this case, on medical devices – we also analyze the growing place that is given to the patient's rights and to the tools put into place to improve the quality of care at a European level. Therefore, we outline the European legal frameworks applicable to patient's rights in cross-border healthcare.

In a **third part** (chapter 4), we describe various initiatives taken in different EU countries to reinforce the control on high-risk medical devices. This section of the study is not limited to national measures implementing a "guided introduction of CE labelled medical devices" because this precise type of measure is rather exceptional. However a critical analysis of other national initiatives provides inspiration for the final part of this study.

The **final part** (chapter 5) of the study stresses that health protection is one of the founding principles under Belgian law and examines how a guided introduction of specific medical devices could be implemented in the Belgian healthcare context. In this analysis, we take into account the centrality of the patient including the different aspects of his rights (information, quality of care, redress).

The following information sources were consulted in the conduct of this study:

- Belgian and European legal databases (BELGIQUELEX, EURLEX)
- Communications, Guidelines and reports of the European Commission, Parliament and Council
- Parliamentary work of the European and national legislation
- Position papers from professional and sectorial associations
- Articles published in scientific or legal publications
- Legal experts and lawyers from across Europe were consulted
- Official websites and documentation from national health products and reimbursement authorities in various European countries

- Representative from the Belgian health product and reimbursement authorities (Federal Agency for Medicines and Health Products (FAMHP - fagg-afmps) and NIHDI), from manufacturers associations, and from hospitals were consulted



## 2 A GENERAL OVERVIEW OF THE EU SYSTEM

In this chapter we give some background information on the classification systems used for medical devices and the related pre-market evaluation requirements. The information is mainly based on two previous KCE reports.<sup>1,4</sup>

The core legal framework consists of 3 directives: Directive 90/385/EEC regarding active implantable medical devices, Directive 93/42/EEC regarding medical devices and Directive 98/79/EC regarding in vitro diagnostic medical devices.<sup>e</sup> We will focus on the Directive on medical devices since this sets the general outline. Currently the legal framework related to medical devices is under revision. A Proposal for a Regulation on medical devices and a Proposal for a Regulation on in vitro diagnostic medical devices will, once adopted by the European Parliament and by the Council, replace the existing three directives and have direct effect in the Member States. For an overview of the main proposed changes included in these proposals, see 3.2.2.

### 2.1 Some definitions

The Directive on medical devices (93/42/EEC) applies the following definitions:

#### Medical devices

*“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,*
- *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.”(93/42/EEC)*

#### Device intended for clinical investigation

*“Any device intended for use by a duly qualified medical practitioner when conducting investigations as referred to in Section 2.1 of Annex X in an adequate human clinical environment.”(93/42/EEC)*

#### Placing on the market

*“The first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished.”(93/42/EEC)*

The placing on the market takes place when the product is transferred from the stage of manufacture with the intention of distribution or use on the Community market.<sup>f</sup> The transfer can consist in a physical hand-over and/or be based on a legal transaction. It can relate to the ownership, the possession or any other right transferred from the manufacturer to a distributor or to the end user. A transfer of a product is considered to have taken place, e.g., when it is sold, leased, given as a gift, rent out or hired. Where a manufacturer operates an own distinct distribution chain, the transfer can also occur to that distribution chain.<sup>g</sup>

<sup>e</sup> [http://ec.europa.eu/health/medical-devices/regulatory-framework/index\\_en.htm](http://ec.europa.eu/health/medical-devices/regulatory-framework/index_en.htm)

<sup>f</sup> “Guide to the implementation of directives based on the New Approach and the Global Approach” (Blue Guide). European Commission (1999), see [http://ec.europa.eu/enterprise/policies/single-market-goods/files/blue-guide/guidepublic\\_en.pdf](http://ec.europa.eu/enterprise/policies/single-market-goods/files/blue-guide/guidepublic_en.pdf), in particular page 18.

<sup>g</sup> “Placing on the market of medical devices”, Interpretative document of the Commission’s services, 16 November 2010, SANCO/B/2/PBE/pdw Ares (2010) 332016.



### Putting into service

This means “the stage at which a device has been made available to the final user as being ready for use on the Community market for the first time for its intended purpose” (93/42/EEC).

Putting into service takes place at the moment of first use within the Union by the end user.<sup>h</sup>

### Clinical data

This means “the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.”(93/42/EEC)

### Implantable device

“Any device which is intended:

- to be totally introduced into the human body or,
  - to replace an epithelial surface or the surface of the eye,
- by surgical intervention which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.”(93/42/EEC)

The Directive 90/385/EEC regarding active implantable medical devices provides the following definitions:

<sup>h</sup> European Commission “Blue Guide on the implementation of EU products”, 2014.

<sup>i</sup> MEDDEV. 2.7.1 Rev.3, December 2009, guidelines on medical devices, clinical evaluation: a guide for manufacturers and notified bodies.

### Active medical device

“Any 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.”(90/385/EEC)

### Active implantable medical device

“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.”(90/385/EEC)

For other definitions for e.g. in vitro diagnostic medical device, custom-made device, etc. we refer to the original directives.

In the Medical Guidelines, the European Commission also defined the following concepts:

### Clinical Performance:

“The ability of a medical device to achieve its intended purpose as claimed by the manufacturer.”<sup>i</sup>

### Clinical Safety

“The absence of unacceptable clinical risks, when using the device according to the manufacturer’s Instructions for Use”<sup>j</sup>

Finally, conformity assessment, and efficacy/effectiveness, important input variables in health technology assessment (HTA), can be defined as follows:

### Conformity assessment

Medical devices are not subject to a pre-market authorisation by a regulatory authority but to a conformity assessment which means that the device is compliant with the requirements stipulated in the Medical Device Directives. For medium and high-risk devices, this involves a so called “Notified Body”.

<sup>j</sup> MEDDEV. 2.7.1 Rev.3, December 2009, guidelines on medical devices, clinical evaluation: a guide for manufacturers and notified bodies.



CE marking indicates that the device has been the subject of a conformity assessment as foreseen in the directives.

### **Efficacy**

*“Efficacy is the extent to which an intervention does more good than harm under ideal circumstances (“Can it work?”).”<sup>5</sup>*

### **Effectiveness**

*“Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances of healthcare practice (“Does it work in practice?”).”<sup>5</sup>*

### **HTA**

*“Health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.*

*Despite its policy goals, HTA must always be firmly rooted in research and the scientific method.”* ([www.eunetha.eu/about-us/faq#t287n73](http://www.eunetha.eu/about-us/faq#t287n73))

## **2.2 The classification of medical devices**

### **2.2.1 EU**

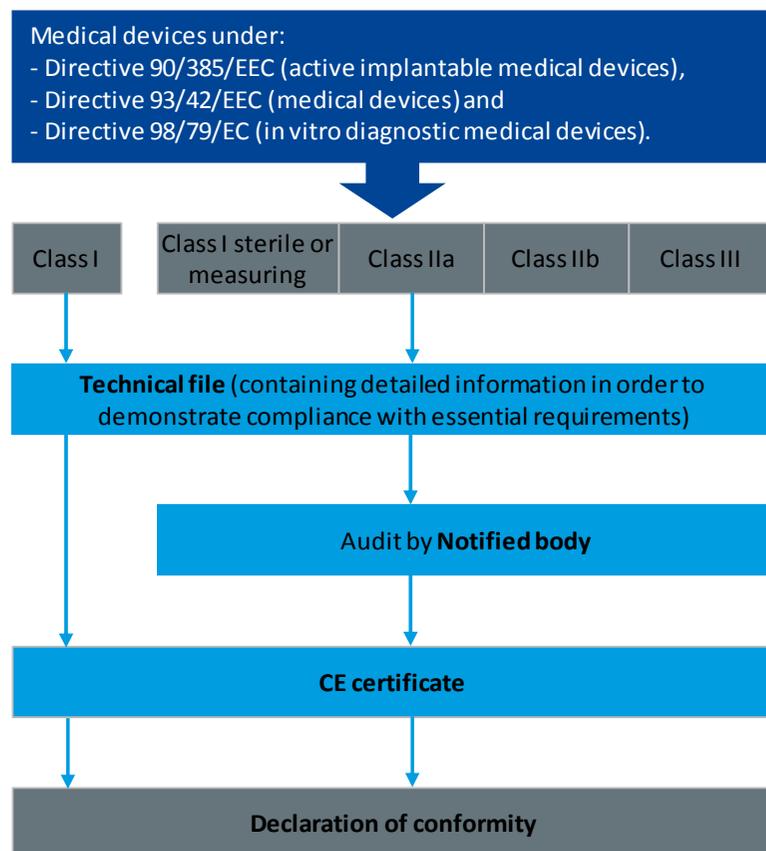
The classification uses a set of criteria described in Annex IX of the Medical Device Directive (93/42/EEC) e.g. duration of contact with the body, degree of invasiveness and local vs. systemic effect. The classification of medical devices follows a ‘risk based’ approach based on the vulnerability of the human body taking into account the potential risks associated with the devices. The higher the classification, the more elaborate the level of assessment required by the notified bodies will be. The general medical devices classes are (Figure 1):

- Class I - generally regarded as low risk
- Class IIa - generally regarded as medium risk
- Class IIb - generally regarded as elevated risk
- Class III - generally regarded as high risk

Medical devices, apart from those that are tailor-made or intended for clinical investigation, which are said to satisfy the essential requirements, must bear the CE marking for conformity when marketed. Medical devices have to be distinguished from pharmaceuticals. Sometimes, however, the distinction is not that clear and this may create a grey zone; for instance if a device is used to insert a drug. The directive provides some guidelines on these borderline cases (art. 1).<sup>4</sup>



**Figure 1 – The main constituents of the European Directives on medical devices**



Source: based on figure from previous KCE report.<sup>4</sup>

<sup>k</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

## 2.2.2 US

A similar classification is applied in the US system with an increasing regulatory control for devices classified into Class I, II, or III. Class I devices are low risk and most are exempted from any pre-market review (subject to limitations). Class II devices present moderate risks to patients and class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health or present a potential, unreasonable risk of illness or injury.<sup>k</sup> Class III devices, which are a.o. the focus of this report, represent the smallest group of devices. In the period from 2002-2007, of the roughly 50 000 devices that entered the market, 71%, 26% and 2% were class I, II and III respectively.<sup>6</sup>

## 2.3 Pre-Market Evaluation of high-risk devices and implants

### 2.3.1 EU

#### 2.3.1.1 Essential requirements

All medical devices must comply with the essential requirements, which aim to ensure that they do not compromise the health and safety of patients, users and any other person and perform as intended by the manufacturer.

General requirements: “*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 the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.*”

This shall include:

- *reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and*



- *consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users).*”(Directive 93/42/EEC)

Requirements regarding design and construction: This relates to issues such as risk assessment and risk management, chemical, physical and biological properties, infection and microbiological contamination, construction and environmental properties, protection against radiation, etc.<sup>4</sup>

### 2.3.1.2 EC declaration of conformity

*“The Directives contain a number of conformity assessment procedures, which depend on the type of products and type of risks involved. It concerns a scheme designed to regulate the level of scrutiny required to deem a medical technology or a medical device safe, based on the level of its inherent risk to the patient. Manufacturers of devices of classes II and III, as well as devices of class I with either measuring function or sterility requirements, must submit to the competent authorities a declaration of conformity to the appropriate EC directives and details of the conformity assessment procedure followed. Devices that meet the essential requirements and have undergone the appropriate conformity assessment procedures will be CE marked by the notified body. Devices, other than devices which are custom-made or intended for clinical research, considered to meet the essential requirements must bear the CE marking of conformity when they are placed on the market. The CE mark denotes a formal statement by the manufacturer of compliance with the directives’ requirements. Other medical devices of class I are exempt from pre-market submissions, although they must follow the essential principles of safety and performance in their design, construction and labelling requirements.”<sup>4</sup>*

*“... the conformity assessment procedures for Class I devices can be carried out, as a general rule, under the sole responsibility of the manufacturers (self-certification, see Figure 1) in view of the low level of vulnerability associated with these products; whereas, for Class IIa devices, the intervention of a notified body should be compulsory at the production stage; whereas, for devices falling within Classes IIb and III which constitute a high risk potential, inspection by a notified body is required with regard to the design and manufacture of the devices; whereas Class III is set aside for the most critical devices for which explicit prior authorization with regard to*

*conformity is required for them to be placed on the market.”(93/42/EEC)* Notified Bodies perform these conformity assessments also for class I devices with a measuring function or supplied under sterile conditions (Figure 1).<sup>7</sup>

### 2.3.1.3 Notified Bodies (NB)

*“A Notified Body is an organization that has been nominated by a member state and notified by the European Commission. A Notified Body will be nominated based on designated requirements, such as knowledge, experience, independence and resources to conduct the conformity assessments. Notified bodies are designated to assess the conformity with the essential requirements, and to ensure consistent technical application of these requirements according to the relevant procedures in the directives concerned.”<sup>4</sup> “Devices that meet the essential requirements and have undergone the appropriate conformity assessment procedures will be CE marked by the notified body.”<sup>4</sup>*

*“The notified body shall inform its competent authority about all certificates issued, modified, supplemented, suspended, withdrawn or refused and the other notified bodies within the scope of this Directive about certificates suspended, withdrawn or refused and, on request, about certificates issued. The notified body shall also make available, on request, all additional relevant information.”(93/42/EEC)* Unfortunately, as shown with examples from previous research in the UK, the Netherlands and Belgium, confidentiality stands above transparency (see 2.3.1.5).

*“The Commission shall publish a list of the notified bodies, together with the identification numbers it has allocated to them and the tasks for which they have been notified, in the Official Journal of the European Communities.”(93/42/EEC)*

The lists of Notified Bodies can be searched with the Nando (New Approach Notified and Designated Organisations) Information System: <http://ec.europa.eu/enterprise/newapproach/nando/index.cfm>. Under the 93/42/EEC Medical devices legislation, 64 Notified Bodies are mentioned,



amongst them two in Belgium (date: 29 April, 2015).<sup>1</sup> A company is free to choose any of the designated Notified Bodies, which are mainly for-profit organisations paid by the manufacturer.<sup>1</sup> This clearly might induce potential conflicts of interest. Companies may work with different Notified Bodies for different devices and Competent Authorities are aware that companies could select a Notified Body that is likely to be less stringent in the assessment of a particular device.<sup>8</sup>

Already in 2006, KCE remarked that “*due to therapeutic advances and the growing complexity and sophistication of devices, scientific and technical expertise by the Notified Bodies cannot always be provided at national level. Therefore cooperation on the European level should be enhanced.*”<sup>4</sup> Some Notified Bodies have only two or three staff.<sup>8</sup> The Notified Body Operations Group (<http://www.nbog.eu/>) is working on this issue. Its aim is “*to contribute to improvement of the overall performance of Notified Bodies in the medical devices sector by primarily identifying and promulgating examples of best practice to be adopted by both Notified Bodies and those organisations responsible for their designation and control.*”<sup>m</sup>

#### 2.3.1.4 Clinical evaluation

Regarding the **clinical evaluation**, “*as a general rule, confirmation of conformity with the requirements concerning the characteristics and performances ..., under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio, must be based on clinical data. ... [This] ‘clinical evaluation’ ... must follow a defined and methodologically sound procedure based on:*

- *Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:*
  - *there is demonstration of equivalence of the device to the device to which the data relates, and*
  - *the data adequately demonstrate compliance with the relevant essential requirements.*

- *Or a critical evaluation of the results of all clinical investigations made.*
- *Or a critical evaluation of the combined clinical data provided in [the above mentioned cases].*

***In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.***

*The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.*

*The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.*

*Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given based on risk management output and under consideration of the specifics of the device/body interaction, the clinical performances intended and the claims of the manufacturer. Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and pre-clinical evaluation alone has to be duly substantiated.”(Directive 93/42/EEC)*

“**The objectives of clinical investigation** are:

- *to verify that, under normal conditions of use, the performance of the devices conform to those referred to in Section 3 of Annex I, and*
- *to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device.”(Directive 93/42/EEC)*

The **notion of efficacy is not mentioned** in the medical devices Directives and thus is not part of the pre-marketing evaluation in Europe.

<sup>1</sup> [http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.notifiedbody&dir\\_id=13](http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=13)

<sup>m</sup> [http://ec.europa.eu/health/medical-devices/dialogue-parties/working-groups/index\\_en.htm](http://ec.europa.eu/health/medical-devices/dialogue-parties/working-groups/index_en.htm)



In the “Guidelines on Clinical Investigation”<sup>n</sup> and in the “Guidelines on Clinical Evaluation”<sup>o</sup>, the European Commission describes the general principles applicable to clinical evaluation in the context of the conformity assessment and in general in the context of any clinical evaluation involving medical devices.

The Guidelines on Clinical Investigations provides useful comments for the management of clinical investigations involving medical devices, in particular regarding the “factors to influence clinical data requirements”:

*“The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address relevant aspects of clinical performance, safety, including undesirable side-effects as well as the residual risks identified in the risk management process. Some factors that may influence the extent of clinical data requirements include, but are not limited to, the following:*

- *type of device and/or regulatory classification;*
- *novel technology/relevant previous experience;*
- *clinical application/indications;*
- *nature of exposure to the product, e.g.: surface contact, implantation, ingestion;*
- *risks inherent in the use of the product, e.g.: risk associated with the procedure;*
- *performance claims made in the device labeling (including instructions for use);*
- *component materials and substances;*
- *disease process (including severity) and patient population being treated;*
- *demographic, geographic and cultural considerations (e.g.: age, race, gender, etc.);*
- *potential impact of device failure;*

- *period of exposure to the device;*
- *expected lifetime of the device;*
- *availability of alternative treatments and current standard of care; and*
- *ethical considerations.”*

These guidelines also contain considerations for the determination of the appropriate study designs:

*“Some of the factors that need to be considered in the study design include, for example:*

- *clear statement of objectives*
- *appropriate subject population(s)*
- *minimization of bias (e.g., randomization, blinding)*
- *identification of confounding factors (e.g., concurrent medications, comorbidities)*
- *choice of appropriate controls (e.g., cohort, sham, historical), where necessary*
- *design configuration (e.g., parallel, crossover, factorial)*
- *type of comparison (e.g., superiority, non-inferiority, equivalence)*

*Investigations should be planned in such a way as **to maximize the clinical relevance of the data** while minimizing confounding factors.*

*Possible study designs include:*

- *randomized controlled trials*
- *cohort studies*
- *case-control studies*
- *case series”*

However, the definition of clinical investigation applied by these guidelines remain limited to the assessment of “clinical safety and performance”.

Moreover, a real an effective control of the compliance of the manufacturers and notified bodies with these (non legally binding) principles is often lacking.

<sup>n</sup> See MEDDEV 2.7/4: “Clinical Investigation: A Guide for Manufacturers and notified Bodies”.

<sup>o</sup> See MEDDEV 2.7.1 Rev.3: “Clinical Evaluation: A Guide for Manufacturers and Notified Bodies”.



### 2.3.1.5 Confidentiality versus transparency

Clinical investigations must be carried out in accordance with the Helsinki Declaration. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.”(Directive 93/42/EEC). One would thus expect that study results supporting the CE-labelling would also be published.

On the other hand, annex X of Directive 93/42/EEC concerns the clinical evaluation of medical devices and foresees that “the clinical evaluation and its outcome shall be documented. This documentation must be included and/or fully referenced in the technical documentation of the device.

**All the data must remain confidential**, in accordance with the provisions of Article 20”.

Article 20 of the Directive mentions that “Member States shall ensure that all the Parties involved in the application of this Directive are bound to observe confidentiality with regard to all information obtained in carrying out their tasks.

This does not affect the obligation of Member States and notified bodies with regard to mutual information and the dissemination of warnings, nor the obligations of the persons concerned to provide information under criminal law.

The following information shall **not be treated as confidential**:

- information on the registration of persons responsible for placing devices on the market in accordance with Article 14;
- information to users sent out by the manufacturer, authorised representative or distributor in relation to a measure according to Article 10(3);
- information contained in certificates issued, modified, supplemented, suspended or withdrawn.”

**Article 15 of Directive 93/42/EEC** obliges the manufacturer or his authorized representative to notify to the competent authorities of the Member States concerned the end of the clinical investigation. An early termination of the investigation for safety reasons must be justified and notified to all the Member States and the Commission. The manufacturer

must keep a written report, which contains a critical evaluation of all the data collected during the clinical investigation, at the disposal of the competent authorities.

Moreover, **article 16 of the Directive 93/42/EEC** obliges the notified body to inform its competent authority about all certificates issued, modified, supplemented, suspended, withdrawn or refused and the other notified bodies about certificates suspended, withdrawn or refused and, on request, about certificates issued. The notified body shall also make available, on request, “**all additional relevant information**”.

This provision does not however detail the nature of this “relevant information” and the person to whom this information shall be made available.

Information exchange on the clinical **evaluation is in the current Directive thus limited to the competent authorities of the Member States** and the Commission. Such information is not accessible to the public (patients, healthcare professionals...).

The Directive 93/42 does not specifically require the Member States to sanction manufacturers and Notified Bodies refusing to cooperate with the competent authorities

As will be discussed later on, the current Directives are under revision and new proposals on medical devices regulations are adopted by the European Commission and Parliament. The call for more transparency and better access to information (including information concerning the clinical investigation) for the public and healthcare professionals can be found throughout the entire text of the new proposal on medical devices and is one of the main modifications. Recital 39a reads as follows:

“According to the policy of the European Medicines Agency (EMA) on access to documents, the EMA releases documents submitted as part of applications for marketing authorisation for medicinal products, including clinical trial reports, on request once the decision-making process for the medicinal product in question has been completed. Corresponding standards on transparency and access to documents should be upheld and reinforced for high-risk medical devices, in particular as they are not subject to pre-market approval. For the purposes of this Regulation, in general the **data included in clinical investigations should not be considered commercially sensitive once compliance of a device with the**



**applicable requirements has been demonstrated** following the applicable conformity assessment procedure. This should be without prejudice to intellectual property rights concerning the data in clinical investigations by the manufacturer with regard to the use of these data by other manufacturers”.

A previous KCE report has shown that for the data behind the CE labelling **confidentiality stands above transparency**, as shown by the following examples:<sup>1</sup>

- Belgium: *“In the absence of robust and public statistics, we have tried to conduct a survey among the Notified Bodies on the number of patients exposed and the type of trial design used before a CE mark is applied to a novel high-risk device. Three major Notified Bodies were requested by the Belgian Competent Authorities to complete a simple questionnaire on the number of patients exposed to the innovative device pre-CE mark and on the type of trial design (randomised or not). This information (without identification of the device) was requested for cardiovascular implantable devices with or without an active substance and for other implantable devices with an active substance. Unfortunately, no reply was obtained within the timeframe of the project. Collecting this type of data turns out to be very difficult, if not impossible.”*<sup>1</sup>

Furthermore *“Based on a large subset of protocols that were reviewed in 2010, representatives of Belgian Ethics Committees reported that nearly all trials with high-risk devices in Belgium are conducted after the CE mark has been obtained, and that the identified pre-CE mark trials were not randomised.”*<sup>1</sup>

- UK: *“This was also the case for 192 recalled devices when researchers from the UK tried to obtain pre-market clinical data from the manufacturers and six Notified Bodies.<sup>9, 10</sup> Only four companies (2%) provided any clinical data. Confidentiality seems to overrule transparency in Europe much more than in the US.”*<sup>8,1</sup>

- The Netherlands: *“Competent Authorities in the Netherlands (legally entitled to control the industry) encountered difficulties in obtaining technical documentation of class III devices from industry.<sup>11</sup> Devices studied included nine coronary stents, seven total hip implants and nine silver-containing wound dressings. It is of interest to note that even Competent Authorities have to rely on a Google internet search to identify class III devices being marketed in Europe (as there is no comprehensive list or database yet). The report states that major shortcomings were identified in the documentation received, in particular concerning the clinical evaluation of the device.”*<sup>11,1</sup>

Based on the grey literature and informal contacts with Competent Authorities, a previous KCE report on medical devices revealed that *“only a few pre-market studies of devices are randomised. Most are feasibility or performance trials, and “performance” completely depends on the extent of the clinical claim the manufacturer wants to make, if any. The studies rarely include a study hypothesis or sample size calculation and the number of patients evaluated varies by the indication, but is typically less than 100 patients (about 300 patients for drug eluting stents). It is important to note that the number of patients exposed and the pre-market trial design are not made public. Thus, we could not generate any hard statistics, despite the support of the Belgian Competent Authority.”*<sup>1</sup> According to expert opinion, NBs would consider small case series of about 50 patients sufficient to judge on clinical performance and safety of new class III devices.

#### 2.3.1.6 EUDAMED

*“The European Databank on Medical Devices - Eudamed - is a secure web-based portal acting as a central repository for information exchange between national Competent Authorities and the Commission in accordance with the Medical Devices Directives.”*<sup>p</sup>

Mandatory use of the Eudamed database started on 1 May 2011.<sup>q</sup> It contains information on manufacturers and authorised representatives, on registration of devices and certificates issued by the notified bodies, and on

<sup>p</sup> [http://ec.europa.eu/health/medical-devices/files/pdfdocs/eudamed\\_evaluation\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/pdfdocs/eudamed_evaluation_en.pdf)

<sup>q</sup> European Commission. Commission decision of 19 April 2010 on the European Databank on Medical Devices (Eudamed) (2010/227/EU). In: Official Journal of the European Union; 2010.



vigilance and clinical investigations (protocol title and primary objective only, entered by the Competent Authority where the trial is notified first).<sup>1</sup>

*“The Eudamed implementation and evaluation ran in parallel with the revision of the Medical Device Directives. The proposals to review the Medical Device Directives foresee a number of substantial changes in relation to Eudamed. These changes were proposed by the Commission based on the experiences collected with Eudamed so far and feedback received from Member States, notably through discussions in the Eudamed Working Group and other forums.”<sup>r</sup> The main critics were that:*

- No complete overview of actors and devices on the EU market is given
- No sufficient coherent rules related to the detail of the registration data exist
- Information is partial and incomplete
- There is no public transparency
- The competent authorities have no sufficient resources to enter data
- Data ownership rules make the database difficult to work with

The Proposal intends to further develop Eudamed, which will in addition to the data on registration, certificates, clinical investigations and vigilance will contain integrated electronic systems on a Unique Device Identification (UDI) and a system on market surveillance.<sup>s</sup> Although more transparency is aimed at, the proposal foresees that with the exception of some general information (the name and contact details of the sponsor, the description of the investigational device, the purpose and status of the clinical investigation,...), the information collated and processed in the new electronic system on clinical investigations will only be accessible to the Member States and to the Commission.

For high-risk medical devices, manufacturers should draw up a report of the safety and performance aspects of the device and the outcome of the clinical

evaluation. A summary of this report should be publicly available via Eudamed.

### 2.3.2 US

In the US, FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval.<sup>t</sup> The following information is retrieved from the FDA website ([www.fda.gov](http://www.fda.gov)).

#### 2.3.2.1 Premarket Approval (PMA) and Premarket Notification (510(k))

##### PMA

*“Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the Federal Food, Drug, and Cosmetic (FD&C) Act in order to obtain marketing clearance. ...*

*PMA is the most stringent type of device marketing application required by FDA. ... The PMA contains sufficient valid scientific evidence to assure that the device is **safe and effective** for its intended use(s). ...*

*A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application. ... **If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it will delay FDA's review and approval.** PMA applications that are incomplete, inaccurate,*

<sup>r</sup> [http://ec.europa.eu/health/medical-devices/files/pdfdocs/eudamed\\_evaluation\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/pdfdocs/eudamed_evaluation_en.pdf)

<sup>s</sup> [http://ec.europa.eu/health/medical-devices/files/revision\\_docs/proposal\\_2012\\_542\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf)

<sup>t</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm>



*inconsistent, omit critical information, and poorly organized have resulted in delays in approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format.*

*Clinical investigations' section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such.”<sup>u</sup>*

### 510(k)

*“Each person who wants to market in the U.S., a Class I, II, and III device intended for human use, for which a Premarket Approval (PMA) is not required, must submit a 510(k) to FDA unless the device is exempt from 510(k) requirements ...*

*A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, **substantially equivalent**, to a legally marketed device ... that is not subject to PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. ...*

*FDA does not perform 510(k) pre-clearance facility inspections. The submitter may market the device immediately after 510(k) clearance is granted. The manufacturer should be prepared for an FDA quality system (21 CFR 820) inspection at any time after 510(k) clearance.*

*... Substantial equivalence means that the new device is at least as safe and effective as the predicate. A device is substantially equivalent if, in comparison to a predicate it:*

- *has the same intended use as the predicate; and*

- *has the same technological characteristics as the predicate;*  
*or*
- *has the same intended use as the predicate; and*
- *has different technological characteristics and the information submitted to FDA;*
  - *does not raise new questions of safety and effectiveness; and*
  - *demonstrates that the device is at least as safe and effective as the legally marketed device.*

*A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labelling, biocompatibility, standards, and other characteristics, as applicable. ...*

*A new 510(k) submission is required for changes or modifications to an existing device, where the modifications could significantly affect the safety or effectiveness of the device or the device is to be marketed for a new or different indication for use.”<sup>v</sup>*

Compared with the PMA process, the 510(k) route is faster, less stringent and less expensive.<sup>6</sup> Contrasting with the EU system, FDA's PMA requires the demonstration of a medical device's clinical effectiveness as a precondition for marketing.<sup>4</sup> For innovative and high-risk devices without a predicate device, representing 79% of the class III devices, the more stringent PMA application is needed.<sup>6</sup>

<sup>u</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

<sup>v</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>



### 2.3.2.2 Investigational or humanitarian device exemption (IDE or HDE)

“An **investigational device exemption (IDE)** allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. **Clinical studies are most often conducted to support a PMA.** Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Clinical evaluation of devices that have not been cleared for marketing requires:

- an investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
- informed consent from all patients;
- labelling stating that the device is for investigational use only;
- monitoring of the study and;
- required records and reports.”<sup>w</sup>

“A **Humanitarian Use Device (HUD)** is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer’s research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content

to a premarket approval (PMA) application, but is **exempt from the effectiveness requirements of a PMA.** ...”<sup>x</sup>

FDA refers to effectiveness, both in the PMA and IDE. If you look at the definitions of efficacy/effectiveness, than it is actually ‘efficacy’ that is demonstrated since a trial is performed under ideal circumstances. This is not a contradiction since the demonstration of efficacy can be seen as a pre-condition to prove an intervention’s effectiveness. “*The results of such trials are very useful: if the intervention doesn't work under such ideal conditions it surely won't work under usual conditions. Most treatments don't survive this stage of testing, and it makes good sense to sequence the testing of all interventions through this efficacy stage.*”<sup>5</sup>

### 2.3.2.3 The 510(k) system and medical device recalls

The 510(k) process has become a major component of medical-device regulation in the United States. About one-third of devices enter the market through this process. The remaining devices are exempt from any premarket review (67%) or enter the market by the PMA pathway (1%) or by other means such as a HDE (1%).<sup>12</sup>

The Institute of Medicine (IOM) reviewed the 510(k) clearance process to find out a.o. whether the current 510(k) clearance process protects patients optimally and promotes innovation in support of public health?

The IOM committee’s report concludes that “*the 510(k) process generally is not intended to evaluate the safety and effectiveness of medical devices and, furthermore, cannot be transformed into a premarket evaluation of safety and effectiveness.*”<sup>13</sup> They also believe that “*there should be an integrated premarket and postmarket regulatory framework that provides a reasonable assurance of device safety and effectiveness throughout the device lifecycle.*”

A study analysed FDA’s high-risk List of Device Recalls from 2005 through 2009 and determined whether the recalled devices were approved by the more rigorous PMA process, the 510(k) process, or were exempt from FDA review.<sup>14</sup>

<sup>w</sup> <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm>

<sup>x</sup> <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/humanitariandevicexemption/default.htm>



The study identified “113 recalls from 2005 through 2009 that the FDA determined could cause serious health problems or death. Only 21 of the 113 devices had been approved through the PMA process (19%). Eighty were cleared through the 510(k) process (71%), and an additional 8 were exempt from any FDA regulation (7%).”<sup>14</sup> The authors concluded that “Most medical devices recalled for life-threatening or very serious hazards were originally cleared for market using the less stringent 510(k) process” and suggest that “reform of the regulatory process is needed to ensure the safety of medical devices”.<sup>14</sup>

These studies show that the US system also has its limitations.

## 2.4 Time to market and reimbursement

One of the arguments in favour of the EU system is that devices usually are sooner available to patients, albeit with less clinical data prior to use. Kramer et al.<sup>15</sup> refer to a study comparing “the time lag between EU and US approval for a convenience sample of 12 medical device companies. For these companies’ 46 devices approved via PMA, the time lag averaged about 3 y, and increased from 1.2 y in 2004 (n = 5) to 3.9 y in 2010 (n = 3). For devices cleared by the 510(k) pathway, differences in EU and FDA approval times were less stark, as clearance in the US lagged by only about 4 mo (range: 1 to 9 mo). In addition, the time lag for 510(k)-cleared devices tightened from 2008 to 2010, with an average delay of only 18 d (n = 61; range 0 to 3 mo) for US clearance by 2010.”<sup>16</sup> They also mention several problems and limitations of studies estimating differences in time to market, a.o. that documents related to rejected PMA applications are not made public unless released along with other materials related to advisory panel meetings.<sup>15</sup>

However, comparing the EU and US system, one should look further than the market access. Reimbursement is probably a more important step in reaching many patients. “**Patient access should be equated with the availability of reimbursement rather than with device approval, because broad patient access to a new device doesn’t occur until reimbursement by a national or third-party payer is available. ... Though a CE marking can be granted on the basis of fewer clinical data than are required for FDA approval, European standards for reimbursement are often similar to or higher than those that the FDA imposes for device approval. European countries may require additional data on the device’s safety and effectiveness, as well as on cost-effectiveness.**”<sup>17</sup> Basu et al. determined

that taking this into account, the time it takes to bring innovative, high-risk devices to patients in the United States is similar to or shorter than that in the top four European markets, being Britain, Italy, France and Germany.<sup>17</sup>

We did not perform a systematic search to identify studies comparing the time to market and/or reimbursement between the EU and US. However, it is obvious that only looking to market access is not providing a complete picture. Reimbursement is another important hurdle to take to bring high-risk devices to the patient.

## 2.5 Examples of failures of the EU (and US) system

The PMA approval process in the US is the only approach that demands data on efficacy/effectiveness. Amongst other reasons, this more stringent regulation results in fewer companies approaching the US market and fewer devices of a particular type being marketed in the US versus Europe.<sup>1</sup> At first glance this might seem to be a disadvantage for the US system. On the other hand, the probability that PMA approved devices offer an added value is much higher and those without benefit for the patients are more likely to be prevented from entering the market. This contrasts with the lack of evidence on efficacy/effectiveness for many devices marketed in Europe and some devices that continue to be marketed in Europe while having failed in the demonstration of efficacy in the RCT required in the context of a PMA in the US.<sup>1</sup>

It is not always clear which devices tried to enter the US market and how many of those failed. A class III device that fails to meet PMA requirements cannot be marketed but while approvals are made public, failures are not. Nevertheless, there are multiple examples showing the failures of devices and thus also the failure of systems that do not require evidence on both safety and efficacy/effectiveness. We quote some examples.

- Unsafe and ineffective devices approved in the EU that were not approved in the US.<sup>2</sup>

The authors of this FDA report illustrate the weaknesses of the EU system by providing a list of 12 examples of dangerous or ineffective devices approved in the EU.



*“This report examines a series of high-risk devices that were approved in the European Union (EU) on the basis of limited scientific data and were later found to be dangerous or ineffective. Most of these devices were ultimately withdrawn from the EU market, but only after thousands of patients were harmed. In many cases, the device’s risks or ineffectiveness were discovered only as a result of studies conducted for approval in the US.”*

*“US law requires sufficient valid scientific evidence in humans that high-risk devices are both safe and effective—that is, that they provide a real benefit to patients in actual use, and that their risks are well-defined. In contrast, EU approval is conducted by [mainly] private companies and based on more limited evidence, often without significant studies in humans, that high-risk devices are safe and that they are mechanically fit to perform the job they are labeled to do. There is no requirement in the EU that a high-risk device provide an actual treatment benefit to patients. As shown in this report, the limited testing required in the EU can fail to predict dangerous risks and lack of effectiveness in actual use.”*

*“A sound approval system for high-risk medical devices should ideally provide two benefits to patients. First, it should make sure that patients receive devices that improve their lives without subjecting them to unnecessary risks. Second, it should provide access to important therapies without unnecessary delay. Because it takes time to produce sound evidence that a device is beneficial and that its benefits outweigh its risks, requiring evidence of safety and effectiveness and providing early access are sometimes in tension. This tension raises questions about the value to patients and society of pre-approval substantiation of safety and effectiveness and of whether producing this evidence as a prerequisite to marketing constitutes an “unnecessary delay.” The US and the EU systems approach these questions differently. US law requires that solid evidence showing the benefits and risks of a high-risk device be weighed before it is widely marketed, while EU law requires far less evidence.”*

*“In many cases, the dangers of these EU-approved devices were not discovered until the manufacturers had to conduct the clinical studies needed to support US approval of a high-risk device. These scientifically robust studies revealed what the limited studies relied on for EU approval could not:*

- *That the testing to show the devices’ technical performance did not accurately predict whether the devices would provide a benefit to patients in actual use; and*
- *That patients who received the devices were dying or being injured at higher rates than those patients receiving better-established treatments.*

*For some of these devices, even the widespread marketing of these devices and exposure of thousands of patients did not reveal their dangers—the dangers were discovered only when the devices were subjected to valid studies in the US. This is because it is difficult to discern the true benefits and risks of a device when there is no control group to make valid comparisons.”<sup>2 y</sup>*

- **Impact of Renal Denervation on 24-hour Ambulatory Blood Pressure: Results from SYMPPLICITY HTN-3<sup>18</sup>**

*“Background: Prior studies of catheter-based renal artery denervation have not systematically performed ambulatory blood pressure monitoring (ABPM) to assess the efficacy of the procedure.*

*Objectives: SYMPPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) was a prospective, blinded, randomized, sham-controlled trial. The current analysis details the effect of renal denervation or a sham procedure on ABPM measurements 6 months post-randomization.*

*Methods: Patients with resistant hypertension were randomized 2:1 to renal denervation or sham control. ...*

*Conclusions: This trial did not demonstrate a benefit of renal artery denervation on reduction in ambulatory BP in either the 24-h or day and*

<sup>y</sup> <http://kce.fgov.be/news/market-introduction-of-high-risk-medical-devices-in-the-eu-vs-us#.VG9Sesm0c4c>

night periods compared with sham.” (Funded by Medtronic Vascular *ClinicalTrials.gov Identifier NCT01418261*)<sup>18</sup>

However, in Europe, 13 countries already reimbursed this CE-labeled technique before results on efficacy were known, “in most cases regardless of the type of device. In the majority of countries, this has been a formal reimbursement decision, i.e. based on (national) policy. In 1 country, Medtronic’s Symplicity® received conditional coverage. In 5 countries a decision on reimbursement is in process, 2 countries do not reimburse RDN, and in 3 countries the reimbursement status is unknown.”<sup>19</sup>

- A randomized study of endobronchial valves for advanced emphysema<sup>20</sup>

“Background: Endobronchial valves that allow air to escape from a pulmonary lobe but not enter it can induce a reduction in lobar volume that may thereby improve lung function and exercise tolerance in patients with pulmonary hyperinflation related to advanced emphysema.

Methods: We compared the safety and efficacy of endobronchial-valve therapy in patients with heterogeneous emphysema versus standard medical care. ...

Conclusions: Endobronchial-valve treatment for advanced heterogeneous emphysema induced modest improvements in lung function, exercise tolerance, and symptoms at the cost of more frequent exacerbations of chronic obstructive pulmonary disease (COPD), pneumonia, and hemoptysis after implantation. (Funded by Pulmonx; *ClinicalTrials.gov number, NCT00129584*)<sup>20</sup>

An improvement in the 6-minute walk test of about 20 meters on a total distance of on average more than 300 meters is difficult to justify “the increased rates at 90 days of exacerbation of COPD requiring hospitalization (7.9% vs. 1.1%,  $P = 0.03$ ) and hemoptysis (6.1% vs. 0%,  $P = 0.01$ ).”<sup>20</sup>

In 2009, KCE published a report on endobronchial valves. KCE recommendations mentioned that “reimbursement of EBVs in patients with end-stage pulmonary emphysema can currently not be supported, because of their poorly demonstrated clinical benefit in combination with the potential adverse effects and their high costs in relation to a limited efficacy. ... This report indicates that the assignment of a CE-label to a medical device does not guarantee its effectiveness or clinical safety. Such labelling may be misleading to both patients and physicians.”<sup>21</sup>

- Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis<sup>22</sup>

“Background: Atherosclerotic intracranial arterial stenosis is an important cause of stroke that is increasingly being treated with percutaneous transluminal angioplasty and stenting (PTAS) to prevent recurrent stroke. However, PTAS has not been compared with medical management in a randomized trial.

Methods: We randomly assigned patients who had a recent transient ischemic attack or stroke attributed to stenosis of 70 to 99% of the diameter of a major intracranial artery to aggressive medical management alone or aggressive medical management plus PTAS with the use of the Wingspan stent system. ...

Conclusions: In patients with intracranial arterial stenosis, aggressive medical management was superior to PTAS with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected. (Funded by the National Institute of Neurological Disorders and Stroke and others; SAMMPRIS *ClinicalTrials.gov number, NCT00576693*)<sup>22</sup>

This example shows that the US system also has its weaknesses. “Devices approved under a humanitarian exemption do not have to have proof of effectiveness, as is required under the usual premarket approval process for high risk devices.<sup>z</sup> ... The FDA approved the Wingspan intracranial stent system in 2005 on the basis of a company

<sup>z</sup> <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/humanitariandeviceexemption/default.htm>



sponsored, single arm study of 45 patients enrolled in 2004 at 12 international centers (none in the US).<sup>23,24</sup> It took until 6 years later, after the above-mentioned government-sponsored RCT was performed, to show how harmful this device was. *“When devices are approved under the humanitarian exemption, restriction of their use to within randomized controlled trials could prevent potentially dangerous devices from obtaining seemingly permanent market approval. A similar system would also be beneficial in Europe.”*<sup>24</sup>

- Other examples studied include the introduction of transcatheter aortic valve implantation (TAVI)<sup>25</sup> and the use of catheter ablation of atrial fibrillation (CA-AF)<sup>26</sup>

In the case of TAVI, *“The contrast between the USA and EU regulation is striking. Evidence of clinical efficacy is required before market entry in the USA but not in Europe.<sup>1</sup> ... In the USA, the PARTNER-US study design is an RCT to demonstrate efficacy. In contrast, in Europe, the PARTNER-EU and other studies are mere registries with no control group. Despite European data from thousands of patients, it remains unclear from these registries for whom the intervention is beneficial due to a lack of a proper research design.”*<sup>27</sup>

In the case of CA-AF, *“based on current evidence<sup>26</sup> and economic considerations, the rationale to support catheter ablation as first-line treatment is lacking and both rate/rhythm control should be considered first. However, based on real-world Belgian data of 830 patients, ... up to 15.8% of patients underwent catheter ablation as a first line therapy of AF.<sup>26, 28,29</sup> Given the current lack of evidence on safety and efficacy of this intervention for this indication, one of the recommendations of the KCE report was that “for other forms of AF, or as first-line treatment for any type of AF, catheter ablations should only be performed within the framework of a randomised trial.”*<sup>26</sup>

Two undercover investigations focus on the role of the Notified Bodies and show the weaknesses of the European system. In both cases, the investigators tried to gain market entry with a fake device similar to other

controversial devices that were withdrawn from the market or for which there were law suits running.

- How a fake hip showed up failings in European device regulation<sup>30</sup>  
The BMJ and the Daily Telegraph invented the fake Changi TMH (total metal hip) to test Europe’s systems for regulating high risk medical devices. In their submission to gain market entry, it was explicitly stated that the device was similar to three controversial implants. *“Even though the dossier we created said that tests had shown that our hip prosthesis produced potentially toxic levels of metal ions in the body, the implant was passed as having an acceptable design for use in patients across Europe. ... We asked the notified bodies what kind of evidence we would have to submit. Even though guidelines say that class III implants should be subject to a premarket clinical study, and many notified bodies recognise they are “risky” devices, only a small number told us that they would insist on a clinical investigation. Others said that a literature review of the evidence from a similar prosthesis might suffice. ... From the first few contacts it quickly became clear that the notified bodies compete for business based on price, speed, and promised rates of successful certification. ... But of the 14 notified bodies we visited, only four raised concerns about the implant being a hip replacement. Others showed little concern. ... Our investigation suggests that few devices fail to obtain approval.”*<sup>30</sup> In a linked editorial, it was stated that patient safety and not trade should take centre stage of the system to regulate medical devices.<sup>31</sup>  
Multiple BMJ articles<sup>32-35</sup> and a video<sup>aa</sup> provide more insights in this undercover story.
- Mandarin Mesh as an implant: Implants approval is a farce<sup>bb</sup>  
The Dutch television program Radar made a reportage to see whether it is easy to develop and sell a medical device. The team invented a mesh for pelvic organ prolapse. They based the mesh on existing models of which some were retrieved from the market due to safety issues or for which lawsuits were ongoing. They explicitly mentioned several problems with adverse events and in the design in their

aa <http://www.bmj.com/content/345/bmj.e7163>

bb <http://www.radartv.nl/nieuws/archief/detail/article/mandarijnennetje-als-implantaat-goedkeuring-implantaten-is-een-farce/>



technical file. The investigators thought this would easily be detected by the experts of the Notifying Bodies. Nevertheless, to their surprise, the application for market approval was not immediately rejected and no link was made to the disastrous consequences with previous similar devices. In contrast, the three visited Notifying Bodies gave the impression that there was a high probability that a CE label would be certified.

#### Key points

- **Medical devices can circulate freely in the EU once they are granted a CE-marking.**
- **The data to support the CE-approval are not made accessible to the general public (patients, HCPs,...). The process is currently not sufficiently transparent.**
- **In the EU, solely the assessment of safety and performance of the device is required.**
- **Evidence on safety in daily practice of all CE-marked medical devices is often lacking and no evidence on efficacy/effectiveness is available.**
- **Such lack of information may threaten the patient's health, especially when using high-risk and implantable medical devices.**
- **In contrast, in the US, safety and efficacy are formally evaluated for most class III medical devices. An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and efficacy data required to support a PMA application.**
- **In the EU, there is a need to better regulate class III and implantable medical devices.**

## 3 REGULATORY FRAMEWORK ON A EU LEVEL

### 3.1 Overall aim of the EU health policies

EU regulations recognise the fundamental role of healthcare and public safety and tend to consider them as autonomous fundamental rights of EU-citizens.

The European Union (EU) shall take into account requirements linked to a higher level of health protection through all European policies and activities (article 9 of the Treaty on the Functioning of the European Union (hereafter "TFEU"). This overall high level of protection is inherent to any Union driven policy: article 114, 3, TFEU states that "*The Commission, in its proposals ... concerning health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts. ... The European Parliament and the Council will also seek to achieve this objective.*" In that same perspective, Member States are invited to share any threats for public health with the European Commission which shall immediately examine whether to propose appropriate measures to the Council (Article 114, 8, TFEU).

In addition, a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities (article 168 TFEU). In particular, the European Parliament and the Council, shall contribute to the achievement of the objectives through adopting (a.o.) specific measures setting high standards of quality and safety for medicinal products and devices for medical use.

However, Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care, including the management of health services and medical care and the allocation of the resources assigned to them.

Thus the Council of the European Union adopted on the 1<sup>st</sup> of June 2006 the Council Conclusions on Common values and principles in European Union



Health Systems. This communication expressly recalls the operating principles that underpin our health care including:<sup>cc</sup>

- **“Quality:**  
*All EU health systems strive to provide good quality care. This is achieved in particular through the obligation to continuous training of healthcare staff based on clearly defined national standards and ensuring that staff have access to advice about best practice in quality, stimulating innovation and spreading good practice, developing systems to ensure good clinical governance, and through monitoring quality in the health system. An important part of this agenda also relates to the principle of safety.*
- **Safety:**  
*Patients can expect each EU health system to secure a systematic approach to ensuring patient safety, including the monitoring of risk factors and adequate, training for health professionals, and protection against misleading advertising of health products and treatments.*
- **Care that is based on evidence and ethics:**  
*Demographic challenges and new medical technologies can give rise to difficult questions (of ethics and affordability), which all EU Member States must answer. Ensuring that care systems are evidence-based is essential, both for providing high-quality treatment, and ensuring sustainability over the long term. All systems have to deal with the challenge of prioritising health care in a way that balances the needs of individual patients with the financial resources available to treat the whole population.*
- **Patient Involvement:**  
*All EU health systems aim to be patient-centred. This means they aim to involve patients in their treatment, to be transparent with them, and to offer them choices where this is possible, e.g. a choice between different healthcare service providers. Each system aims to offer*

*individuals information about their health status, and the right to be fully informed about the treatment being offered to them, and to consent to such treatment. All systems should also be publicly accountable and ensure good governance and transparency.*

- **Redress:**  
*Patients should have a right to redress if things go wrong. This includes having a transparent and fair complaints procedure, and clear information about liabilities and specific forms of redress determined by the health system in question (eg. compensation).*
- **Privacy and confidentiality:**  
*The right of all EU citizens to confidentiality of personal information is recognised in EU and national legislation.”*

The implementation of these principles and basic rules has led the European Union to adopt regulations in the field of health products and, gradually, in the field of health care provision.<sup>dd</sup> In order to put in place a phased introduction of medical devices, both sets of rules must be analyzed:

- The regulations concerning **health products** and more specifically medical devices (see 3.2)

These regulations are part of the more general legislative framework regulating the free circulation of “products” within the EU.<sup>ee</sup> Provisions adopted in this context, only concern the placing on the market and the putting into service of medical devices. The rules and derogations contained in this regulation only apply **to the products themselves**. Therefore, this legislation does not concern the organisation of medical care associated with medical devices or the rights of the patients in the context of such medical care.

Another part of this “product-oriented” framework relates to product liability rules. These rules, however, fall outside the scope of our study.

<sup>cc</sup> [http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52006XG0622\(01\)](http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52006XG0622(01))

<sup>dd</sup> B. FONTEYN & P. SLEGGERS, « La directive 2011/24/UE relative à l'application des droits des patients en matière de soins de santé transfrontaliers : bien

plus qu'une codification », in *European Journal of Consumer Law*, Larcier, n° 1/2012, pp. 61-79

<sup>ee</sup> European Commission “Blue Guide on the implementation of EU products”, 2014.



- The regulations concerning **patient care** (see 3.3). Member States remain competent for the definition of their health policy and for the organisation and delivery of health services and medical care. However, in the context of cross-border health care, the EU recalled some fundamental rights of the patient, including the right to be correctly informed.

### 3.2 The free movement of goods and the medical devices directives

The principle of the free movement of goods is one of the economic freedoms established by the TFEU. It is one of the cornerstones of the European Union's internal market which implies that national barriers to the free movement of goods within the EU need to be removed.

However, the principle is not an absolute value. In specific circumstances, restrictions or even prohibitions are acceptable or even mandatory when serving important purposes such as the protection of the environment or the human health. The main Treaty provisions governing this principle are:

- Article 34 TFEU, which relates to intra-EU imports and prohibits 'quantitative restrictions and all measures having equivalent effect' between Member States;
- Article 35 TFEU, which relates to exports from one Member State to another and similarly prohibits 'quantitative restrictions and all measures having equivalent effect';
- Article 36 TFEU, which provides for derogations to the internal market freedoms of Articles 34 and 35 TFEU that are justified on certain specific grounds.

Article 36 TFEU lists the defences that could be used by Member States to justify national restrictive measures (public morality, public policy or security, protection of health, etc.). The Court of Justice of the EU (hereafter "the

CJEU") interprets narrowly this list of derogations and any measure must respect the principle of proportionality (title 3.2.5.3). The burden of proof lies in principle with the Member State<sup>ff</sup>, but when a Member State provides convincing justifications it is then for the Commission to prove that the measures are not appropriate<sup>gg</sup>.

Harmonised legislation in many areas has specified the meaning of the internal market and has framed the principle of the free movement of goods in concrete terms for specific products. An example of such harmonization are the directives in the field of medical devices as mentioned hereunder (title 3.2.1).

The Treaty articles do not apply when a full harmonisation of the free movement of a certain product is foreseen by specific EU legislation. As a consequence, article 36 TFEU cannot be relied on to justify deviations from harmonised areas. Nevertheless, these provisions have not become redundant and still act as a safety net when either certain circumstances and/or products are not harmonised at all or they are only subject to partial harmonisation. When harmonisation legislation cannot be identified, the Articles 34-36 TFEU can still be relied on<sup>hh</sup>.

#### 3.2.1 The core legislation

Rules relating to the placing on the market and putting into service of medical devices were harmonised in the European Union in the 1990s.

The core legal framework consists of 3 directives which cover a huge spectrum of products:

- **Directive 90/385/EEC** of 20 June 1990 regarding active implantable medical devices (hereafter "Directive 90/385")<sup>ii</sup>,

<sup>ff</sup> Judgment of 8 November 1979, Denkavit Futtermitel, C-251/78, ECR p.3369.

<sup>gg</sup> Judgment of 14 December 2000, France/ Commission, C-55/99, ECR p. I-11499.

<sup>hh</sup> Guide to the application of Treaty provisions governing the free movement of goods, [http://ec.europa.eu/enterprise/policies/single-market-goods/files/goods/docs/art34-36/new\\_guide\\_en.pdf](http://ec.europa.eu/enterprise/policies/single-market-goods/files/goods/docs/art34-36/new_guide_en.pdf)

<sup>ii</sup> OJ L 189, 20.7.1990, p. 17.



- **Directive 93/42/EEC** of 14 June 1993 concerning medical devices (hereafter “Directive 93/42”)<sup>jj</sup> and,
- **Directive 98/79/EC** of 27 October 1998 regarding *in vitro* diagnostic medical devices (hereafter “Directive 98/79”)<sup>kk</sup>.

These 3 main directives have been supplemented over time by several modifying and implementing directives, including the last technical revision brought about by **Directive 2007/47/EC** of 5 September 2007<sup>ll</sup>.

As explained in the introduction, these directives intend to harmonise the laws relating to medical devices within the European Union and foresee that once a medical device bears the CE marking, it benefits from the ‘free movement of goods principle’ which means that Member States are in principle prohibited to create any obstacle to the placing on the market or the putting into service within their territory.

In addition, legally non-binding Guidance documents MEDDEV<sup>mm</sup>, consensus statements<sup>nn</sup> and interpretative documents<sup>oo</sup> pursue the objective of ensuring uniform application of the relevant provisions of the directives within the EU.

### 3.2.2 Proposal for new Regulations

The necessity to revise the medical devices legislation intensified after the breaking up of the PIP (Poly Implant Prothèse) scandal involving fraudulent breast implants which affected tens of thousands of women in Europe and around the world.<sup>36</sup> In September 2012, the European Commission released a proposal for new European medical device regulations. The Commission recognized that in an internal market with 32 participating countries<sup>pp</sup> and subject to constant technological and scientific progress, substantial divergences in the interpretation and application of the rules have emerged.

Therefore, on 26 September 2012, the European Commission adopted a **Proposal for a Regulation on medical devices**<sup>qq</sup> (hereafter “the Proposal on medical devices”) and a Proposal for a Regulation on *in vitro* diagnostic medical devices<sup>rr</sup> which will, once adopted by the European Parliament and by the Council, replace the existing three directives and have direct effect in the Member States. The directives on implantable medical devices and on medical devices in general will be merged into one Regulation.

Since its release, the Proposal on medical devices has been amended several times. Currently, the most significant changes to the current rules are the following:

- Clarification and enhancement of the position and powers of the Notified Bodies, that will also be able to undertake **unannounced audits**.
- **Stricter supervision of the Notified Bodies** by the Member States and the European Commission. Notified Bodies will be audited for compliance with the new Regulation jointly by Competent Authorities.
- Possibility for the European Commission to create common technical specifications (CTS) for all devices.
- **An additional pre-market scrutiny process for high-risk medical devices:** Only new created Special Notified Bodies (designated by the European Medicines Agency) will be able to issue EU certificates for high-risk medical devices of class III. An additional case-by case check can be conducted by a new expert group (the Medical Device Coordination group (MDCG)). In making its opinion, the MDCG may seek a clinical assessment from the relevant experts of the Assessment Committee for Medical Devices (ACMD).

<sup>jj</sup> OJ L 169, 12.7.1993, p. 1.

<sup>kk</sup> OJ L 331, 7.12.1998, p. 1

<sup>ll</sup> OJ L 274, 21.9.2007, p.21.

<sup>mm</sup> [http://ec.europa.eu/health/medical-devices/documents/guidelines/index\\_en.htm](http://ec.europa.eu/health/medical-devices/documents/guidelines/index_en.htm)

<sup>nn</sup> [http://ec.europa.eu/health/medical-devices/documents/consensus-statements/index\\_en.htm](http://ec.europa.eu/health/medical-devices/documents/consensus-statements/index_en.htm)

<sup>oo</sup> [http://ec.europa.eu/health/medical-devices/documents/interpretative-documents/index\\_en.htm](http://ec.europa.eu/health/medical-devices/documents/interpretative-documents/index_en.htm)

<sup>pp</sup> EU Member States, EFTA countries and Turkey.

<sup>qq</sup> [http://ec.europa.eu/health/medical-devices/files/revision\\_docs/proposal\\_2012\\_542\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf)

<sup>rr</sup> [http://ec.europa.eu/health/medical-devices/files/revision\\_docs/proposal\\_2012\\_541\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf)



- More transparency and traceability by the introduction of a **Unique Device Identification (UDI)** system and the further development of the European Databank on medical devices (Eudamed).
- For high-risk medical devices, manufacturers should draw up a report of the safety and performance aspects of the device and the outcome of the clinical evaluation. A summary of the **safety and performance report** should be **publicly available** via Eudamed.
- Stricter rules on the clinical investigations throughout the life of the device (also new requirements for manufacturers to undertake a **post-market clinical follow up**). Introduction of a 'sponsor' (the manufacturer, the authorized representative or another organisation) which takes responsibility for beginning and managing a clinical investigation. **For devices classified as class III and implantable devices, the summary of safety and clinical performance shall be updated at least annually with clinical evaluation reports.**
- New rules on the reprocessing of single-use medical devices: all devices should be reusable as a rule, except if they are included in a list established by the Commission, after consultation of the ACMD, of categories and groups of medical devices which are unsuitable for reprocessing.
- Improvement of the vigilance and market surveillance and a better cooperation between the Member States.
- **Obligation of a 'qualified person'**: Manufacturers need to have at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of medical devices.
- Reclassification of some devices as high-risk class III devices.

The European Parliament adopted its position at first reading on the 2<sup>nd</sup> of April 2014. The proposed amendments clearly express a stricter and more cautious approach towards high-risk medical devices. The amended proposal was debated in June 2014 and we are now expecting the position of the European Council<sup>ss</sup>. On 1<sup>st</sup> of December 2014, the Council discussed the two draft regulations. Following these discussions, the presidency intends to draft a text that can be used by the Latvian presidency, starting in January, to conclude the work on the proposal<sup>tt</sup>.

The Proposal foresees that the new Regulation will become applicable three years after its entry into force to allow manufacturers, Notified Bodies and Member States time to adapt to the new requirements.

Central to our study are the introduction of a pre-market scrutiny procedure (3.2.2.1) and the revision of clinical evaluation requirements (3.2.2.2). Moreover, Member States remain competent to take safeguard measures (see 3.2.4). The problem underlying this study is indeed partly related to the lack of useful data on the effectiveness of certain medical devices. This problem could be partially solved if some of the measures proposed were actually adopted. The proposal also contains proposals for the improvement of market surveillance, traceability etc. However, as these mechanisms relate to the post market introduction phase they fall outside the scope of the present study.

### 3.2.2.1 The introduction of a pre-market scrutiny procedure

#### The proposal of the European Commission

The European Commission aims at improving the preliminary assessment procedure of high-risk medical devices by introducing an extra scrutiny procedure. This procedure would be performed by the newly formed committee of Member State authorities, the Medical Devices Coordination Group (MDCG)<sup>uu</sup>. This Group will be made up of members appointed by the

<sup>ss</sup> [http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?lang=en&reference=2012/0266\(COD\)](http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?lang=en&reference=2012/0266(COD))

<sup>tt</sup> <http://consilium.europa.eu/homepage/highlights/council-discusses-safety-and-innovation-in-medical-devices?lang=en>.

<sup>uu</sup> The MDCG is made up of members appointed by the Member States due to their role and experience in the field of medical Devices.

*"Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate providing expertise in the field of this Regulation, and one member and one alternate providing expertise in the field of Regulation (EU) No [.../...] [on in vitro diagnostic medical devices]. A Member State may choose to appoint only one member and one alternate providing expertise in both fields.*



Member States due to their role and experience in the field of medical devices.

The Notified Bodies are obliged to notify the Commission of applications for conformity assessments for high-risk medical devices of Class III. This notification will immediately be transmitted to the MDCG which may request the Notified Body to submit a summary of the preliminary conformity assessment within 28 days. At the latest 60 days after this submission, the MDCG may submit comments and at the latest 30 days after submission the MDCG may request for additional information to analyse the Notified Body's preliminary conformity assessment. This may include a request for samples or an on-site visit to the manufacturer's premises.

This extra scrutiny procedure should provide improvement but the effectiveness of it will still be highly dependent on whether the MDCG will play an active role or not. As this procedure will not take place automatically for all high-risk medical devices, but depends on the action of the MDCG, it forms no global solution for a better control of all medical devices of class III. It is a random extra control on the conformity assessment done by the Notified Bodies for some high-risk medical devices, rather than a real strengthening of the current system. Moreover, the Proposal of the Commission mentions that the use of this procedure should be the exception rather than the rule.

However, the following consideration identifies devices that could be considered as posing a higher risk and which can thus be subjected to a stricter control:

*“(22) For high-risk medical devices, authorities should be informed at an early stage about devices which are subject to conformity assessment and be given the right, on scientifically valid grounds, to scrutinise the preliminary assessment conducted by Notified Bodies, in particular regarding novel devices, devices for which a novel technology is being used, devices belonging to a category of devices with increased serious incident rates, or devices for which significant discrepancies in the*

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*The members of the MDCG shall be chosen for their competence and experience in the field of medical devices and in vitro diagnostic medical devices. They shall represent the competent authorities of the Member*

*conformity assessments by different Notified Bodies have been identified in respect of substantially similar devices”.*

This identification shows a clear interest for a higher patient protection and provides guidelines of what is considered, by the European Commission, to be a reasonable market segment for which a stricter control could be acceptable.

### **The amendments of the European Parliament**

The European Parliament strengthens the procedure by a clarification of the role and responsibilities of the national authorities and the MDCG. The focus of the case-by case assessment lays on the clinical aspects and the amendments introduce a possible additional clinical assessment by a group of independent scientific experts, the Assessment Committee for Medical Devices (ACMD). The ACMD should be composed of clinical experts in the medical fields relevant to the medical device being assessed, one representative of the European Medicines Agency (hereafter “EMA”) and one representative of patients' organisations.

On the other hand, the amendments seem to reduce the scope of the scrutiny compared to the Commission's proposal as not all high-risk medical devices are mentioned. The procedure would only cover implantable devices in class III, class IIb devices intended to administer and/or remove a medicinal product and devices utilising tissues and cells of human or animal origin (class III). The procedure can be extended to other devices when necessary for the protection of patient safety and public health.

In addition, the amendments foresee that the scrutiny procedure can only be triggered when the MDCG invokes the novelty of the device or an adverse change of the risk-benefit profile or an increased rate of serious incidents of a specific category or group of devices to which the device belongs. The assessment procedure cannot be triggered if Common Technical Specifications (CTS) or harmonised standards exist.

The Parliament foresees the instalment of special Notified Bodies with a high level of expertise to assess the conformity of the following devices:

*States. The names and affiliation of members shall be made public by the Commission.*

*The alternates shall represent and vote for the members in their absence.”*



- implantable devices;
- devices incorporating a substance, as referred to in Article 1(4) and point 6.1. of Annex VII (Rule 13);
- Class IIb devices intended to administer and/or remove a medicinal product, as referred to in Article 1(5) and point 5.3. of Annex VII (Rule 11);
- devices manufactured utilising tissues or cells of human or animal origin, or their derivatives, which are non-viable or are rendered non-viable; or
- all other class III devices.

Manufacturers of these devices are thus obliged to turn to special Notified Bodies to obtain an approval. If a Notified Body considers that it fulfils the reinforced requirements for special Notified Bodies regarding qualifications and training of their staff (Annex VI, point 3.5), it must submit an application to the EMA. The manufacturer may apply to a special Notified Body of his choice whose application is validated by the EMA and whose name appears in the electronic system. Those special Notified Bodies should meet in a Network in order to exchange good practice and ensure convergence in their work. The Commission and the MDCG shall establish, host, coordinate and manage this Network.

Who will pay for this Special Notified Bodies is not specified in the proposed amendments. We therefore assume that they will also be funded by the manufacturers of the devices and that they can freely choose one of these Special Notified Bodies.

We note however that regarding the fees for Notified Bodies, the Parliament mentions in its amendment 53 that “Member States should adopt provisions on standard fees for notified bodies, which should be **comparable across Member States**. The Commission should provide guidelines to facilitate the comparability of those fees. Member States should transmit their list of standard fees to the Commission and ensure that the notified bodies registered on their territory make the lists of standard fees for their

conformity assessment activities publicly available”. This amendment is accepted by the Commission.

The information the MDGC can request to submit is much wider than only a summary of the preliminary assessment and includes:

- the clinical evaluation report as referred to in Annex XIII, including the clinical investigations report as referred to in Annex XIV;
- the post market clinical follow-up plan referred to in Annex XIII, and
- any information regarding the marketing or not of the device in third countries and, where available, the results of evaluation conducted by competent authorities in those countries.

The MDCG has 60 days to deliver an opinion, during which it can consult the ACMD and take into account its clinical assessment. Where the special Notified Body concerned disagrees with the MDCG's opinion, it may request a re-examination. Where the final opinion of the MDCG is favourable, the special Notified Body may proceed with the certification. Where it is unfavourable, the special Notified Body shall not (yet) deliver the certificate for the device. At the request of the manufacturer, the Commission has to organise a hearing allowing scientific discussion and action which it can take to address the MDCG's concerns.

In its response of 9 July 2014 to these amendments<sup>w</sup>, the European Commission considered the following:

*“The pre-market assessment should also include the summary of the preliminary conformity assessment of the notified body, not only the clinical aspects. Moreover, it is problematic that the amendments reduce the scope of the scrutiny compared to the Commission proposal, which foresees the procedure for all class III devices. It is also necessary to keep the existence of “significant discrepancies in the conformity assessments carried out by Notified Bodies” as one of the criteria to trigger the assessment procedure. The existence of Common Technical Specifications or harmonised standards should be taken into account but should not prevent the procedure to be triggered, when necessary. The*

<sup>w</sup> See: [http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?lang=en&reference=2012/0266\(COD\)#tab-0](http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?lang=en&reference=2012/0266(COD)#tab-0)



*outcome of the procedure after the hearing, as foreseen by the Parliament, is not clear”.*

As to the designation of Special Notified Bodies for high-risk medical devices by the EMA, the Commission response reads as follows:

*“The Commission could support more stringent criteria for Notified Bodies which process the conformity assessment of high-risk devices. However, the added value of EMA involvement will need to be thoroughly analysed, in particular since the relevant resources and financing have not been foreseen. Furthermore, it is also necessary to analyse the issue of the legal basis for the involvement of EMA”.*

### **The summary of the Council**

It follows from the publication of a summary of the debate in Council that further discussions are needed.

One of the outstanding issues concerns the scrutiny mechanism for certain high-risk medical devices. The document mentions that *“almost all delegations state that the scrutiny procedure as proposed by the Commission is not possible to apply. Many delegations argue that a scrutiny mechanism before devices are placed on the market is not necessary. On the other hand, some delegations would wish to include a “pre-market scrutiny mechanism” for implantable devices in the highest risk class “Class III devices”. There is scope for a possible compromise on this issue”<sup>ww</sup>.*

To our opinion, the added value of this random procedure is rather doubtful as the efficiency will be highly dependent on the active role that the MDCG will play and the procedure consists merely in a duplication of the conformity assessment of the (Special) Notified Bodies. The introduction by the Parliament of an additional clinical assessment by the ACMD is an improvement but stays also optional. The responsibility for the conformity assessment remains thus mainly with the (special) Notified Bodies which are selected and whose activities are funded by the companies who put those devices on the market. The introduction by the Parliament of Special Notified Bodies (which are subject to stricter criteria) to assess high risk medical devices is a positive development that seems, with the exception of the EMA involvement, also acceptable for the Commission.

The changes and comments of the Commission and Parliament indicate however that they are aware of the current deficiencies and that they recognise the need for a stricter control on (certain) high risk medical devices.

### **3.2.2.2 Revised clinical requirements**

#### **The proposal of the European Commission**

The Proposal on medical devices provides more details on clinical requirements in order to improve the clarity and harmonization of the system. The detailed clinical requirements are set out in Annex XIII which addresses the pre-market clinical evaluation and the post market clinical follow up.

Article 50 of the Proposal reads as follows:

*“Clinical investigations shall be subject to Articles 50-60 and Annex XIV if they are conducted for one or more of the following purposes:*

*(a) to verify that, under normal conditions of use, devices are designed, manufactured and packaged in such a way that they are suitable for one*

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<sup>ww</sup> Summary of the debate in Council of 1 December 2014, (2012/0266(COD)), <http://www.europarl.europa.eu/oeil/popups/summary.do?id=1369346&t=e&l=en>

*or more of the specific purposes of a medical device referred to in number (1) of Article 2(1), and achieve the performances intended as specified by the manufacturer;*

*(b) to verify that devices **achieve the intended benefits to the patient** as specified by the manufacturer;*

*(c) to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device”.*

The process of clinical investigations is further developed by the introduction of a sponsor:

*“(46) To ensure a high level of safety and performance, demonstration of compliance with the general safety and performance requirements should be based on clinical data that, for class III medical devices and implantable medical devices should, as a general rule, be sourced from clinical investigations to be carried out under the responsibility of a sponsor who can be the manufacturer or another legal or natural person taking responsibility for the clinical investigation”.*

In practice this sponsor is often a contract research organisation which conduct the clinical investigations for the manufacturers.

The Proposal strengthens the role of Eudamed for the collection of clinical investigations related data and introduces a new central system for the notification and reporting of severe adverse events (article 53). It is however unfortunate that the proposal foresees that with the exception of some general information that is described in article 52 (the name and contact details of the sponsor, the description of the investigational device, the purpose and status of the clinical investigation,...), the information collated and processed in the new electronic system on clinical investigations shall be accessible only to the Member States and to the Commission.

The Commission also provides in its proposal the possibility to conduct a clinical trial in more than one Member State.

The proposal leaves it to the Member States to define the organizational set-up for the approval of clinical investigations at a national level. It moves away from the legally required dualism of two distinct bodies: the national competent authority and an ethics committee.

The Commission extends the scope of the post market clinical follow up by manufacturers by imposing the obligation to adopt a post market surveillance plan.

In spite of these improvements, the Proposal **stays limited to a clinical evaluation of the safety and performance** requirements of the devices (not the efficacy/efficiency) and does not foresee the obligation of randomised controlled trials. As in the current Directives, we did not find a clear definition of the notion “performance”. The Proposal only foresees that *“devices shall achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose, taking into account the generally acknowledged state of the art”.*

Another limitation is the fact that there is also a possibility to benefit from an exemption when the demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate and an adequate justification can be given.

### The amendments of the European Parliament

Some of the shortcomings of the Commission’s Proposal on medical devices are met in the proposed amendments of the European Parliament.

In its amendments, the Parliament removes the possibility to be exempted from the conformity demonstration through clinical investigations for all class III devices.

For the first time, we also find a clear definition of the notion of ‘performance’ in the new point 31a of article 2: *“performance means any technical characteristics, any effects **and any benefit of the device** when used for the intended purpose and in accordance with the instructions of use”.*

According to the Parliament, performance does thus not only mean that the devices achieve technically their aim, but also bring benefit to the patient.

Benefit is defined as *“the positive health impact of a medical device based on clinical and non-clinical data”* (new point 31b of article 2).

Another novelty is the fact that a ‘clinical evaluation’ is defined as the assessment and analysis of clinical data pertaining to a device in order to not only verify the safety and performance of the device, **but also the clinical benefits**.





With the introduction of these definitions, the Parliament is clearly going towards an extra control on the efficacy and efficiency of medical devices.

The Parliament also mentions for the first time explicitly the concept of efficacy.

*“Amendment 175*

*Proposal for a regulation: Article 50 – paragraph 1 – point b*

*Clinical investigation shall be subject to Articles 50-60 and Annex XIV if they are conducted for one or more of the following purposes:*

*(b) to verify the clinical safety **and efficacy** of the device, including the intended benefits to the patient, when used for the intended purpose, in the target population and in accordance with the instructions of use*

*“Amendment 187*

*Proposal for a regulation: Article 56 – paragraph 1*

*Where a Member State has refused, suspended or terminated a clinical investigation, or has called for a substantial modification or temporary halt of a clinical investigation, or has been notified by the sponsor of the early termination of a clinical investigation on safety **or efficacy** grounds, that Member State shall communicate such facts and its decision and the grounds for that decision to all Member States and the Commission by means of the electronic system referred to in Article 53.*

*Amendment 335*

*Proposal for a regulation: Annex XIV – Part I – paragraph 2 – point 2.1.*

*2.1. Clinical investigations shall be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the technical performance of the device, the clinical safety **and efficacy***

*of the device when used for the intended purpose in the target population and in accordance with the instructions of use, and the manufacturer's claims for the device as well as the safety, performance and benefit/risk related aspects referred to in Article 50(1); these investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions”.*

Further on, the amendments foresee the introduction of national independent ethics committees<sup>xx</sup> who need to give their authorisation before a clinical investigation can start.

The proposed amendments also introduce the use of Randomised Controlled Trials (RCTs) as the appropriate form of investigation as they generate a higher level of evidence for clinical efficacy and safety. The use of any other design or study must be justified:

*“Amendment 340*

*Proposal for a regulation: Annex XIV – Part II – point 1 – point 1.11*

*1.11. Summary of the clinical investigation plan (objective(s) of the clinical investigation, number and gender of subjects, criteria for subject selection, subjects under 18 years of age, design of the investigation such as controlled and/or randomised studies, planned dates of commencement and of completion of the clinical investigation). As randomised controlled investigations usually generate a higher level of evidence for clinical efficacy and safety, the use of any other design or study has to be justified. Also the choice of the control intervention shall be justified. Both justifications shall be provided by independent experts with the necessary qualifications and expertise”.*

In doing so, the Parliament clearly states that an effective evaluation of clinical efficacy and safety of a (new) device is to become a new minimum standard. Any evaluation should at least try to provide reliable evidence as granted through an RCT.

<sup>xx</sup> An ethics committee is defined as “an independent body in a Member State, consisting of health-care professionals and non-medical members including at least one well-experienced, knowledgeable patient or patient representative. Its responsibility is to protect the rights, safety, physical and

*mental integrity, dignity and well-being of subjects involved in clinical investigations and to provide public assurance of that protection in full transparency. In cases of such investigations involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise”*



Another novelty is the fact that for devices classified as class III and implantable devices, the summary of safety and clinical performance referred to in Article 26(1) shall be updated at least annually with clinical evaluation reports drawn up in a way that is easy for a lay person to understand.

The Parliament strengthens the already improved rules on transparency and foresees that upon completion of the clinical investigation, the sponsor shall enter in the electronic system on clinical investigations a clinical investigation report and a summary of its results. The amendments mention explicitly that data on adverse events and safety data shall **not** be considered as commercially sensitive information. Together with the report and the summary of the sponsor, they are added as information that is not only accessible to the Member States and the Commission, but to the public in general.<sup>yy</sup> The Parliament also foresees that the Commission shall ensure that healthcare professionals have access to the electronic system and that *“upon a reasoned request, all information on a specific medical device available in the electronic system shall be made accessible to the party requesting it, save where the confidentiality of all or parts of the information is justified in accordance with Article 52(3)”*. Article 52 (3) refers to the protection of personal data and commercially sensitive information.

The call for more transparency and a decent access to information for the public and healthcare professionals can be found throughout the entire text of the Parliament. The new recital 39 a) reads as follows:

*“(39a) According to the policy of the European Medicines Agency (EMA) on access to documents, the EMA releases documents submitted as part of applications for marketing authorisation for medicinal products, including clinical trial reports, on request once the decision-making process for the medicinal product in question has been completed. Corresponding standards on transparency and access to documents should be upheld and reinforced for high-risk medical devices, in particular as they are not subject to pre-market approval. For the*

<sup>yy</sup> The data on the outcomes of the RCTs forms part of the clinical investigation report and are thus in principle accessible to the public. But exceptions still apply for personal data and commercially sensitive information. At this stage, the amendment only contains exceptions related to adverse events and

*purposes of this Regulation, in general the **data included in clinical investigations should not be considered commercially sensitive once compliance of a device with the applicable requirements has been demonstrated** following the applicable conformity assessment procedure. This should be without prejudice to intellectual property rights concerning the data in clinical investigations by the manufacturer with regard to the use of these data by other manufacturers”*.

The European Parliament clearly wants to meet the current deficiencies as it also follows from the explanatory statement of the rapporteur. Concerning clinical investigations, we can read the following:

*“The Commission has introduced important provisions on clinical investigations and yet some terms such as “performance” or “safety” are not defined although manufacturers should collate data to prove that their devices meet performance and safety requirements.*

*Performance should notably be understood broadly **so as to encompass efficacy and benefit to the patient**, which shall be checked in cases where clinical investigations apply. This is crucial to ensure that devices are technically achieving the aim for which they were designed and produced, **but also bring benefit to the patient and are efficient when used in real-life**. It should also be ensured that, where clinical investigations apply, they shall be designed in a way that **the best methodology available is used and randomized controlled clinical investigations are included**. The Commission proposal also mirrors the provisions of the proposed regulation on clinical trials in which the reference to ethics committees has disappeared. However, your rapporteur believes that clinical investigations should only start after having been granted a positive evaluation result by an independent ethics committee. Member States should take the necessary measures to establish ethics committees where such committees do not exist. Lastly, it should also be ensured that, in case of an early termination of a*

safety data. In any case, after the conformity assessment, the data should not be considered as commercially sensitive. We need to note that the forgoing only applies to the outcome of RCTs and not to the raw elements which are not accessible.



*clinical investigation, information on the reasons for this is provided to all Member States, so that they can inform sponsors conducting similar clinical investigations of the results of that clinical investigation at the same time throughout the EU. This will enable to bring more transparency and to avoid having several studies being run in parallel and successively providing clinical evidence concluding that a device may pose a risk to the patient”<sup>zz</sup>.*

**The Parliament’s proposal clearly takes into account the concerns about the current gap regarding the clinical efficacy of high-risk medical devices on an EU level and the lack of transparency. The introduction of RCTs as the appropriate form of clinical investigation is a very positive evolution,** but the notion of independent experts with the necessary qualifications and expertise is rather vague. It is not specified who will be responsible to appoint these experts.

Despite a non-explicit definition of the term of efficacy, the description of a procedure to provide the evidence of clinical efficacy and safety of high-risk medical devices is central and therefore adequate to address the aimed solution. The fact that the notion of performance of a device is defined for the first time and that it includes the benefit of the device for the patient is an important step forward.

We need however to mention that **not all the Parliament’s proposals are welcomed by the European Commission.** In its response of 9 July 2014, the Commission accepted partially or subject to rewriting amendment 187 and 335, but rejected amendment 175 and 340. **The Commission is thus not in favour of the concept of efficacy as one of the general requirements for clinical investigations and rejects the obligation to choose for randomised controlled investigations.** It also rejects the introduction of a definition of the notions ‘performance’ and ‘benefit’ and the introduction of ‘clinical benefits’ in the definition of a clinical evaluation.

<sup>zz</sup> Explanatory statement of the Rapporteur in the Committee report tabled for plenary of 9 October 2013, <http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&mode=XML&reference=A7-2013-0324&language=EN>

It will be interesting to see the Council’s position on this matter which will be decisive for the final version of the Regulation. Whether or not the Parliament’s (innovative) proposals will be adopted is now depending on the Council. At this stage of the procedure, the European Commission has no more voting power. However, if, the European Commission gives a negative advice, the Council must adopt its decision unanimously (instead of a

The last update we received is that at the meeting on 19 June 2015, the Council agreed the substance of its negotiating stance (“partial general approach”) on the two proposals on medical devices and in vitro diagnostic medical devices (on all articles and annexes – not yet on the recitals). This agreement reached in the Council under Latvian presidency is a decisive step forward and will allow the next presidency (Luxembourg) to take contact with the European Parliament to start up negotiations between Council and Parliament to reach a political agreement.<sup>aaa</sup>

### 3.2.3 The Joint Plan for Immediate Actions

In February 2012, the European Commission and the Member States agreed on the so called PIP **Joint Action Plan** as a consequence of the PIP scandal. The plan focuses on four key areas: the functioning of Notified Bodies, market surveillance, coordination in the fields of vigilance and communication and transparency. The Member States were asked for their co-operation **within the existing legal framework** to tighten controls, in order to provide a better guarantee of the safety of medical technology, especially high-risk devices. This while waiting for the new legislation to come into force. As the plan is based on the current legislation, it can however only provide a partial answer to the weaknesses identified. For some of them, new legal provisions in the context of the revision are needed.

This Joint Action Plan led to the following recent initiatives:

<sup>aaa</sup> <http://www.consilium.europa.eu/en/press/press-releases/2015/06/19-medical-devices-council-ready-talk-with-ep/>



- Commission Recommendation of 5 April 2013 on a common framework for a unique device identification system of medical devices in the Union<sup>bbb</sup>;
- Commission Implementing Regulation of 24 September 2013 on the designation and the supervision of Notified Bodies under Council Directive 90/385/EEC on active implantable medical devices and Council Directive 93/42/EEC on medical devices<sup>ccc</sup>;
- Commission Recommendation of 24 September 2013 on the audits and assessments performed by Notified Bodies in the field of medical devices<sup>ddd</sup>;

The Commission Staff Working Document of 13 June 2014 on the Implementation of the Joint Plan for Immediate Actions under the existing Medical Devices legislation<sup>eee</sup> communicates the achievements of the Plan.

The above mentioned interim measures include a requirement on Notified Bodies **to conduct unannounced inspections** of manufacturers and to check samples, as well as rules on conflicts of interest. Importantly the measures require Notified Bodies to ensure that they are properly resourced, whether that involves the assistance of subcontractors or subsidiaries or not, and that their staff are fully qualified to carry out the assessments required. In particular there are restrictions on what may be subcontracted by Notified Bodies. The measures also require Member States and the Commission to take a more active role in the assessment, regular surveillance, monitoring and investigation of Notified Bodies<sup>fff</sup>.

The interim measures clarify the tasks of the Notified Bodies and their evaluation, but concrete qualification criteria are missing. For concrete minimum requirements, we will need to wait for the entry into force of the new Regulations.

These interim measures are clearly adopted to bring a quick improvement to the current situation but offer no solution to the current lack of reliable evidence on the efficiency and efficacy of (high risk) medical devices.

<sup>bbb</sup> OJ L 99 of 9 April 2013.

<sup>ccc</sup> OJ L253 of 25 September 2013.

<sup>ddd</sup> OJ L 253 of 25 September 2013.

<sup>eee</sup> [http://ec.europa.eu/health/medical-devices/files/swd\\_pip\\_14\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/swd_pip_14_en.pdf)

### Key points

- **The last years, and more specifically after the PIP scandal, it became clear that stricter enforcement and additional rules on high-risk medical devices were needed. In this context, the European Commission adopted some interim measures which strengthen and clarify the tasks and evaluation of the Notified Bodies and which are focused on more transparency and traceability with the introduction of the Unique Device Identification system.**
- **Most weaknesses of the current climate can however only be resolved by new legal provisions and that is why the Commission adopted two proposals for new Regulations on medical devices and in vitro diagnostic medical devices which will have direct effect in all the Member States.**
- **The current version of the European Parliament's proposal on medical devices does certainly strengthen the transparency, conformity assessment and clinical requirements for high-risk medical devices:**
  - **Introduction of an additional pre-market scrutiny process for high-risk medical devices that can be conducted by a new expert group (MDCG) which may seek a clinical assessment from the Assessment Committee for Medical Devices (ACMD).**
  - **The conformity assessment for high-risk medical devices must be done by Special Notified Bodies who need to fulfill stricter requirements regarding qualifications and training of their staff and who need to be appointed by the EMA.**
  - **Introduction of an electronic system on clinical investigations which will be accessible to the European Commission, the Member States and healthcare professionals.**

<sup>fff</sup> S. MASON and L. FOX, "French PIP/TÜV decision: what it means for medical devices regulation", 19.02.2014, <http://www.law-now.com/law-now/2014/piptuvfeb2014.htm?cmckreg=true>



- The clinical investigations of high-risk medical devices must be conducted under the responsibility of a sponsor.
- For the first time, in the proposal of the Parliament, the notion of performance is defined and the benefit for the patient is included. Reference to the clinical benefits for the patient is also found in the definition of a clinical investigation.
- Introduction by the European Parliament of the notion of efficacy and the standard use of RCTs as the appropriate clinical investigation procedure.

Despite these improvements, the proposal may not completely meet the current issues:

- The additional scrutiny procedure must remain exceptional and the effectiveness will be highly dependent on whether the Medical Device Coordination group (MDCG) will play an active role or not;
- The (Special) Notified Bodies will still be selected and mainly funded by the manufacturers and there is no consensus on the EMA involvement in the appointment of Special Notified Bodies;
- The introduction of the notion of efficacy in the context of clinical investigations is not (fully) accepted by the Commission and the same goes for the obligation of RCTs and the definition of performance.

We can conclude that the proposed amendments of the Parliament are going in the right direction, but the Commission does not agree with all of them and we cannot predict the Council's position. In addition, it is not clear yet when the legislation will enter into force, especially given the current disagreements.

### 3.2.4 Possible restrictions on the free movement of medical devices

Limitations to the free movement of products may be imposed in the case of **non-compliance of a product with the essential or other legal requirements of the harmonized legislation**. It may however occur that products complying with the requirements of harmonised legislation present, nonetheless, a **risk to the health or safety of persons or to other fundamental aspects of public interest**. In that case, Member States must require the relevant economic operator to take corrective actions. It is thus not only possible to limit the free movement of a product in case of non-compliance of the product with the relevant legislation but also in the case of compliance when the essential or other requirements do not entirely cover all of the risks related to the product.<sup>999</sup>

#### 3.2.4.1 Restrictions on the free movement of medical devices foreseen in Directive 93/42

Once a medical device bears the CE marking, it benefits from the 'free movement of goods principle'. This being the general principle, Directive 93/42 foresees however certain safeguard measures. The presumption of compliance may be rebutted. A CE marking does not make a medical device infallible. That is why Member States have the obligation to organise and carry out market surveillance on a continuing basis to check that medical devices meet the essential requirements laid down in Directive 93/42.

**Article 8(1)** of Directive 93/42 requires Member States which have found there to be risks linked to medical devices which have been certified as being in compliance with that directive to take **all appropriate interim measures** to withdraw those non-compliant medical devices from the market or prohibit or restrict their being placed on the market or put into service. In those circumstances, the Member State concerned is required by that same provision to notify the Commission immediately of the measures taken, indicating the reasons for the measures and in particular whether non-compliance is due to:

- a failure to meet the essential requirements referred to in Article 3;

<sup>999</sup> Blue Guide on the implementation of EU product rules, 2014. European Commission.



- an incorrect application of the standards referred to in Article 5; or
- shortcomings in the standards themselves.

Under **Article 8(2)** of Directive 93/42, the Commission must in turn examine whether those interim measures are justified and, in both cases (justified or not), inform immediately the Member State which initiated such measures and the other Member States. The Member States are able to take these interim measures immediately and are not obliged to await the outcome of the Commission's investigation. They will however be obliged to withdraw their measures when considered unjustified.

Article 8(2) foresees that if the measures are justified, the Commission can adopt, when necessary in the interests of public health, appropriate measures designed to amend non-essential elements of this Directive relating to withdrawal from the market of devices referred to in paragraph 1 or to prohibition or restriction of their placement on the market or being put into service or to introduction of particular requirements in order for such products to be put on the market", and this "in accordance with the regulatory procedure with scrutiny referred to in Article 7(3), or in case of urgency, the procedure referred to in Article 7(4)".

Under **Article 8(3)** of Directive 93/42, where a non-complying medical device bears the CE marking, the Member State concerned is to take appropriate action against whoever has affixed the mark and to inform the Commission and the other Member States.

Moreover, **Article 18** of that same directive provides that where a Member State establishes that the CE marking has been affixed unduly, the manufacturer or his authorised representative established within the European Union is to be obliged to end the infringement under conditions imposed by the Member State.

*In short, Article 8(3) and 18 of the Directive specifies the measures Member States have to adopt if they establish that CE marking has been affixed unduly to a device. They must oblige the manufacturer to end the infringement in accordance with national law and are obliged to inform the European Commission. As follows clearly from a judgment of the General Court of January 2014, the Commission must only be informed but there is no obligation for the Commission to act on such notification<sup>hhh</sup>. If non-*

compliance continues and the product (may) compromises health or safety, Member States should use the more demanding procedure in Article 8 (1) and (2) to restrict or prohibit the placing on the market of the product in question or to ensure that it is withdrawn from the market.

Article 8 and 18 of Directive 93/42 are thus only useful to adopt restrictive measures with regard to medical devices that are not compliant with the Directive's provisions.

An example of an "Article 8(1) notification" is the notification of interim measures taken by the French government to withdraw and prohibit the use of the PIP breast implants after the discovery of their non-conformity.

If it is demonstrated that a specific device does not meet the claims/intended purposes made by the manufacturer, a member State can apply restrictions based on the fact that the product is not conform. Claims are indeed part of the product itself.

**Article 14b** of Directive 93/42 foresees the possibility to adopt particular health monitoring measures:

*"Where a Member State considers, in relation to a given product or group of products, that, in order to ensure protection of health and safety and/or to ensure that public health requirements are observed, such products should be withdrawn from the market, or their placing on the market and putting into service should be prohibited, restricted or subjected to particular requirements, it may take **any necessary and justified transitional measures**.*

*The Member State shall then inform the Commission and all other Member States, giving the reasons for its decision. The Commission shall, whenever possible, consult the interested Parties and the Member States. The Commission shall adopt its opinion, indicating whether the national measures are justified or not. The Commission shall inform all the Member States and the consulted interested Parties thereof."*

<sup>hhh</sup> Judgment of 21 January 2014, Klein v. Commission, T-309/10, site Eurlex.



Similarly to Article 8, the Commission can, by amending the Directive, also proceed to the adoption of these measures on an EU level through the regulatory Committee procedure, on the condition they are considered justified and only amend nonessential elements of the Directive.

Contrary to Article 8, Article 14b contains no reference to non-compliance with the Directive. Under Article 14b, Member States are thus given the possibility to take transitional measures in case the device creates a risk or a potential risk, even if non-compliance with the current regulatory framework cannot be established. **In other words, it provides the possibility to address the deficiencies of the current directive.**

It must however be underlined that the application of a safeguard clause does not entail more than a **temporary** aberration and is not strictly speaking an exception. This Article provides in essence an opportunity to react on shortcomings of the actual regulatory framework by adopting proportional and justified measures. Given the strict condition of necessity, it will be difficult to introduce an extra pre market control on the efficiency and efficacy of all high-risk medical devices based on the possible risks for health and safety but Article 14b can be a useful tool to take transitional measures towards specific high-risk medical devices that are characterised by scientific uncertainty as to the potential risks for health and safety and to trigger a permanent modification on a EU level.

An example of the use of article 14b is the adoption of Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/ 42/EEC with respect to medical devices manufactured utilising tissues of animal origin (hereafter "*Directive 2003/32*")<sup>iii</sup>. The adoption of this Directive was the result of a French measure prohibiting the manufacture, placing on the market, distribution, import, export and use of medical devices manufactured from materials of animal origin, where these are used as dura mater substitutes. France justified the measure by the uncertainties that existed with regard to the risk of transmission to humans of animal spongiform encephalopathies from such medical devices, and by the fact that alternatives were available, in the form of synthetic materials or autologous materials taken from the patient. Also other Member States had taken unilateral national measures in relation to the use of certain raw materials originating from animal tissues

and presenting specific risks of transmitting animal spongiform encephalopathies.

If, for example, devices manufactured from materials of animal origin contain a substance or uses working mechanisms for which a specific risk can be identified, article 14b can be used. The specific risk could be identified for specific devices or even a group of devices with a high number of similar incidents associated with the product.

However, under this article, it would be extremely difficult to justify a restriction to the placing on the market and putting into service of a medical device based on the fact that not enough data is available on its efficacy, especially if these devices or similar devices are already on the market.

If the limitation to selected specialists or centres is only justified by the necessity to collect clinical data on the efficacy and efficiency, such restrictive measure would not fall within the scope of this Article 14b. Indeed this is an area that falls outside the scope of the Directive (non-harmonised area). There is therefore no need for a notification to the Commission. These restrictions however still need to be justified and fulfil the conditions of proportionality and necessity.

Central in evaluating restrictive measures to be included or not in the harmonised fields, is the actual aim of that measure: Where the safeguard measure is aimed at restricting the placing on the market or the putting into service of a medical device (for example because of a problem with the product as such) it falls within the scope of the medical devices Directive. Where, on the other hand, the measure is intended to evaluate and control a medical practice, the measure falls outside the harmonised area.

<sup>iii</sup> OJ L 105, 26.04.2003.



## Key Points

- Given the specific aim and mechanism set out by articles 8 and 18 of Directive 93/42, it will not be possible to introduce a premarket control (in the form of a guided introduction) based on a lack of evidence on the safety of use in daily practice or efficacy/effectiveness of the medical device as this is not foreseen as a compliance condition by Directive 93/42. As there exists no explicit requirement in Directive 93/42 to demonstrate the clinical efficacy of high-risk devices in the premarket phase, such restriction cannot be imposed based on the Articles 8 and 18 of the Directive.
- Contrary to articles 8 and 18, article 14b could be used for a transitional guided introduction of specific medical devices while awaiting a modification of the EU regulatory framework. However, the identified risk should in that case be related to the product and not to the associated care. The possible measures will need to be proportionate, necessary and justified. The Member State will need to provide evidence of a specific (possible) risk to the safety and health of patients and will need to limit its restrictive measures to what is strictly necessary.

### 3.2.4.2 Possible restrictive measures in the Proposal on medical devices

The possible safeguard measures Member States can take under the new Proposal on medical devices are regulated more extensively and described more clearly than in the current Directives.

Similarly to the current Directives, this Proposal makes a distinction between corrective actions towards non-compliant and compliant devices presenting a risk to health and safety. The Proposal however also makes a clear distinction between a compliant medical device that presents an actual risk and a compliant medical device or group or category of compliant medical devices that present a potential risk (possibility to adopt provisional protection measures). The last possibility will be of most interest for our study.

## Non-compliant devices presenting a risk to health and safety

The procedure to deal with non-compliant devices presenting a risk to health and safety is described in **Article 70** of the Proposal:

- “1. Where ... the competent authorities find that the device, which presents a risk to the health or safety of patients, users or other persons, does not comply with the requirements laid down in this Regulation, they shall without delay require the relevant economic operator to take all appropriate and duly justified corrective action to bring the device into compliance with those requirements, to prohibit or restrict the making available of the device on the market, to subject the making available of the device to specific requirements, to withdraw the device from the market, or to recall it within a reasonable period, proportionate to the nature of the risk.*
- 2. Where the competent authorities consider that non-compliance is not restricted to their national territory, they shall inform the Commission and the other Member States ... by means of the electronic system.*
- 3. The economic operators shall ensure that all appropriate corrective action is taken in respect of all the devices concerned....*
- 4. [If no] adequate corrective action [is taken within the required delay], the competent authorities shall take all appropriate provisional measures to prohibit or restrict the device's being made available on their national market, to withdraw the device from that market or to recall it. They shall notify the Commission and the other Member States, without delay, of those measures, by means of the electronic system....*
- 5. [This] notification ... shall include all available details, in particular the data necessary for the identification of the non-compliant device, the origin of the device, the nature of and the reasons for the non-compliance alleged and the risk involved, the nature and duration of the national measures taken and the arguments put forward by the relevant economic operator.*



6. Member States other than the Member State initiating the procedure shall without delay inform the Commission and the other Member States of any additional information at their disposal relating to the non-compliance of the device concerned and of any measures adopted by them in relation to the device concerned. In the event of disagreement with the notified national measure, they shall without delay inform the Commission and the other Member States of their objections, by means of the electronic system....

7. Where, within two months of receipt of the notification referred to in paragraph 4, no objection has been raised by either a Member State or the Commission in respect of a provisional measure taken by a Member State, that measure shall be deemed justified.

8. All Member States shall ensure that appropriate restrictive measures are taken without delay in respect of the device concerned”.

This article is similar to Article 8 of the current Directive 93/42. When a Member State, in the context of the more strict market surveillance activities, discovers that a certain medical device does not comply with the provisions of the regulation and poses or can pose a risk to the health or safety of patients, it must oblige the relevant economic operator to end the infringement and inform the Commission when the non-compliance is not restricted to its territory. If non-compliance continues, the Member State must take all appropriate provisional measures itself and must notify these measures to the Commission. A novelty is the fact that **when no objection has been raised by either another Member State or the Commission within two months after the notification, the measure shall be deemed justified**. The Proposal also describes the necessary information that must be communicated when filing the notification.

An additional novelty is the fact that the Proposal on medical devices provides more clarity on the procedural steps after such notification. In particular, the Commission can adopt immediately applicable implementing acts on duly justified imperative grounds of urgency relating to the health and safety of humans.

### Compliant devices presenting a risk to health and safety

Contrary to the current Directive 93/42, the Proposal on medical devices also provides a similar procedure for compliant devices presenting a risk to health or safety in its **Article 72**:

*“1. Where, having performed an evaluation pursuant to Article 69, a Member State finds that although a device has been legally placed on the market or put into service, it presents a risk to the health or safety of patients, users or other persons or to other aspects of the protection of public health, it shall require the relevant economic operator or operators to take all appropriate provisional measures to ensure that the device concerned, when placed on the market or put into service, no longer presents that risk, to withdraw the device from the market or to recall it within a reasonable period, proportionate to the nature of the risk.*

*2. The Member State shall immediately notify the Commission and the other Member States of the measures taken, by means of the electronic system referred to in Article 68. That information shall include the data necessary for the identification of the device concerned, the origin and the supply chain of the device, the findings of the Member State's evaluation specifying the nature of the risk involved and the nature and duration of the national measures taken.*

*3. The Commission shall evaluate the provisional national measures taken. On the basis of the results of that evaluation, the Commission shall decide, by means of implementing acts, whether or not the measure is justified. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(3). On duly justified imperative grounds of urgency relating to the health and safety of humans, the Commission shall adopt immediately applicable implementing acts in accordance with the procedure referred to in Article 88(4).*

*4. Where the national measure is considered justified, Article 70(8) shall apply. If the national measure is considered unjustified, the Member State concerned shall withdraw the measure”.*



This Article will provide the possibility to restrict the placing on the market or the putting into service of a compliant medical device (CE marked) which appears, after evaluation, to present a risk to the safety or health of patients, users, or other persons or to other aspects of the protection of public health. It also follows from the above that the Commission will proceed to the adoption of implementing acts on a EU level when the measures are justified and **not only when** it is appropriate and concern **non-essential elements of the regulation** as currently is foreseen in Article 8 and 14b of Directive 93/42.

### Formal non-compliance of devices

The procedure to put an end to a formal non-compliance of a medical device as currently described in Article 8 (3) and 18 of Directive 93/42 is foreseen in the Proposal on medical devices by **Article 73**:

*“1. Without prejudice to Article 70, a Member State shall require the relevant economic operator to put an end to the non-compliance concerned within a reasonable period that is proportionate to the non-compliance where it makes one of the following findings:*

*(a) that the CE marking has been affixed in violation of the formal requirements laid down in Article 18;*

*(b) that the CE marking has not been affixed to a device contrary to Article 18;*

*(c) that the CE marking has been inappropriately affixed in accordance with procedures in this Regulation on a product that is not covered by this Regulation;*

*(d) that the EU declaration of conformity has not been drawn up or is not complete;*

*(e) that the information to be supplied by the manufacturer on the label or in the instructions for use is not available, not complete or not provided in the language(s) required;*

*(f) that the technical documentation, including the clinical evaluation, is not available or not complete.*

*2. Where the economic operator does not put an end to the non-compliance within the period referred to in paragraph 1, the Member State concerned shall take all appropriate measures to restrict or prohibit the product being made available on the market or to ensure that it is recalled or withdrawn from the market. That Member State shall inform the Commission and the other Member States without delay of those measures, by means of the electronic system referred to in Article 68”.*

### Preventive health protection measures

The possibility to adopt provisional health protection measures with respect to a device or a specific category or group of devices (the current Article 14b of Directive 93/42) that present a potential risk will probably be regulated in the future in the following manner:

*“1. Where a Member State, after having performed an evaluation which indicates a potential risk related to a device or a specific category or group of devices considers that the making available on the market or putting into service of such device or specific category or group of devices should be prohibited, restricted or made subject to particular requirements or that such device or category or group of devices should be withdrawn from the market or recalled in order to protect the health and safety of patients, users or other persons or other aspects of public health, it may<sup>iii</sup> take any necessary and justified provisional measures.*

*2. The Member State shall immediately notify the Commission and all other Member States, giving the reasons for its decision, by means of the electronic system referred to in Article 68.*

*3. The Commission shall assess the provisional national measures taken. The Commission shall decide, by means of implementing acts, whether the national measures are justified or not. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(3). On duly justified imperative grounds of*

<sup>iii</sup> The proposed amendment of the Parliament foresees that “it shall take any necessary and justified provisional measures”.



*urgency relating to the health and safety of humans, the Commission may adopt immediately applicable implementing acts in accordance with the procedure referred to in Article 88(4).*

*4. Where the assessment referred to in paragraph 3 demonstrates that the making available on the market or putting into service of a device, specific category or group of devices should be prohibited, restricted or made subject to particular requirements or that such device or category or group of devices should be withdrawn from the market or recalled in all Member States in order to protect the health and safety of patients, users or other persons or other aspects of public health, the Commission shall be empowered to adopt delegated acts in accordance with Article 89 to take the necessary and duly justified measures. Where in this case imperative grounds of urgency so require, the procedure provided for in Article 90 shall apply to delegated acts adopted pursuant to this paragraph<sup>kkk</sup>.*

The Article forms an example of the application of the precautionary principle in a harmonised area as we will further discuss later on (see title 3.2.4.3). **It provides on a much clearer way the possibility for Member States to take justified provisional measures towards a category or a group of compliant or non-compliant medical devices which poses a potential risk** to the health and safety of patients, users or other persons or other aspects of public health.

This Article is interesting for our study as it offers the possibility to the Belgian State to restrict in a provisional way **the placing on the market** of a group or category of high-risk medical devices that can pose a risk to the health or safety of patients **even if the risk is not yet established**. Limiting the market introduction of specific high-risk medical devices to certain centres with the necessary training and expertise, would be considered as a “particular requirement” and, thus could be justified as a provisional measure under this Article. The Belgian State shall however need to show that, after having performed an evaluation, these specific devices entails a potential risk.

As the measure must be provisional, the Commission will only accept such restriction for a limited period of time while awaiting a decision/measure on a EU level. It cannot be excluded that the Commission will consider that, taken into account the stricter rules on high-risk medical devices (extra scrutiny procedure, stricter clinical requirements, more transparency, etc.), such measure is unnecessary and unjustified.

This Article is not meant to test or evaluate a high-risk medical device. Instead it aims to change something on a permanent and higher EU level which also means a strict evaluation of the justification of the restrictions after a notification to the Commission. This safeguard clause can be used to notify this risk and to achieve a restriction or even prohibition of the placing on the market of these devices not only in Belgium, but in all the Member States (for example the French measure which led to the adoption of Directive 2003/32/EC (see description of article 14b under title 3.2.4.1)).

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<sup>kkk</sup> Article 74 of the Proposal on medical devices.



## Key points

- Similarly to the current Directives, the Proposal makes a distinction between non-compliant and compliant devices presenting a risk to health and safety. But it also makes a clear distinction between a compliant medical device that presents an actual risk and a compliant medical device or group or category of compliant medical devices that present a potential risk (possibility to adopt provisional protection measures). The last possibility will be the most interesting for our study.
- **Article 72** provides the possibility to restrict the placing on the market or the putting into service of a CE marked medical device which appears, after evaluation, to present a risk to the safety or health of patients, users, other persons or to other aspects of the protection of public health.
- **Article 74** makes it possible for Member States to take justified provisional measures towards the placing on the market or the putting into service of a category or a group of compliant or non compliant medical devices which poses a potential risk. The Belgian State can thus in principle provisionally restrict the market introduction of a certain group or category of high risk medical devices which can pose a risk to safety or health to certain specialised centres. The restriction must however be provisional and thus limited to a certain period of time until the Commission takes its decision. This Article is useful to achieve a permanent modification on a higher EU level.
- We also need to bear in mind that once the new Regulation with the stricter rules enters into force, it will be more difficult to justify the necessity and proportionality of such restrictions.

### 3.2.4.3 Other possible restrictions

The above mentioned safeguard-measures are foreseen in the directives and future regulations themselves. Therefore, those measures only apply to the scope of the directives and regulations, i.e. the placing on the market and the putting into service and they do not concern the non-harmonised areas. Moreover, those measures do not limit the possibility to rely on the precautionary principle.

Consequently, besides the above-mentioned safeguard measures foreseen in the directives and future regulations, Member States can also intervene on the market of medical devices:

- **in non-harmonised areas** (still subject to the principle of free movement of goods, as described in Articles 34 to 36 of the TFEU);
- and by means of **the precautionary principle** (in harmonised and non-harmonised areas).

#### Non-harmonised areas

Directive 93/42 and 98/79 determines the conditions under which medical devices and *in vitro* diagnostic medical devices can be placed on the market and put into service. They do not harmonise other aspects in relation to medical devices, such as **their distribution, in-use requirements or reimbursement**<sup>III</sup>.

<sup>III</sup> Working Paper of 19 March 2004 of The European Association for Medical devices of Notified Bodies concerning the Clarification of Article 14 b of

Directive 93/42/EEC, <http://www.team-nb.org/documents/2007/BackgroundRevisionArt14b%20rev1%20CB.pdf>



In this regard the European Commission examined the national provisions concerning HIV testing kits notified under Article 95 (4) of the EC Treaty<sup>mmm</sup> by the United Kingdom as regards Directive 98/79 on *in vitro* diagnostic medical devices<sup>nnn</sup>.

These provisions were, according to the notification:

- Provisions that prohibit **to sell, supply or advertise** HIV testing kits or any component part of such a kit **to a member of the public**.
- Provisions that prohibit **to sell or supply** a HIV testing kit that is not accompanied at the time of sale or supply by a notice indicating that it may not be supplied to a member of the public, that a positive test should not be relied upon unless confirmed by at least one other test result, and that a negative test may not have detected recently acquired HIV.

The Commission considered that measures relating to the **restriction of the distribution of HIV testing kits** did not require any notification as they fell outside the scope of the Directive.

The Commission ruled that:

*“13. Directive 98/79/EC provides for the prohibition of any restriction regarding the placing on the market or the putting into service of devices complying with the Directive. Article 2 of the Regulations introduce restrictions to the distribution of HIV testing kits, limiting their availability to the medical profession. Directive 98/79/EC does not contain any rules concerning the distribution of in vitro diagnostic medical devices after their placing on the market or their putting into service.*

*Consequently, the national measure corresponding to Article 2 of the Regulations does not fall under the scope of Directive 98/79/EC.*

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<sup>mmm</sup> Now article 114(4) TFEU: “If, after the adoption of a harmonisation measure by the European Parliament and the Council, by the Council or by the Commission, a Member [State deems it necessary to maintain national provisions on grounds of major needs referred to in Article 36, or relating to the protection of the environment or the working environment](#), it shall notify the Commission of these provisions as well as the grounds for maintaining them.”

*14. The **labelling requirements** of Directive 98/79/EC, are related to **the product and its characteristics**. They concern, among others, its proper and safe use, particular storage or handling conditions, instructions for use and particular operating instructions and also any other relevant information related to the product. The notified national measures, as far as they require a notice indicating that the product must not be sold or supplied to a member of the public, intend to give information regarding restrictions to the distribution of the HIV testing kits. Directive 98/79/EC does not contain neither any provisions regarding the distribution of in vitro diagnostic medical devices, nor any labelling requirements regarding their distribution and marketing. Consequently, this national measure, corresponding to Article 3(2)(a) of the Regulations, does not fall under the scope of Directive 98/79/EC.”*

This conclusion does not mean that Member States enjoy total freedom to intervene on aspects that are not covered by the Directive. It only clarifies that Member States maintain the possibility to take restrictive measures in non-harmonised areas (distribution, use, reimbursement ...) without the obligation to respect the notification requirement in the Directive. They still however need to respect the principle of free movement of goods and derogations to this principle need to be justified and proportional (Article 36 TFEU).

In the above mentioned Decision of 25 January 2002, the European Commission recalled in that regard that:

*“(16) Article 95(6) of the EC Treaty, aims at approving or rejecting a national measure that derogates from a harmonisation measure. National provisions that are either falling outside the scope of a harmonisation Directive or intended to implement such a Directive cannot be assessed under this procedure.*

<sup>nnn</sup> Decision of 25 January 2002 on the national provisions concerning HIV testing kits notified under Article 95 (4) of the EC Treaty by the United Kingdom as regards Directive 97/79/EC on *in vitro* diagnostic medical devices (2002/65/EC)1).

*(17) In the light of the above considerations and without prejudice to any assessment that the Commission can make as regards the compatibility of the notified national measures with the EC Treaty, the Commission is of the opinion that the notification of the United Kingdom for maintaining the measures in the HIV Testing Kits and Services Regulations 1992, as submitted on 31 July 2001, with reference to Article 95(4) of the Treaty, is inadmissible,”*

The Commission clearly states that the selling, supplying or advertising of medical devices is not regulated in Directive 98/79. As it is considered as a non-harmonised aspect, it is up to the Member States to define (without any obligation of notification) their own levels of protection within the scope of Article 36 TFEU.

The same goes for the implantation of the devices. As this is an area that falls under the responsibility of the Member States as part of their health care policy, it is up to them to decide to what extent they want to regulate and protect it. Protective measures in this area are not subjected to a notification to the European Commission, but will need to be compatible with the TFEU as it cannot be excluded that the Commission will examine these measures voluntarily or compulsory after a complaint. Despite the fact that such measures could seem to be similar to the above mentioned safeguard measures, their aim and effects are different, as the latter aims to protect the entire European Union population after a (potential) risk has been identified. Specific rules on the implantation of devices – on the other hand aim to collect evidence on the product, i.e. in order to identify the above mentioned (potential) risk.

In the *De Peijper* case of 1976, the CJEU ruled the following;

*“Health and the life of humans rank first among the property or interests protected by Article 36 and it is for the Member States, within the limits imposed by the Treaty, to decide what degree of protection they intend to assure and in particular how strict the checks to be carried out are to be.*

*National rules or practices do not fall within the exception specified in Article 36 if the health and life of humans can as effectively protected by measures which do not restrict intra-Community trade so much.*

*In particular Article 36 cannot be relied on to justify rules or practices which, even though they are beneficial, contain restrictions **which are explained primarily by a concern to lighten the administration's burden or reduce public expenditure**, unless, in the absence of the said rules or practices, this burden or expenditure clearly would exceed the limits of what can reasonably be required”<sup>ooo</sup>.*

Moreover, in January 2008, the European Commission (informally) confirmed that the Belgian legislator was entitled to restrict the installation and use of PET-scans to certain health care facilities. The Commission accepted that such restriction was not disproportionate. The number of scanners PET in Belgium appeared to be superior to the number justified with regard to the currently accepted clinical indications and Belgium had a very higher number of PET scanners per inhabitant comparing to other countries. However, the Commission added that this will only remain proportionate if the criteria set for this limitation allow the authorities to adapt the limitation to the evolving needs of the population but also to the needs and activities of the health care facilities.

The protection of human health is one of the most popular justifications when trying to introduce obstacles to the free movement of goods in non-harmonised areas. The CJEU's judgments are numerous, and there are some principal rules that can be observed;

- The protection of health cannot be invoked if the real purpose of the measure is to protect the domestic market;
- The measures adopted have to be proportionate, i.e. restricted to what is necessary to attain the legitimate aim of protecting public health;
- Measures at issue have to be well-founded – providing relevant evidence, data (technical, scientific, statistical, and nutritional) and all other relevant information<sup>ppp</sup>.

<sup>ooo</sup> Judgment of 20 May 1976, *De Peijper*, Case 104/75, ECR. p. 00613.

<sup>ppp</sup> Guide of the European Commission to the application of Treaty provisions governing the free movement of goods, 2010,



### Application of the precautionary principle

The precautionary principle can be used by Member States to derogate from free movement provisions in non-harmonised areas based on Article 36 TFEU. It is also possible to make use of it in harmonised areas by invoking the exemptions included in Article 114 §4 and §5 TFEU:

*“If, after the adoption of a harmonisation measure by the European Parliament and the Council, by the Council or by the Commission, a Member State deems it necessary to maintain national provisions on grounds of major needs referred to in Article 36, or relating to the protection of the environment or the working environment, it shall notify the Commission of these provisions as well as the grounds for maintaining them.*

*Moreover, without prejudice to paragraph 4, if, after the adoption of a harmonisation measure by the European Parliament and the Council, by the Council or by the Commission, a Member State deems it necessary to introduce national provisions based on new scientific evidence relating to the protection of the environment or the working environment on grounds of a problem specific to that Member State arising after the adoption of the harmonisation measure, it shall notify the Commission of the envisaged provisions as well as the grounds for introducing them”.*

Although the precautionary principle is mentioned in the Treaty only in connection with environmental policy (Article 191 §2 TFEU), it is broader in scope. As recognised by the General Court *“it is intended to be applied in order to ensure a high level of protection of health, consumer safety and the environment in all the Community's spheres of activity. In particular, [Article 4(k) TFEU] includes 'a contribution to the attainment of a high level of health protection' among the policies and activities of the Community. [...] Moreover, the requirements relating to that high level of protection of the environment and human health are expressly integrated into the definition*

*and implementation of all Community policies and activities under [Article 9 TFEU] and [Article 153(1) TFEU] respectively. It follows that the precautionary principle can be defined as a general principle of Community law requiring the competent authorities to take appropriate measures to prevent specific potential risks to public health, safety and the environment, by giving precedence to the requirements related to the protection of those interests over economic interests. Since the Community institutions are responsible, in all their spheres of activity, for the protection of public health, safety and the environment, the precautionary principle can be regarded as an autonomous principle stemming from the abovementioned Treaty provisions”<sup>qqq</sup>.*

Article 14b of Directive 93/42 and Article 74 of the Proposal on medical devices form an example of the application of the precautionary principle in a harmonised area.

The application of this principle is also frequently used as a shield against the free movement of products in non-harmonised areas.

According to the case law of the CJEU, “a Member State may, in accordance with the precautionary principle, take protective measures without having to wait until the existence and gravity of those risks are fully demonstrated”<sup>sss</sup>.

Any precautionary measure at a Member State level must comply with the requirements as set out in the case law of the CJEU. According to this case law, the Member States have to perform a risk assessment before they can take any precautionary measure under Article 34 and 36 TFEU<sup>ttt</sup>. Once scientific uncertainty has been demonstrated, it is then up to the Member States to decide which measures to take provided that they are not based on purely hypothetical considerations and that they are proportional and non-discriminatory.

In the Dutch Vitamins case of December 2004, the CJEU held that;

<sup>qqq</sup> Judgment of 26 November 2002, *Artegodan*, Joined cases T-74/00, T-76/00, T-83/00, T-84/00, T-85/00, T-132/00, T-137/00 and T-141/00, ECR. p. II-04945

<sup>rrr</sup> Judgment of 5 May 1998, *National Farmers' Union and Others*, C-157/96, ECR p.I-2211

<sup>sss</sup> Ibidem, paragraph 63.

<sup>ttt</sup> Judgment of 2 December 2004, *Commission v. Netherlands*, C-41/02, ECR p. I-11375; judgment of 23 September 2003, *Commission v. Denmark*, C-192/01, ECR p. 1963, Judgment of 5 February 2004, *Commission v. France*, C-24/00, ECR. p. I-1277.



*“As regards the question whether the Netherlands administrative practice may be justified on the basis of Article 36 of the Treaty, it is for the Member States, in the absence of harmonisation and to the extent that uncertainties continue to exist in the current state of scientific research, to decide on their intended level of protection of human health and life and on whether to require prior authorisation for the marketing of foodstuffs, always taking into account the requirements of the free movement of goods within the Community.*

*That discretion relating to the protection of public health is particularly wide where it is shown that uncertainties continue to exist in the current state of scientific research as to certain substances, such as vitamins, [...] are not as a general rule harmful in themselves but may have special harmful effects if taken to excess as part of the general nutrition, the composition of which cannot be foreseen or monitored”<sup>uuu</sup>.*

The Member States bear the initial burden of showing that precautionary measures can be taken under article 36 TFEU.

*“A proper application of the precautionary principle presupposes, in the first place, the identification of the potentially negative consequences for health [...], and, secondly, a comprehensive assessment of the risk to health based on the most reliable scientific data available and the most recent results of international research”<sup>vvv</sup>.*

They are however not obliged to show a definite link between the evidence and the risk. It is sufficient to show that the area in question is surrounded by scientific uncertainty.

*“Where it proves to be impossible to determine with certainty the existence or extent of the alleged risk because of the insufficiency, inconclusiveness or imprecision of the results of studies conducted, but the likelihood of real harm to public health persists should the risk materialise, the precautionary principle justifies the adoption of restrictive measures”<sup>www</sup>.*

<sup>uuu</sup> Judgment C-41/02, aforementioned, par 42-43.

<sup>vvv</sup> Judgment C-192/01 aforementioned, par. 51.

<sup>www</sup> Judgment C-42/02 aforementioned, par. 54.

Since Article 36 TFEU provides for an exception on the general principle of free movement of goods, the CJEU applies a strict interpretation and the Member States will need to show, even if they can be justified based on public health reasons, the necessity and proportionality of their restrictive measures. The means Member States choose must therefore be confined to what is actually necessary to ensure the safeguarding of public health. To that extent, the precautionary principle can be interpreted as a general description of the article 14b safeguard measure as described above.

Based on the case law, the European Commission adopted in 2000 its communication on the precautionary principle.<sup>xxx</sup> According to the Commission, the principle may be invoked when a phenomenon, product or process may have a dangerous effect, identified by a scientific and objective evaluation, if this evaluation does not allow the risk to be determined with sufficient certainty.

The Commission stresses that the precautionary principle may only be invoked in the event of a potential risk and that it can never justify arbitrary decisions.

The three following preliminary conditions need to be met:

- identification of potentially adverse effects;
- evaluation of the scientific data available;
- the extent of scientific uncertainty.

<sup>xxx</sup> Communication of 2 February 2000 on the precautionary principle, COM (2000)1, [http://ec.europa.eu/dgs/health\\_consumer/library/pub/pub07\\_en.pdf](http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf)



### Key points

- The distribution, sale, in-use requirements, advertising or reimbursement of medical devices are all aspects that are not regulated by the current Directive and future EU regulations on medical devices. These are non harmonised areas which can be restricted without the obligation to respect the conditions of these regulations (for ex. the obligation to notify). Restrictions on aspects that are not covered by the current and future rules on medical devices however still need to respect the principle of free movement of goods and derogations to this principle need to be justified and proportional (article 36 TFEU).
- The precautionary principle can be used by Member States to derogate from the free movement of goods principle in non-harmonised areas (article 36 TFEU) and in harmonised areas (current article 14b of the Directive). Any precautionary measure at a Member State level must comply with the requirements of the EU case law. According to these case law a Member State may take protective measures without having to wait until the existence and gravity of those risks are fully demonstrated. These measures can not be based on purely hypothetical considerations and must be proportional and non-discriminatory. The Member State bears the initial burden of proof but is not obliged to show a definite link between the evidence and the risk. It is sufficient to show that the area in question is surrounded by scientific uncertainty.

### 3.2.5 Case law

The appreciation of the justification, necessity and proportionality of national measures restricting the circulation of health products (within or outside a harmonized area) has been progressively sharpened by the Court of Justice of the European Union. This following sections summarize main outcomes of these judgments.

#### 3.2.5.1 *The judgment of 8 June 1993 on sterile medical supplies (C-373/92) v. Belgium*

In this case, the CJEU had to examine the requirement of an additional examination of sterile medical supplies upon their entry into Belgium where a similar examination has already been carried out in the Member State of origin in the light of the free movement of goods.

The CJUE recalled that “in the absence of comprehensive Community rules in this matter, Member States may adopt measures seeking to ensure that imported products are not capable of adversely affecting public health, provided that the measures adopted are suitable for achieving the objective of protection of health and that that objective cannot be achieved by measures which are less restrictive of intra-Community trade.”

*“The requirement of an examination is superfluous where the imported products have already been subjected in the Member State of origin to an examination similar to that taking place on the national territory and where the results of that examination may be made available to the national authorities.”*

The CJEU concluded that Belgium has failed to fulfil its obligations under Articles 34 and 35 TFEU.

However, the judgment did not exclude any such measures, provided however that those measures had an added value. When they are only duplicating similar measures taken by other Member States, without identifying a specific need, this measure appears to be unnecessary and/or disproportionate.

#### 3.2.5.2 *The Toolex Alpha case of 11 July 2000 (C-473/98)*

In the Toolex Alpha case, the Swedish Court of Appeal asked the CJEU whether it was possible for a Member State to prohibit the use of the chemical ‘trichloroethylene’ for industrial purposes and to grant, under certain conditions, individual exemptions.

The CJEU concluded that the national legislation was a measure having an effect equivalent to a quantitative restriction on imports. It ruled that the general prohibition it laid down and the obligation for economic operators to apply for an exemption constituted measures liable to bring about a reduction in the volume of imports of trichloroethylene into Sweden.



However, the CJEU accepted this ban as a necessary and proportionate measure to protect human health:

*“Taking account of the latest medical research on the subject, and also the difficulty of establishing the threshold above which exposure to trichloroethylene poses a serious health risk to humans, given the present state of the research, there is no evidence in this case to justify a conclusion by the Court that national legislation such as that at issue in the case in the main proceedings goes beyond what is necessary to achieve the objective in view”.*

In this judgment, the CJEU positively stated what has been described implicitly in the above mentioned *Sterile Medical Supplies v. Belgium* case: restrictive measures are conceivable provided that those measures are necessary and proportionate to their aim. The existence of scientific evidence or scientific uncertainty about the possible risks will be of major importance to describe the necessity of the measure.

### 3.2.5.3 *The judgment of 14 December 2000 (C-55/99) v. France*

On 10 August 1998, the European Commission issued a reasoned opinion concerning the French legislation on imports into France of reagents used with *in vitro* diagnostic medical devices<sup>yyy</sup>.

At that time, the French legislation required these products to be registered with the French Agency for medicines before they could be placed on the market in France. It also imposed a series of labelling requirements (including the obligation to indicate on each package the registration number obtained in France) and did not foresee mutual recognition of conformity assessment tests carried out in other Member States.

The Commission considered that such a registration procedure could be justified for certain types of diagnostic medical devices such as those used to test for the AIDS and hepatitis viruses but that such a procedure could not be justified for all diagnostic medical devices. The Commission found that these restrictions were unjustified restrictions to the import of *in vitro* diagnostic medical devices, lawfully manufactured and/or sold in other Member States.

The Commission also recalled that the mutual recognition of conformity tests carried out in other Member States is a requirement under European law.

As the French authorities' reply to this reasoned opinion did not meet the requirements of the Commission, the Commission brought the case before the CJEU.

In the *Commission v. France* case of December 2000, the Commission asked the CJEU to declare that France failed its obligations by introducing in its legislation a registration and labelling requirement for all medical reagents (chemical or biological substances specially prepared for use *in vitro* for medical biology analyses).

The CJEU has been invited to assess the issue of proportionality in the light of the provision made for an allegedly less restrictive registration system for *in vitro* medical diagnostic devices in a European harmonising measure (Directive 98/79) which had not yet entered into force at the time.

The Commission accepted that the measure pursued the protection of human health but decided that both requirements were disproportionate and not appropriate. The registration procedure was considered disproportionate because it imposed a single system of registration prior to placing on the market on all reagents without distinguishing according to the seriousness of the diseases they were intended to detect or the level of risk any unreliability might present for public health and because it required the manufacturers to produce documentation which included unnecessary information. The Commission based this findings on the distinction made in Directive 98/78 (not yet in force at the time) between reagents which are liable to create a direct risk to patients and those which are not.

The obligation to state the registration number on the external packaging and to mention the registration on the notice accompanying each reagent was considered not appropriate to protect human health as such label did nothing more than providing users with information relating to the fulfilment of an administrative formality, not with information concerning actual verification that there is no risk to health.

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<sup>yyy</sup> [http://europa.eu/rapid/press-release\\_IP-98-602\\_fr.htm](http://europa.eu/rapid/press-release_IP-98-602_fr.htm).



The CJEU recalled “that with respect to products liable to create a danger to health, in the absence of harmonising rules, it is for the Member States to decide on their intended level of protection of human health and life and on whether to require prior authorisation for the marketing of such products. Nevertheless, the **principle of proportionality** which underlies the last sentence of [Article 36 TFEU] requires that the power of the Member States to impose restrictions in trade in products from other Member States should be limited to what is necessary to attain the objectives of protection being legitimately pursued”.

As it was a procedure for failure to fulfil an obligation, it was for the Commission to prove this failure. In the case at hand, the CJEU criticized the lack of evidence showing that the legislation was disproportionate and unnecessary:

*“As to the Commission’s assertion at the hearing that the prior registration procedure is unnecessary for at least 60% of reagents, it has not identified clearly the reagents which are said not to require prior registration. By merely stating that, for reagents which do not present a direct risk to health, registration under the contested decree could be replaced by a declaration to the authorities by the manufacturer or distributor of such reagents, in the same way as provided for by Directive 98/79, the Commission has not shown that, in the absence of harmonisation, the registration prescribed by the contested decree is unnecessary. Finally, the Commission has not produced any other information to show that the provisions of that decree are not proportionate”.*

The CJEU accepted the French argument that the registration requirement was necessary because registration allowed for detection of unreliable or ineffective reagents:

*“The French Government, on the other hand, submits that the documentation required and the obligation to update the file are necessary because they enable unreliable or ineffective reagents to be detected. The documentation, combined with the obligation to update the file, makes it possible to establish a data bank which is updated regularly with a view to permanent ‘reacto-vigilance’, allowing products which prove less reliable or less effective to be withdrawn or substituted following checks by sampling or in the light of inconsistencies in the file.*

*On this point, it must be held that the Commission has not produced evidence to show that the documentation required and the updating of the registration file are unnecessary”.*

On the other hand, the CJEU struck down the labelling requirement as disproportionate:

*“Mentioning the registration, in particular by stating the registration number, merely guarantees the user that the reagent has been registered with the competent authorities, and does not provide any additional information which might effectively protect public health. By contrast, the other requirements [...] that the name and address of the distributor and the batch number of manufacture must appear on both the external packaging and the primary packaging of the reagent itself, while the name and address of the manufacturer, distributor and, if any, the importer must appear on the accompanying notice, constitute measures which are sufficient to ensure that reagents are traceable”.*

In this case, the CJEU mainly stressed the absolute need for proportionality when a Member State intends to adopt restrictive measures.

#### 3.2.5.4 The Medipac case of 14 June 2007 (C-6/05)

In the Medipac case of 2007, the CJEU was asked whether under the general principles of EU law applicable to tendering procedures, a contracting authority which has initiated such a procedure for the purchase of medical devices could directly exclude a tender for products for public health reasons although those products bear the CE marking as required by the specifications of the invitation to tender, or whether that authority is required to apply the safeguard clauses provided for in Articles 8 and 18 of Directive 93/42.

Venizelio-Panania, the general hospital of Heraklion (Greece), had issued a tender for the supply of various surgical sutures. Medipac was one of the companies that participated. The committee conducting the tender procedure issued however a recommendation to exclude the PGA type sutures proposed by Medipac due to several earlier problems with PGA type materials.



The CJEU decided that when certain products bearing the CE marking give rise to concerns as to patient health or safety, the contracting authority is not able to reject the tender. Given the harmonisation foreseen by Directive 93/42, the contracting party should inform the competent national authority and follow the safeguard procedure foreseen in Directive 93/42.

The CJEU recalled in that regard that:

*“(…) Directive 93/42 harmonises the essential requirements to be met by medical devices falling within its scope of application. Once those devices comply with the harmonised standards and are certified in accordance with the procedures provided for by that directive, they must be presumed to comply with those essential requirements and therefore be deemed to be appropriate for the use for which they are intended. Those medical devices must also be allowed to circulate freely throughout the Community.*

*The Court notes, however, as pointed out by the Advocate General in point 92 of her Opinion, that the presumption of compliance of medical devices may be rebutted. In that respect, Directive 93/42 provides for **the implementation of safeguard measures where a finding is made that certain medical devices bearing the CE marking may nevertheless pose risks for patients or users.***

*However, not only the wording of Article 8 of Directive 93/42 but also the purpose of the harmonisation system established by it preclude a contracting authority from being entitled to reject, outside that safeguard procedure and on grounds of technical inadequacy, medical devices which are certified as being in compliance with the essential requirements provided for by that directive.*

*Directive 93/42, in so far as it amounts to a harmonisation measure adopted pursuant to Article 100a of the EEC Treaty (which became Article 100a of the EC Treaty, itself now, after amendment, Article 95 EC), is intended to promote the free movement of medical devices (...).*

*In that context, the need to reconcile the free movement of those devices with the protection of patients' health implies that, **in the event of the emergence of a risk linked to devices which have been certified as being in compliance with Directive 93/42, the Member State concerned must implement the safeguard procedure provided for***

*in Article 8 of that directive; bodies which are not empowered to do so may not themselves decide unilaterally on the action to be taken in such circumstances.”*

In this judgment, the CJEU repeated that restrictive measures are allowed under specific circumstances. Safeguard measures are authorised if sufficient evidence is brought that the medical device may pose risk for the users. The CJEU in addition stated that if the Member State is willing to use a safeguard measure, it is bound to comply with the specific safeguard procedures of Directive 93/42 and that these procedures can only be invoked by the Member States (and not by private actors).

### 3.2.5.5 *The Doc Morris Case of 11 December 2003 (Case C-322/01)*

On 11 December 2003, the CJEU ruled that a national prohibition on the sale of medicinal products by mail order is compatible with European Union law where it applies to prescription medicines. However, the CJEU considered that such a prohibition is contrary to the free movement of goods under Article 34 TFEU if it applies to non-prescription medicines. The CJEU distinguished between prescription and non-prescription drugs on the ground of the advertising regulation that provides that advertising for non-prescription medicines is allowed towards the general public.

In that specific case, the CJEU allowed the Internet sale of medicines under certain conditions:

- The medicines must belong to the non-prescription category according to the classification in the country of destination;
- The medicinal products must be sold through an Internet page by traditional pharmacies;
- The medicines must hold a European or national authorisation in the country of destination.

By contrast, the CJEU recognised that the supply to the public of prescription medicines needs to be more strictly controlled. According to the CJEU, such control can be justified first in view of the greater risks which these medicines involve. The risks mentioned by the CJEU are namely:

- The differences among Member States in classifications;



- The need to be able to check effectively and responsibly the authenticity of doctors' prescriptions and that the medicine is collected by customer himself or somebody who has been entrusted by the costumer;
- The possibility of different languages on the prescription.

Additionally, the CJEU referred to the German system of fixed prices for prescription medicines as a justification for the German prohibition. In this regard the CJEU said: "*Although aims of a purely economic nature cannot justify restricting the fundamental freedom to provide services, it is not impossible that the **risks of seriously undermining the financial balance of the social security system** may constitute an overriding general interest reason*".

In that judgment, the CJEU recognized that measures of economic aim could be acceptable, if the economic approach is necessary and proportionate to fulfil the public health policy.

### 3.2.5.6 *The Nordiska Dental AB case of 19 November 2009 (C-288/08)*

In the Nordiska Dental Case, the CJEU concluded that the Swedish prohibition on exporting dental amalgams containing mercury was incompatible with Directive 93/42 on the ground that the Directive also covers environmental considerations.

The CJEU recalled its findings in the *Medipac* case and ruled that:

*"Article 4(1) of Directive 93/42 must be interpreted as precluding legislation of a Member State, such as the legislation at issue in the main proceedings, under which the commercial exportation of dental amalgams containing mercury and bearing the 'CE' marking provided for in Article 17 of that directive is prohibited on grounds relating to protection of the environment and of health."*

The CJEU further repeated the general finding that "*it should be borne in mind that that presumption of compliance can be rebutted in certain circumstances*". Moreover, the CJEU indirectly indicated that exemptions could occur in legislation which falls outside the scope of the directive. To that extent, it is noteworthy that the CJEU has comprehensive understanding of the scope of the measures and legislation, where the CJEU is not bound by the scope given by the Member State. In the case at

hand, the reference to the protection of the environment was not sufficient, since it appeared that, through that measure, the Swedish government was seeking not only to protect the environment, but moreover the public health:

*"The aim of Directive 93/42, on the other hand, is – as is apparent notably from the recitals in the preamble thereto – not only the protection of health stricto sensu but also the safety of persons. Moreover, that directive does not concern only patients and users of medical devices but, more generally, 'third parties' or 'other persons'.*

*In those circumstances, it cannot be accepted that a measure prohibiting the exportation of dental amalgams containing mercury, such as that laid down by the legislation at issue in the main proceedings, can be regarded as outside the scope of Directive 93/42 merely by virtue of the fact that, although one of the aims of that legislation is health protection, it is also based on considerations relating to protection of the environment".*

### 3.2.5.7 *The Ker-Optica case of 2 December 2010 (C-108/09)*

The European regulation on medicinal products foresees a clear distinction between prescription and non-prescription medicinal products for the purpose of distribution and sales to consumers. Such a distinction does not exist in the domain of medical devices.

As a consequence, the freedom for Member States to define what sort of clinical supervision they exercise on the release of medical devices falls under the principle of 'the free movement of goods'.

The modalities of sale (e.g. online via website) are not prescribed for medical devices on an EU level. Consequently, the following question arises: to what extent are EU member states allowed to regulate modalities of sale for medical devices? This question has been addressed by the CJEU in the *Ker-Optika* case concerning online sales of contact lenses.

The case concerned a dispute about the Hungarian legislation that reserved the sale of contact lenses to shops specialised in the sale of medical devices and, consequently, prohibited the online sale of these products.

The CJEU held that EU member states were not under all circumstances allowed to restrict the sale of medical devices to only physical outlets that specialise in medical devices. First of all, it ruled that national rules seeking how to regulate in which way medical devices are supplied to the consumers



do not fall under the scope of the e-commerce directive. Those national rules need to be assessed under the general EU rules on free movement of goods.

The CJEU examined whether there was a restriction on the free movement of goods and decided first of all, with reference to the pre mentioned DocMorris case, that these national rules hindered access to the market of the Member State that has those rules more for foreign traders than for local traders.

A justification for that restriction was therefore necessary if the Member State wanted to be able to maintain it. However, the CJEU found that the type of devices in question did not justify this type of restriction and that the legislation in question was disproportional. Any restriction on Internet sales, even if it is intended to protect consumer health, must also be proportionate to that objective. As a consequence, **whether or not a justification can be accepted, will depend on the type of device we are dealing with.**

It follows from this case that the CJEU seems to have a different view on medical devices compared to medicinal products. In the *DocMorris* Case, it accepted that the supply of prescription medicines needs to be more strictly controlled but that a total ban on the online sale of both prescription and non-prescription medicines could not be justified. It will be interesting to see if the CJEU holds a similar position in the case of prescription or high-risk medical devices. This seems however likely to happen<sup>zzz</sup>.

Although this case concerned restrictions on internet sales, the reasoning of the CJEU can be transposed to restrictions on the sale and use of medical devices in general. **Restrictions are possible, but they need to be proportionate to their objective, namely the protection of consumer health and will therefore differ from device to device.**

### 3.2.5.8 *The Case Pierre Fabre of 13 October 2011 (C-439/09)*

The company Pierre Fabre manufactures and markets cosmetics products. Distribution contracts for those products in respect of certain brands

stipulated that sales needed to be made exclusively in a physical space, in the presence of a qualified pharmacist.

With regard to cosmetic products, the CJEU considered that this restriction of competition could not be justified either by the need to provide individual advice to the customer and to ensure his protection against the incorrect use of products, or by the need to maintain the prestigious image of the products.

The CJEU held in that regard that:

*“42 Although it is for the referring court to examine whether the contractual clause at issue prohibiting de facto all forms of internet selling can be justified by a legitimate aim, it is for the Court of Justice to provide it for this purpose with the points of interpretation of European Union law which enable it to reach a decision (see L’Oréal, paragraph 14).*

*43 It is undisputed that, under Pierre Fabre Dermo-Cosmétique’s selective distribution system, resellers are chosen on the basis of objective criteria of a qualitative nature, which are laid down uniformly for all potential resellers. However, it must still be determined whether the restrictions of competition pursue legitimate aims in a proportionate manner in accordance with the considerations set out at paragraph 41 of the present judgment.*

*44 In that regard, it should be noted that the Court, in the light of the freedoms of movement, has not accepted arguments relating to the need to provide individual advice to the customer and to ensure his protection against the incorrect use of products, in the context of non-prescription medicines and contact lenses, to justify a ban on internet sales (see, to that effect, Deutscher Apothekerverband, paragraphs 106, 107 and 112, and Case C-108/09 Ker-Optika [2010] ECR I-0000, paragraph 76).”*

Similar to the other cases, the CJEU ruled that a restriction might be possible, provided however that the measure is necessary and proportionate to the aim.

<sup>zzz</sup> Erik Vollebregt, “Consequences of the EU Ker-Optika Case for e-commerce in Physical Medical Devices and Apps for eHealth Services”, June 15, 2012, [http://www.ejbi.org/img/ejbi/2012/2/Vollebregt\\_en.pdf](http://www.ejbi.org/img/ejbi/2012/2/Vollebregt_en.pdf)



### 3.2.5.9 Conclusion

The current Directive 93/42 foresees certain safeguard and monitoring measures to ensure the protection of public health (see Articles 8, 14b and 18 of the Directive) but they are limited. A notification of such measures to the European Commission will be necessary.

The directives in the domain of medical devices only determine the conditions under which medical devices can be placed on the market and be put into service. The same goes for the current version of the new Regulations.

Restrictions on the use, distribution, sale and promotion of medical devices need therefore to be assessed under the general rules on free movement of goods. Based on the EU case law, we can conclude that restrictions on the free movement of medical devices are possible but that they need to be necessary and proportionate and will be dependent on the type of device.

Given the higher risks associated with the use of medical devices of class III, a guided introduction by specialized centers seems to be acceptable as a form of stricter control that is justified in the light of consumer health protection. It will be however necessary to justify such need for each or at least a specific category of high risk medical devices which are characterised by a minimum of clinical data and a certain risk to health or safety of the users/patients. It cannot be excluded that a general restriction towards all medical devices of class III will be considered as disproportionate. Based on the case law discussed before, it will be very important to identify the potentially negative consequences for health by introducing certain high-risk medical devices before high-quality clinical evidence is obtained and to proceed to a comprehensive assessment of the risk to health based on the most reliable scientific data available and the most recent results of international research.

A positive element is certainly the fact that Member State's discretion relating to the protection of public health is particularly wide where it is shown that uncertainties continue to exist in the current state of scientific research which is definitely the case for certain innovative high-risk devices. A limitation of their use by physicians with the necessary training and expertise while gathering more clinical evidence can therefore to be justified.

Given the necessity and proportionality of restrictive measures, those measures should be monitored on their adequacy to fulfil the Members States' expressed aim and the by the CJEU's identified aim.

However, the possible stricter rules on the pre- and post-market evaluation in the future regulations, can, once directly applicable in the Member States, be an argument to conclude that any additional restrictions are disproportional. As the current proposal is still the object of debate, we cannot predict the outcome and **it is not clear whether the Parliaments proposals on efficacy and RCTs will be accepted by the Council or not.**

### Key Points

- **Restrictive measures falling within the “harmonised fields” (measures that restrict the placing on the market or the putting into service of high-risk medical devices) need to be compatible with the Medical Device Directive (Articles 8, 18 and 14b). The safeguard measures in Article 8 are only useful to restrict the circulation of medical devices that does not comply with the Directive's provisions on safety and performance (non-compliant devices). Restrictive measures towards compliant devices can be adopted based on article 14b (possible risks associated with the product), but must be limited to transitional measures pending an amendment of the Commission of nonessential elements of the Directive.**
- **The Proposal on medical devices foresees the possibility to adopt restrictive health protection measures towards the placing on the market of a group or category of medical devices with a “potential risk” for safety and health of the patient. They must however be provisional while awaiting a decision on a EU level. The Commission will examine their necessity which will be more difficult to prove if the proposed stricter conformity assessment by Special Notified Bodies and the broader clinical requirements foreseen in the current version of the Proposal will be accepted.**



- Restrictive measures falling within the “**non-harmonised fields**” (measures that restrict the use, distribution, sale etc. of high-risk medical devices) need to be compatible with the principle of free movement of goods (articles 34-36 TFEU). The implantation of the devices is a non-harmonised area.
- It is possible to take appropriate measures to prevent specific potential risks to public health based on the precautionary principle. The Member State shall need to perform a risk assessment before it can take any precautionary measure and once the scientific uncertainty has been demonstrated, it is then up to the Member State to decide which measures to take, provided that they are not based on purely hypothetical considerations and that they are proportional and non-discriminatory.

### 3.3 The patients' rights in cross-border healthcare

Reflecting the increasing recognition of patient's health and safety as a cornerstone of health-care policies, the European Directive 2011/24/EU on the application of patients' rights in cross-border health care was adopted on 9 March 2011. This Directive aims at facilitating the access to **safe and high-quality cross-border healthcare** and at promoting cooperation on healthcare between Member States.

Pursuant to article 3 of the Directive 2011/24/EU, “healthcare”, means “*health services provided by health professionals to patients to assess, maintain or restore their state of health, including the prescription, dispensation and provision of medicinal products and medical devices*”.

This directive does not focus on health products but on the patient's rights in cross-border healthcare. In this context, the Directive 2011/24/EU recalls certain fundamental rights of the patients, including **the right to be informed about their treatment**.

According to Art. 4, 2°, b) of the Directive 2011/24/EEC Member States shall ensure that healthcare providers provide relevant information to help individual patients to make an informed choice. This article contains a non-limitative enumeration of such information: **treatment options**, availability,

quality and **safety of the healthcare** provided in the Member State of treatment, clear invoices and clear information on prices, as well as on the authorisation or registration status of the healthcare provider, the insurance cover or other means of personal or collective protection with regard to professional liability. Although there is an overlap with the right to informed consent (cfr. art. 8 Belgian Patients' Rights Act), the right to make an informed choice seems to be more patient-consumer oriented.<sup>aaaa</sup> Whereas the right to informed consent rather seems to incorporate an act of confirming the option(s) that were proposed by the healthcare professional, the notion of an informed choice stresses the active process of comparing health care products and services that will ultimately result in an informed choice.

Member States shall also adopt transparent complaints procedures and mechanisms allowing patients to seek remedies in accordance if they suffer harm arising from the healthcare they receive.

The effectiveness of the right to be informed and to obtain redress in case of harm is questionable when patients are treated with high risk medical devices without any evidence to support their (long-term) safety and efficacy. Therefore, the right to an informed choice should be interpreted as a **right to accept or refuse a treatment on the basis of all relevant information and to be sure that the involved HCP's have the required expertise and knowledge**.

In the present state of the European Regulation, it is questionable, however, whether health care providers today are capable of giving complete device-related information as they do not have access to the relevant data themselves (cfr 2.3.1.5 on transparency). Furthermore, it might be time consuming for physicians to obtain from the manufacturers all relevant information related to a device. Therefore, a more collective approach, where the relevant data is centralised (EUDAMED) and can be accessed by healthcare providers (in the proposal for new Regulations on medical devices, see 3.2.2) shall be promoted.

<sup>aaaa</sup> H. NYS, “The right to informed choice and the Patients' Rights Directive”. European Journal of Health Law 19 (2012) 327-331.



Although this Directive shall not affect laws and regulations in Member States relating to the organisation and financing of healthcare in situations not related to cross-border healthcare, it consistently underlines the importance of a high quality of health-care in every Member State.

To achieve that aim, the Directive expressly promotes the creation of excellence centres. Recital # 54 of the Directive stipulates that:

*“The Commission should support the continued development of European reference networks between healthcare providers and centres of expertise in the Member States. European reference networks can improve the access to diagnosis and the provision of **high-quality healthcare to all patients who have conditions requiring a particular concentration of resources or expertise**, and could also be focal points for medical training and research, information dissemination and evaluation, especially for rare diseases. This Directive should therefore **give incentives to Member States to reinforce the continued development of European reference networks**. European reference networks are based on the **voluntary participation** of their members, but the Commission should develop criteria and conditions that the networks should be required to fulfil in order to receive support from the Commission.”*

Moreover, article 12 expressly “encourages” Member States to facilitate the development of European reference networks:

*“(a) by connecting appropriate healthcare providers and centres of expertise throughout their national territory and ensuring the dissemination of information towards appropriate healthcare providers and centres of expertise throughout their national territory;  
(b) by fostering the participation of healthcare providers and centres of expertise in the European reference networks.”*

In the framework of this Directive, the European legislator emphasizes the link between the quality of healthcare and the concentration of expertise.

This Directive underlines the prominence of the patient's health in the determination of the policies of the European Union and the Member States and lists a series of tools to achieve this common goal. Among these, access to and sharing of information, are valued tools. Based on this idea, **the creation of centres of excellence must ensure quality care notwithstanding the increasing specialisation of health technologies**.

The principles and justifications developed in the context of the Directive 2011/24/EU should be taken into account while limiting the use of certain medical devices and the performance of certain medical procedures to e.g. a selection of centers of expertise.

Indeed, for some medical devices, specifically new innovative high risk medical devices, the comparison with rare disease (in terms of need for concentration and sharing of expertise) is particularly relevant.

To that aim, the various guidelines, in particular the guidelines on Excellence centers developed by the European Union Committee of Experts on rare diseases (EUCERD) can be used.

According to this group, the criteria should be based on « *leadership and credibility, multidisciplinary and inclusiveness, as well as on their capacity to create links and collaborations and on the existence of an evaluation mechanism* »<sup>bbbb</sup>.

Moreover, MSs should adopt transparent designation criteria, ensure an ongoing evaluation process and facilitate the access to the patients.

In addition, “*the designation process at MS level should ensure that the designated CEs have the capacity and the resources to fulfil their obligations according to the criteria and that they have a strategy in place to meet all the criteria during a set period of time*”.

Additional developments on the selection method of excellence centers can be found in a previous KCE report 219 on “*organisation of care for adults with rare cancers and cancers with complex diagnosis and/or treatment*”.

<sup>bbbb</sup> Domenica Taruscio et. Al “: « Centres of Expertise and European Reference Networks: key issues in the field of rare diseases. The EUCERD Recommendations ». Blood Transfus. 2014 Apr; 12(Suppl 3): s621–s625.



## Key Points

- Health-protection involves both product-quality and safety and health-care safety.
- The Directive on patient's right clarifies that a comprehensive health policy implies taking into account those patient's rights.
- The Directive recalls that safety in health-care is central and fundamental.
- In this context, the Directive refers to centres of excellence as a tool to ensure high quality in medical care.

## 4 EXAMPLES OF MEASURES ON A NATIONAL LEVEL

European Medical devices Directives harmonize the rules regarding the placing on the market and putting into service of medical devices in all Member States. Outside these harmonised fields, Member States can adopt their own rules to medical devices.

In the majority of the Member States, stricter rules and guidelines apply to high-risks medical devices and implants. Classically, those devices are subjected to additional restrictions or conditions regarding their distribution, their promotion, the persons authorized to deliver them etc.

However, in some Member States, public authorities and/or stakeholders are trying to integrate an additional aspect: the safety and efficacy of medical devices. In parallel with the ongoing discussions at the European level, these authorities and stakeholders are looking for "*alternative pathways to establishing the safety and efficacy of medical devices and systems for enhanced patient care and to promote access to and uptake of effective and novel medical devices.*"<sup>cccc</sup>

Without claiming to be exhaustive, this chapter points out classical and more innovative mechanisms pursuing this objective. Particularly interesting examples were found in France, the Netherlands and the United Kingdom.

### 4.1 Restrictions on the distribution

Most European countries have taken measures to restrict the sale, supply and advertisement of medical devices **after their placing on the market and putting into service**, especially high-risks medical devices or implants.

Advertisement to the general public is sometime prohibited for high-risk, reimbursed<sup>dddd</sup> or implantable<sup>eeee</sup> medical devices.

Some medical devices can only be sold and supplied by pharmacists or other competent persons to doctors or health care facilities.<sup>ffff</sup> In Belgium, for

<sup>cccc</sup> Establishing high-level evidence for the safety and efficacy of medical devices and systems" (available at [http://www.raeng.org.uk/publications/reports/establishing\\_high\\_level\\_evidence](http://www.raeng.org.uk/publications/reports/establishing_high_level_evidence)).

<sup>dddd</sup> For instance in France.

<sup>eeee</sup> For instance in Belgium (article 9 of the Law of 25 March 1964 on medicines).

<sup>ffff</sup> For instance in the United Kingdom.



instance, certain type of devices, including implantable medical devices, can only be sold to other distributors or to pharmacists.<sup>9999</sup> These devices can only be received, held and delivered by pharmacists or dentists.<sup>hhhh</sup> Moreover, active implantable medical devices can only be received, kept and delivered by hospital pharmacists.<sup>iiii</sup>

The selling and/or supplying of some medical devices can also be subjected to notifications procedures.

In Belgium, for instance, all medical devices distributors, even if they do not have a registered place of business in Belgium, must declare their distribution activities.<sup>jjjj</sup> <sup>kkkk</sup> The law of 15 December 2013 concerning medical devices also foresees an obligation for the distributor of medical devices to register the product's specifications<sup>llll</sup>

## 4.2 Medical guidelines

Clinical practice guidelines are non-mandatory instruments and can be issued by different sources, including national and international public health authorities. Medical practitioners will usually be expected to comply with national and international guidelines. If they do not, this can have an impact on their liability. However, **it usually takes time to set up clinical practice guidelines, which may render it not very suitable for a timely guided introduction of high-risk medical devices and implants.** Furthermore, clinical practice guidelines are not binding and usually do not take into account economic considerations. It is not exceptional that relatively expensive treatments supported in clinical practice guidelines are not reimbursed. For example, the European guidelines on the management of valvular heart disease mention TAVI should be considered in high-risk

patients with severe symptomatic aortic stenosis who may still be suitable for surgery.<sup>37</sup> However, in Belgium, this intervention is only reimbursed for anatomic inoperable patients.<sup>mmmm</sup>

Some authorities are much more active than others in developing and implementing medical guidelines. In the UK, for instance, the National Institute for Health and Care Excellence (NICE) is a special health authority<sup>nnnn</sup> set up to reduce variation in the availability and quality of NHS treatments and care. The NICE develops public health guidance to help prevent ill health and promote healthier lifestyles. This Institute's work relates to which treatments are available (i.e. funded by the NHS) in the UK and clinical intervention guidance for medical practitioners and healthcare providers on using these treatments.

The recommendations are based on the best available evidence. Clinical guidelines can cover any aspect of a condition. This may include recommendations about providing information and advice, prevention, diagnosis, treatment and longer-term management.

The NICE have set up several National Collaborating Centers bringing together expertise from the royal medical colleges, professional bodies and patient/carer organisations which draw up the guidelines.

The National Collaborating Centre appoints a Guideline Development Group whose job it is to work on the development of the clinical guideline. This group consists of medical professionals, representatives of patient and carer groups and technical experts. They work together to assess the evidence for the guideline topic (e.g. clinical trials of competing products) before preparing a draft guideline. There are then two consultation periods in which

<sup>9999</sup> Article 10bis § 3 of the Royal Decree dated 18th March 1999 and article 10bis and 10ter of the Royal Decree dated 15th July 1997 concerning active implantable medical.

<sup>hhhh</sup> Article 10bis § 6 of the Royal Decree dated 18th March 1999.

<sup>iiii</sup> Article 19 of the Royal Decree dated 15th July 1997 concerning active implantable medical devices.

<sup>jjjj</sup> This notification differs from the notification for the first placing on the market foreseen in the Medical device Directive.

<sup>kkkk</sup> Article 10bis § 1 of the Royal Decree dated 18th March 1999 concerning medical devices and 50 of the law of 13 December 2013.

<sup>llll</sup> Article 50 of the law of 15 December 2013, entered into force since 17<sup>th</sup> February 2015 (Royal Decree of 3 February 2015 implementing the law of 15 December 2013).

<sup>mmmm</sup> <http://www.riziv.fgov.be/nl/professionals/individuelezorgverleners/verstrekkers-van-implantaten/akkoord/Paginas/klepstent-aortapositie.aspx#.VUpxEpMnJnk>

<sup>nnnn</sup> Statutory footing are set out in the Health and Social Care Act 2012.



stakeholder organisations are able to comment on the draft guideline. After the second consultation period, an independent Guideline Review Panel reviews the guideline and stakeholder comments and ensures that these comments have been taken into account. The Guideline Development Group then finalises the recommendations and the National Collaboration Centre produces the final guideline<sup>oooo</sup>.

**NICE guidance** (on specific products) and also interventional procedure guidance do **in some cases specify that specific procedures should only be undertaken in specialist units and by clinicians and teams with special training and experience in complex procedures** (see e.g. the par. 1.2 of the guideline on balloon dilatation of systemic to pulmonary arterial shunts in children<sup>pppp</sup> or par. 1.5 of the guideline on transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction<sup>qqqq</sup>).

NICE guidelines are not compulsory but they have an important impact on medical practice. Healthcare and other professionals in the NHS are expected to take these clinical guidelines fully into account when exercising their professional judgment. Healthcare professionals and others should record their reasons for not following clinical guideline recommendations. The guidance does not override the responsibility of healthcare professionals and others to make decisions appropriate to the circumstances of each patient.

In October 2014 Andy Burnham, British Labour Party politician, revealed that there are ongoing discussions to make it mandatory for UK commissioners to follow NICE clinical guidelines.

### 4.3 Professional and traceability registries

The use of registries expanded across Europe and abroad in the last years. From a legal point of view, there are however few countries where the use of such registries is mandatory and systematic. The data contained in these registries and the use of these data is also highly variable.

Belgium was one of the first Member States to enact a plan to strengthen the control and monitoring of the medical device sector and ensure better traceability of medical devices after the PIP scandal. The “Medical devices plan” announced in 2012<sup>rrrr</sup> focuses on **implantable medical devices**, which are considered to pose higher risks to the patient’s health. The plan aims at the improvement of their **traceability**. The law of 15 December 2013 on medical devices implements the plan with various measures:

- An obligation **for the distributor** of medical devices to register with the FAMHP **and to register the products specifications** intended for the final user or retailer<sup>ssss</sup>.
- An obligation **for the medical practitioner to register the implantation, removal and replacement of each implantable medical device** and to communicate certain personal data of the patients to the FAMHP.

This obligation is rather remarkable in Europe and will allow the public authorities to build a databank of all the implantable medical devices used in Belgium. This will also allow the authorities to collect information on major incidents and eventually to take measure to protect public health.

The King should define which implantable medical devices are subjected to this obligation and could extend it to other medical devices<sup>tttt</sup>.

<sup>oooo</sup> <http://www.nice.org.uk/about>.

<sup>pppp</sup> <https://www.nice.org.uk/guidance/ipg77>.

<sup>qqqq</sup> <https://www.nice.org.uk/guidance/ipg504>.

<sup>rrrr</sup> [http://www.fagg-afmps.be/fr/plan\\_dispositifs\\_medicaux/](http://www.fagg-afmps.be/fr/plan_dispositifs_medicaux/).

<sup>ssss</sup> This article entered into force on 17<sup>th</sup> February 2015 (Royal Decree of 3 February 2015 implementing the law of 15 December 2013).

<sup>tttt</sup> Article 51 of the Law of 15 December 2013 on medical devices. At the time of the writing of this report, this article was not yet entered into force.



- An obligation for the medical practitioner to inform the patients on their implantable medical devices and to provide them for an “implant card” containing useful information about the device (e.g. type of device, specifications, date of expiry).

The King will define the information requirement and the content of the so called implant card.<sup>uuuu</sup>

This system will allow the authorities, in case of incidents, to identify where a device is located and to alert the concerned healthcare professionals and patients.

The traceability measures taken in the context of the law of 15 December 2013 were qualified by the Council of State<sup>vvv</sup> as measure falling (at least partially) within the non-harmonised fields of European law. In its advice, the Council of State raised some concerns regarding the compatibility of these measures with the free movements of goods and in particular the obligation for the distributors to register with the FAMH. The Council of State found, *a priori*, that such measures pursue a legitimate aim. However, the Council of State left the question on the proportionality of these measures open.

At the time of the writing of this report, the above described measures are not fully in force. The plan should be fully in force in 2016.

The use of some registries are already mandatory in Belgium but only in the context of reimbursement (see for instance the use of the registers Qermid@pacemakers, Qermid@tuteurs, Qermid@orthoprïde, etc.<sup>wwww</sup>). These registries are not designed to be a data collection system serving primarily scientific purposes.

Scandinavian countries, especially Sweden, use registries in a very organized way and are now able to use them efficiently as tools improving efficiency in health care. The UK also seems to use registers in a more efficient way<sup>xxxx</sup>.

In the UK, particularly concerning hip and knee implants, and more recently following the PIP breast implant scandal, certain **product registries** have been established, via the English and Welsh National Joint Registry, which is currently funded via a subscription fee collection arrangement, and a pilot Breast and Cosmetic Implant Registry.

Additionally, there is a **voluntary pilot scheme** known as Beyond Compliance Services (<http://www.beyondcompliance.org.the> UK/) which has been initiated by a surgeons' professional association, the British Orthopaedic Association, in collaboration with the Association of British Healthcare Industries (ABHI) and NHS Supply Chain. This envisages **voluntary restricted supply** of novel hip and knee implants by manufacturers to a very low specified number of the UK implanting centers (hospitals) for a period of time until individual implant procedures have been assessed in detail by an independent surgeons' group together with the implanting surgeons, using data provided by both the manufacturer as well as by the implanting centers and also from other sources to intensify the scrutiny of novel hip and knee implants. The aim is to identify potential failure trends at an early stage and to complement and expand the post-market clinical follow-up of manufacturers.

In The Netherlands, the use of registries is required by some professional associations. In practice, certain registers are already working such as:

- The Dutch Breast implant registry (DBIR)
- The national register for orthopedic implants (LROI)
- The national register for vaginal implants

However, not all the implants used in the Netherlands are currently covered by these registries.

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<sup>uuuu</sup> Article 53 of the Law of 15 December 2013. This article was not yet into force at the time of the writing of this report.

<sup>vvv</sup> Advice of the Council of State, n°53.500/1-2 of 10 July 2013, Doc. Parl., 3057/001, p. 114-124.

<sup>wwww</sup> <http://www.inami.fgov.be/fr/professionnels/sante/fournisseurs-implants/qermid/Pages/default.aspx#.VWR-3BCJhnU>.

<sup>xxxx</sup> BRADFORD H. GRAY, “Registries as Knowledge-development Tool: The experience of Sweden and England”, July 2013, Urban institute, Health Policy Center.



The Dutch minister of public health decided to set up a national implant registry handled by public health authorities. This registry should be based on the existing registries used by hospitals<sup>yyyy</sup>.

In France, the Decree 2006-1497 dated 29 November 2006 and the Decree dated 26/01/2007 require healthcare structures to comply with traceability obligations regarding certain medical devices. The concerned devices **are long-term implantable devices**, including dental implants, but excluding the osteosynthesis devices and ligatures and surgical sutures.

#### 4.4 Limitation of the use of certain medical devices to reference centres / specialists

France is the only country that enacted, within the medical devices regulations (and outside the reimbursement scheme), national rules potentially restricting the prescription and use of a specific medical device.

Article L1151-1 of the French Code of Public Health foresees that:

«*The **performance** of some acts, processes, techniques and methods for diagnostic or therapeutic purposes, and the **prescription** of certain medical devices requiring a specific supervision for reasons of public health or likely to result in unjustified expenditures **may be subject to rules:***

- *Regarding the training and qualification of professionals that may prescribe or implant them in accordance with the code of medical ethics;*
- *Regarding the technical conditions of their execution*

*They may also be subject to rules of good practice.*

*These rules are established by joint order of the Ministers of health and social security, after the advice of the Health Authority (HAS).*

*The **use** of these medical devices and the performance of such acts, methods, techniques and methods for diagnostic or therapeutic purposes may be **restricted during a given period of time to certain health care facilities**. The Ministers responsible for health and social security set, after the advice of the Haute Health Authority (HAS), the list of these facilities or specify the criteria in the light of which the regional health agencies fix this list.*

*The provisions of this article are applicable without prejudice to the provisions relating to biomedical research as defined in title II of this book and those relating to authorizations, the conditions for the implementation of certain activities of care and functioning technical conditions laid down in chapters II, III and IV of title II of book I of the sixth part.*

This article was introduced in 2002 in order to control the performance of some acts, processes, techniques and methods for diagnostic or therapeutic purposes, and the prescription of certain medical devices requiring a specific supervision likely to pose serious risks for patients (according to the current medical knowledge)<sup>zzzz</sup>.

This article was only implemented once, by two executing decrees concerning the same medical device, namely the valvular aortic bioprostheses:

- A decree adopted in 2009<sup>aaaaa</sup> sets up for two years a list of 33 institutions in which the implantation of this prosthesis should be exclusively carried out;

<sup>yyyy</sup> Registratie van implantaten in Nederland, Inventarisatie en pilot, RIVM Rapport 2014-0089.

<sup>zzzz</sup> Projet de loi de modernisation social présenté au nom de M. Lionel Jospin, Premier ministre, par Mme Martine Aubry, ministre de l'emploi et de la solidarité – Exposé des motifs.

<sup>aaaaa</sup> Arrêté du 29 déc. 2009 limitant la pratique de l'acte de pose de bioprothèses valvulaires aortiques par voie artérielle transcutanée ou par voie transapicale à certains établissements de santé en application des dispositions de l'article L.115-1 du code de la santé publique (JO 31 déc.).



- A decree of 2012<sup>bbbb</sup> sets the criteria for this implantation. This decree imposes technical requirements, minimum numbers of procedures and specific qualifications for the medical practitioners performing the implantation.

These two adoptions are the only execution of article L1151-1 of the Code of Public Health. French public authorities preferred to use the legislation on reimbursement to limit the use of such medical devices.

The 2012 decree contains very detailed rules for the implantation on valvular aortic bioprostheses (through percutaneous or transapical approaches):

- Those implantations can only be performed in health care facilities authorised for certain surgeries;
- The decree defines the way premises need to be organised within the authorised health care facilities;
- The decree defines the required material and the composition of the team involved;
- The decree requires the authorised health care facility to have performed 200 replacement surgeries of valvular aortic in the year preceding the implantation of valvular aortic bioprostheses (through percutaneous or transapical approaches);
- The decree sets up a minimal number of 24 implantations of valvular aortic bioprostheses (through percutaneous or transapical approaches per year for each authorised health care facility).

The decree also requires the health care facility to send specific data to public authorities.

The conformity of these provisions with European law was never challenged before a French or a European jurisdiction.

Rather than restrictions concerning specific medical devices and associated surgeries, some countries preferred to limit certain difficult surgeries to

certain specialized centres. Finland has for instance established a **list of procedures that should be carried out in centres of reference** (like neonatal heart surgery or bone marrow transplants)<sup>cccc</sup>.

In the UK, since at least 2010, there has been overt recognition within the NHS in England that change and improvement is required in the model of care and that this entails an appropriate configuration of hospitals, primary care centres and specialist and general services. This led to clinical reviews of service provision and the development of 'cases for change' from English region to region and across different areas of healthcare (see e.g. the cardiovascular project proposed model for care which was the starting point for the implementation of this change program for the NHS in London in relation to cardiovascular care<sup>dddd</sup>).

The London cardiovascular clinical review specifically recognised that patients benefit (in terms of improved patient outcomes) from treatment in hospitals (and by clinicians) that perform high volumes of vascular, cardiac or cardiology procedures and which use modern technology more frequently. Consequently, proposed models of care to be commissioned by healthcare commissioners in the cardiovascular field aim to:

- concentrate specialist elective and emergency care in considerably fewer, high volume Healthcare Organisation (HCOs) and to require more local HCOs to refer and/or transfer patients to the high volume specialist units;
- require sub-specialism qualification by MPs for teams undertaking specialist procedures such as mitral valve procedures in order to ensure appropriate expertise and specialism. Referring local HCOs should only refer patients to units with appropriate mitral valve specialists;
- ensure all surgeons participate in the release of cardiovascular services across the network to ensure they gain experience at a high volume unit and of complex emergency procedures;

<sup>bbbb</sup> Arrêté du 3 juil. 2012 limitant la pratique de l'acte de pose de bioprothèses valvulaires aortiques par voie artérielle transcutanée ou par voie transapicale à certains établissements de santé en application des dispositions de l'article L. 1151-1 du code de la santé publique (JO juil.).

<sup>cccc</sup> Rare diseases task force. Overview on national listings of centres of reference in Europe.

[http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/overview\\_national\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/overview_national_en.pdf).

<sup>dddd</sup> <http://www.londonhp.nhs.uk/wp-content/uploads/2011/03/Cardiovascular-model-of-care.pdf>.



- make central, specialist HCOs also serve as training centres of excellence to ensure surgeons develop expertise and skills under the guidance of specialist surgeons and that they have greater exposure to complex arterial surgery, training in endovascular techniques and in multidisciplinary working.
- make central units also function as leading centres for research.
- ensure that regarding new specialist technology and techniques (e.g. transcatheter aortic valve implantation (TAVI)) there must be development of organised implementation strategies to concentrate the roll out of new technology in a few designated HCOs with appropriate infrastructure and experience initially in order to develop standards for other HCOs within the London area cardiovascular network. This is in order to avoid situations where an unlimited number of cardiac HCOs start to perform new types of procedures but fail to reach critical mass and sufficient experience to be able to participate in controlled clinical trials, which also results in a prolonged learning curve with associated difficulties in gathering and analysing the results of such new clinical techniques to assess whether they are suitable for roll out to more HCOs.

**The limitation to centres of excellence is a mechanism that is rather uncommon in Europe when it concerns the use of medical devices.**

However, this limitation becomes increasingly common with regard to the treatment of rare diseases, and in particular of some rare cancers.

There might be **different reasons to work with centres of excellence.**

First, this might lead to better outcomes by minimizing the learning curve effect and promoting the concentration of expertise. Next, for high-risk devices where evidence on efficacy/effectiveness is lacking, the limitation to a number of centres of excellence might be linked to limiting the number of procedures and gathering further evidence in a research setting before widely spreading the device which might expose patients to potential risks. In the end, evidence on benefit for the patient, which is necessary to take

good policy decisions, usually can only be gathered by linking new procedures to trial participation.

#### 4.5 HCP's behavior rules and liability

As explained above, redress and, more broadly, accountability of HCPs is seen commonly as a tool to enhance the quality of care. Today, the responsibility of the care provider forms an integral part of the patients' rights and, beyond this, the involvement of the patient in the determination of its care is now a standard<sup>eeeee</sup>. In this way, the information becomes a tool and a measure of responsibility for care providers.

##### 4.5.1 Belgium

Medical practitioners should not be subjected to any regulatory restrictions while choosing the means to diagnose or treat their patients. This freedom is essentially recognized under articles 11 and 12 of the Royal Nr. 78 of 10 November 1967.

This freedom implies however that the medical practitioner is responsible for his choices. The medical practitioner will indeed be liable if, amongst various possibilities, he chooses a method or a mean that would not have been chosen by any other normally prudent and diligent doctor, placed in the same circumstances. If the medical practitioner is aware of a predictable damage, he must do everything to control the risk, or at least to reduce it to the maximum extent compatible with the therapeutic objective pursued<sup>ffff</sup>.

In order to determine whether a physician has violated his duty of care, courts will apply an objective and heightened standard of care. In particular, courts will consider whether the conduct of the medical practitioner is consistent with the conduct of a reasonable and prudent professional colleague in similar circumstances. The good practices of the medical profession – where this refers to the practice of the prudent HCP – are a criterion that can be used by the courts for their assessment; however, courts are by no means bound by them. In Belgium, therapeutic guidelines are not deemed mandatory<sup>99999</sup>.

<sup>eeeee</sup> Council Conclusions of 1-2 June 2006 on Common values and principles in European Union Health Systems, OJ C 146, 22.6.2006, p. 1.

<sup>ffff</sup> See judgment of the Court of first instance of Brussels 23/01/2007.

<sup>99999</sup> CALLENS, S., VOLBRAGT, I., NYS, H., "Kostenbesparende richtlijnen, kwaliteitsvolle zorg en medische aansprakelijkheid", Intersentia, Antwerpen, 2006.



Moreover, when an HCP is working in a hospital institution – which will generally be the case for the implantation of high risk medical devices – the Hospital Act provides (art. 30) by default for a liability for the healthcare institution. In addition, that same article poses a direct responsibility of the hospital regarding the respect for patient rights legislation: the hospital must itself ensure patients the rights granted to them by the law of 22 August 2002.

Once a medical device bears a CE-marking, it can be placed on the market. However, the question arises whether the use of such medical devices can be considered as a violation of the duty of care of the medical practitioner.

The use of specific medical devices can only be seen as a violation of their duty of care if this conduct is not consistent with the conduct of a reasonable or prudent professional colleague in similar circumstances. Three main criteria will be used by the courts to assess this:

- A first criterion that can be used to assess this are the **practices that are deemed prudent**.
- A second criterion that can be used is **whether the medical practitioner had a scientific basis for the specific use of this device**. Indeed, a medical act is only consistent with the conduct of a reasonable or prudent professional colleague if it is scientifically justified.  
The use of certain medical devices can be scientifically justified by medical guidelines.
- The third criterion that will be used is whether the patient has given his **informed consent**. The informed consent of the patient is dealt with in article 8 of the Act of 22 August 2002 on patients' rights. Article 8 provides that a patient has the right to give this informed, prior and free consent for each intervention of the medical practitioner. The consent should be explicit, except when the medical practitioner can reasonably assume the patient's consent from the patient's behaviour.

The law provides, in this regard, that the information to be provided to the patient to enable him to give his consent shall cover the purpose, nature, degree of urgency, the duration, frequency, counter-indications, **side effects and risks involved in the intervention**. The law also states that the information must be relevant to the patient. The HCP, moreover, must also **indicate alternatives to the proposed treatment**.

To evaluate the relevance of this information, the general level of knowledge of the treatment at issue should be taken into account. When a treatment or therapy is innovative, the level of information to be provided by the HCP to his patient shall be higher and more stringent.

Besides negligence, Belgian law also punishes the breach of an express rule of conduct. Accordingly, breach of the Law (e.g. de patient's rights act), constitutes a fault which may engage the responsibility of the HCP. Accordingly, if the scope of the patient's rights legislation is recalled to doctors, the **lack of information constitute a direct and extended fault**.

Therefore, we are of the opinion that **the fact that a medical devices bears a CE marking would not suffice to allow the patient to express an informed consent**. The information on the risk associated with the use of high risk medical device shall include information on the safety and efficacy of the device. The level of information that is required to qualify a consent as to be "informed" depends on the overall available information. In principle, any treatment of any kind would need a complete information to the patient. However, for standard treatments, this information may be more limited than for innovative approaches. Therefore, **when introducing and using new (high-risk) medical devices, the practitioner will need to better and more formally inform the patient on all elements of his diagnostic and treatment choices**. It is our opinion, that a doctor should inform his patient that he uses innovative or poorly known devices and compare this with more standard alternative treatments. To that extent, the doctor should inform the patient of the comparative efficacy of the suggested treatment and the more standard approach. The major problem for doctors is that they do not always have complete access to this information. However, **when using new treatments without having evaluated this choice (especially when information is lacking), the doctor would raise his liability**.

If physicians working at a hospital fail to obtain informed consent, provide insufficient or false information related to the safety or efficacy of a high risk device or omit to suggest a more appropriate alternative, the liability of the hospital might also be at stake. The respect of patients' rights has been integrated in the Belgian Hospital law (art. 30 Hospital Law). As such, hospitals need to respect the relevant patients' rights and need to make sure that self-employed health care professionals working in the hospital respect the patients' rights. Furthermore the hospital is liable for the breaches of the patients' rights committed by the health care professionals working at the



hospital (self-employed, employee or statutory), except if the hospital explicitly and previously informed the patient that it will not be liable.<sup>hhhhh</sup> The hospital can solely appeal to the exception for self-employed physicians since according to the civil liability rules hospitals can be held liable for the wrongful acts (or omissions) of their personnel working under subordination (art. 1384, al. 3 Civil Code). The advantage of such a so called centralized liability is that patients know who to direct their claim at in case of presumed violation of patients' rights.

#### 4.5.2 UK

The National Health Service (NHS) is the main provider of health care in the UK. This public organisation “employs” doctors, dentists etc. and provides in principle “free health care” in the UK. In parallel, the private sector provides non-publicly subsidized health care. Many NHS consultants operate their own separate private practices, sometimes from NHS facilities.

Registration requirements for both healthcare professionals individually and also for healthcare and surgical providers (e.g. clinics and hospitals) could effectively restrict the use of certain high-risk medical devices, such as implantable medical devices, to surgeons with the relevant experience and registrations.

##### 4.5.2.1 Medical Practitioner registration and licensing requirements

The UK respects the freedom of patients to seek out whatever manner of healthcare treatment they desire from whomever they may wish.

Nonetheless, **acceptable standards of medical care and treatment** in the UK are maintained via a series of statutory prohibitions (enforceable via the criminal law) set out in *The Medical Act 1983*. These prevent: (1) recovery of any fees or charges for any medical treatment; or (2) the holding of any appointment as a physician, surgeon or other medical officer in any National Health Service (NHS) or other hospital (with only very limited exceptions). They also invalidate any sickness or other certificate issued, unless in all the foregoing cases the person in question is both registered and licensed to practise medicine in the UK by the General Medical Council (**GMC**).

#### Registration

- The Act mandates the GMC to maintain a public register of MPs in the UK. Registration must be either provisional (broadly, this is for MPs who have completed undergraduate medical school and have entered postgraduate medical training) or else full registration (broadly, MPs who have completed undergraduate medical school and have also successfully completed postgraduate medical training). GMC has additional statutory functions to regulate and set the standards for the UK medical schools providing basic medical training and to determine which postgraduate medical training programmes are an acceptable foundation for future practice as a fully registered MP.
- Registered MPs in the UK must comply with the GMC's good medical practice guidance and are subject to the GMC's fitness to practise regime. Failure to comply can result in MPs being struck off, or suspended from, the GMC register, amongst other sanctions.

The GMC **is unlikely to issue rules regarding use of specific medical devices** as GMP contains fairly high level conduct requirements. However, medical practitioners could face fitness to practice proceedings and/or clinical negligence claims in the event they treat patients with medical devices without any (or sufficient) experience and/or training in using specific devices, in circumstances where successful use of a particular device is recognised to require prior training and experience. In such proceedings the question of whether the medical practitioner has followed applicable clinical guidelines (e.g. those issued by NICE (see below) is likely to be taken into account by the GMC and/or a civil court as such guidelines are likely to provide a starting benchmark as to what is considered to be an appropriate standard of care.

<sup>hhhhh</sup> S. CALLENS, “Aansprakelijkheid van het ziekenhuis en de naleving van de Patiëntenrechtwet”, T.Gez. 2003-04, afl. 2, 125-130.



#### 4.5.2.2 Healthcare Organisation (HCO) registration requirements

- If a provider carries on a 'regulated activity' in England as defined in the *Health and Social Care Act 2008 (the 2008 Act)* and set out in Schedule 1 of the *Health and Social Care Act 2008 (Regulated Activities) Regulations 2010 (the Regulated Activities Regulations)*, they are required to be registered as a service provider by the Care Quality Commission (CQC) under section 10(1) of the 2008 Act. The regulated activities include, amongst other matters, treatment of disease, disorder or injury; surgical procedures; diagnostic and screening procedures; management of the supply of blood and blood derived products and nursing care.
  - To be registered, the provider must show that they are meeting essential standards of quality and safety in all of the regulated activities that they undertake. These standards are set out in the Regulated Activities Regulations and in guidance published by the CQC (note that these standards are due to be replaced by fundamental standards from 1 April 2015). For the purpose of compliance with the requirements of the Regulated Activities Regulations the registered service provider must have regard to guidance issued by the CQC and any code of practice issued by the Department of Health (i.e. the health ministry for England). Compliance with the requirements of the 2008 Act and of the Regulated Activities Regulations is enforced via the criminal law.
  - The Regulated Activities Regulations require, amongst other matters, the registered service provider to make suitable arrangements to protect patients and others who may be at risk from the use of unsafe equipment by ensuring that equipment (which is expressly stated to include medical devices) is properly maintained and suitable for its purpose and also that it is used correctly. The guidance issued by the CQC (which is mandated by the 2008 Act) states that service providers must manage risk through effective procedures, including ensuring that all staff involved in using the equipment have the competency and skills needed, and where this is not possible, know what to do to ensure the people remain safe. Effective procedures also include the arrangements for adverse events, incidents, errors and near miss reporting.
- Specifically in relation to healthcare provided involving medical devices the CQC guidance states that where people who use services receive care, treatment or support that involves the use of medical devices, the provider must have clear procedures that are followed in practice, monitored and reviewed for the use of medical devices and that wherever they are required these procedures should include: (1) implementing guidance issued by experts or professional bodies in relation to the medical devices used; and (2) acting on alerts from an expert or professional body or a product manufacturer.
  - Service providers must also ensure the medical devices used to meet patient needs are: (1) not reused if they are manufactured for single use only; (2) only modified in line with manufacturer's instructions or guidance; (3) only purchased if they meet the necessary legal requirements; (4) available when they are required for use; (5) supplied with the necessary technical information so that the risk of using them incorrectly is minimised; (6) permanently installed where appropriate, in accordance with manufacturer's requirements and published guidance; (7) only used by the person, or by staff, once they know how to use and operate them correctly; (8) monitored while being used and action taken if they do not appear to be working correctly; (9) routinely maintained in line with the manufacturer's instructions and by people who are competent to do so; (10) repaired when they break down by people who are competent to do so; and (11) disposed of or recycled, safely and securely

Rather than legislation dictating or controlling the level of specialism required in the English public sector (NHS), responsibility for this has effectively been passed to healthcare commissioners in the form of NHS England (which operates countrywide via its regional offices) and the various Clinical Commissioning Groups (CCGs) across the country which are responsible for commissioning healthcare at a local level and are comprised of consortia of primary care practitioners within a specific geography. Both NHS England and the CCGs must operate within the legal framework of the NHS Act 2006 (as amended) and the Health and Social care Act 2012, which first established these two sets of NHS commissioning bodies. However, both sets of commissioners have considerable scope to specify which services they will commission and which HCOs (i.e. providers) will provide these. It is therefore via improved commissioning that the NHS seeks to



force improved training and specialism for MPs and HCPs using high risk medical devices.

#### 4.5.3 The Netherlands

All hospitals including university hospitals closed a “Covenant for a safe application of medical technology in hospitals”. This convention was drafted under the supervision of the National hospitals association (NVZ) and the Dutch federation of University medical centres (NFU).

The Covenant foresees an “*introduction phase of medical technology and medical devices*”.

3.1. *The hospital sets up a procedure in which prior to the implementation of a specific medical technology or the purchase of a specific medical device, a plan is established. This plan should at least include the following elements: the need for the implementation or purchase, a risk analysis, the skill requirements with related training of future users and technicians as well as a periodic evaluation plan. For each purchase, a purchase file is opened and archived. **The hospital must justify in the purchase file why it decides to purchase and use other types or configurations of medical devices than those that are already present in the hospital.***

3.2. *The hospital has an investment policy supporting the purchase of medical devices. In the implementation of this policy, the hospital should ensure that the relevant disciplines are involved.*

(...)

4.8. *The hospital has a procedure in which in case of a deviation from the established medical device purchase policy, a risk assessment is made to see if the patients are not exposed to undue risk ”.*

## 4.6 Conclusion

**Safety and efficacy of medical devices are central for all public stakeholders.** The ongoing discussions on the adoption of new regulations on medical devices reveal a tendency to strengthen the control on certain class III medical devices in some Member States.

In the meantime, different tools are used by European countries in order to strengthen the control over medical devices:

- Distribution restrictions (sale, delivery and advertisement);
- Issuance of medical guidelines for the use of medical devices;
- Traceability registers and implant cards on a mandatory or voluntary basis;
- Restrictions on the use of certain medical devices and the performance of certain surgeries with data registration.

Among the Member States having put into place controlling mechanisms, only France seems to have implemented a legal mechanism for a guided introduction of medical devices via the limitation to certain centres. Even in this case, the controlling mechanism does not only focus on the product but also on the medical care and actors involved in the implantation.



## 5 POSSIBLE SOLUTIONS FOR BELGIUM

### Founding principles under Belgian law

Health protection is basic for a State as Belgium. In this sense, article 23 of the Constitution provides that:

*“Everyone has the right to lead a life in human dignity.*

*To this end, the laws, federate laws and rules (...) guarantee economic, social and cultural rights, taking into account corresponding obligations, and determine the conditions for exercising them.*

*These rights include among others:*

*(...) 2° the right to social security, to health care and to social, medical and legal aid; (...)*”

It is recognized that this provision creates no active duty for the public authorities, it encompasses a standstill principle which prohibits public authorities to adopt measures that reduce - without valid justification - the protection of social and political rights contained in this article. As reminded by Aurélien Vandeburie, *“the text has no other claims but to express a political philosophy in which the constituent intended to register the Belgian society. It actually belongs to the various competent legislators to concretely implement economic, social and cultural rights as enshrined.”*<sup>iiii</sup> To that extent, this article 23 would at least play its role as an interpretation tool for existing regulations.<sup>jjjj</sup>

It should be noted that in its assessment of the conformity of the national provisions with the rights guaranteed by article 23 of the Constitution, the Constitutional Court will apply, beyond national law, international treaties and texts which guarantee a right comparable to that contained in the Belgian Constitution.

In practical terms, this means that **when evaluating the measures the Belgian legislator can adopt** - and in particular when determining a health care policy – the Court will have to **take into account the obligation to**

**ensure a high protection of the public health** as recognized, inter alia, at the level of the European Union.

### Objective of a guided introduction

As underlined under section 1.2, the objective of a guided introduction of medical devices in Belgium is to guarantee an optimal and safe use of these health technologies after their market access. The development of new medical devices may offer enormous therapeutic opportunities and raises great expectations to effectively fight against debilitating diseases. Therefore, if they provide an added value to the patient and are affordable to society, their utilisation should be organised and promoted.

However a legal framework needs to be provided for the use of certain devices in a *“scientifically and clinically responsible manner”*<sup>kkkkk</sup>.

The goal of any health care policy must be to ensure an increased, efficient and effective health protection. Access to new medical technology and new devices cannot take place without taking into account the potential risks of these new products on patient’s safety.

Belgium must therefore find a coherent set of measures which:

- Do not affect the provisions of the Medical Devices Directives;
- Guarantee the patient’s rights to a high level of health protection;
- Are necessary, justified and proportionate restrictions to the free movement of goods and services, the therapeutic freedom or other rights and freedoms guaranteed by European and Belgian Law.

Considering this framework, Belgium can adopt two kind of measures:

- If it is demonstrated that a medical device is non-compliant (articles 8 and 18 of the Directive 93/42) or if a risk associated with the product can be identified (art. 14b of the Directive 93/42), the State can withdraw this product from the market, or decide that its placing on the market and putting into service should be prohibited, restricted or subjected to

<sup>iiii</sup> Aurélien VANDEBURIE « Le rôle de la Cour Constitutionnelle de Belgique dans la protection des droits économiques, sociaux et culturels garantis par l’article 23 de la constitution - l’article 23 de la Constitution (avant et après la loi spéciale du 9 mars 2003). Mise en perspective de l’arrêt de la Cour d’arbitrage n°66/2007 du 26 avril 2007 », *CDPK*, p. 128.

<sup>jjjj</sup> Idem, p. 129.

<sup>kkkkk</sup> See section 1.1.2.

particular requirements. In this case, the specific procedures foreseen in the Directive 93/42 must be applied (5.1).

However, this kind of measures does not directly address the questions related to the efficacy and added value for the patient of a medical device.

- If a medical device complies with the CE marking and does not present a specific risk, the Legislator can implement various measures in order to evaluate and monitor the risks associated with the use of a specific medical device (5.2). However, this type of measure cannot restrict the placing on the market and putting into service of a medical devices.

When implementing these measures, it appears that **access to information on the use of such devices, including the benefit for the patient, is a central element**. This information should enable to have **better knowledge of the product**. In addition, it must allow to measure the risks that will, where appropriate, justify special protective measures.

## 5.1 Measures within the harmonized fields

The European medical devices regulations allow the Member States to limit the placing on the market and putting into service of medical devices not only in case of non-compliance of the product with the requirements set up by the relevant legislation but also in the case of compliance when the essential or other requirements do not entirely cover all of the risks related to the product as such.<sup>lml</sup>

These restrictions only concern the placing on the market and putting into service of medical devices that are justified by a non-conformity or a risk associated with the product itself.

### 5.1.1 Non conformity of medical devices

If data and evidence are available and reveal the non-conformity of the medical device (non-compliance with the essential requirement, lack of safety or performance, the devices does not meet the claims made etc.), Belgium can trigger the mechanisms laid down in article 8 or 18 of Directive 93/42. On this basis Belgium can restrict or prohibit the placing on the

Belgian market and the putting into service of **non-compliant medical devices**.

Articles 8 and 18 of Directive 93/42 were implemented in Belgian law under articles 13 and of the Royal Decree dated 18 March 1999 on medical devices, article 14 of the Royal Decree dated 15 July 1997 on active implantable medical devices and article 8 § 1 of the IVD medical devices Royal Decree dated 14 November 2001.

Given the specific aim and mechanism set out by these articles, **it is not possible to implement a guided introduction based on a mere lack of evidence on the efficacy/effectiveness of the medical device as this is not foreseen as a conformity condition** by Directive 93/42<sup>mmmm</sup>. In other words, the medical device will not qualify as a “non-conform” product because of the mere uncertainty regarding its efficacy.

### 5.1.2 Threat to health and safety

If data and evidence are available and reveal a threat to health and safety, Belgium can rely on article 14b of Directive 93/42. This will potentially be possible when the device is manufactured with a component, contains a substance or uses working mechanisms for which specific risks can be identified. The specific risk could for instance be identified for devices or a group of devices with an extremely high number of similar incidents associated with the device, its components or its working mechanism.

Article 14b of Directive 93/42 is implemented in art. 13 of the Royal Decree of 18 March 1999. According to this article, the competent service is hold to submit a report to an Evaluation Commission if a medical device is appropriately placed and maintained and used according to the intended use, but nevertheless compromises the health and/or safety of patients, users or other persons. This Commission advices the Minister of Public Health, who can take all necessary measures to withdraw the devices from the market or to prohibit or restrict their use. The FAMHP needs to report the measures and their justification to the European Commission.

On this basis, Belgium could transitionally restrict the placing on the market and putting into service of specific medical devices while awaiting a

<sup>lml</sup> Blue Guide on the implementation of EU product rules, 2014. European Commission.

<sup>mmmm</sup> There exists no explicit requirement in Directive 93/42 to demonstrate the clinical efficacy of high-risk devices in the premarket phase.



modification of the EU regulatory framework. **Belgium could for instance transitionally bar the entrance to its market or require specific precautions** if there is evidence that it is the only way to control the risk linked to the devices, its component or its working mechanisms.

As explained above, a “potential risk” may be sufficient but **the mere uncertainty on the efficacy of a medical device will not be sufficient to bar or restrict the market access of certain medical devices. A (potential) risk must be identified and documented.**

The possible **measures**, however, **will need to be justified, necessary and proportionate.** Belgium will need to provide the evidence of possible risks to the safety and health of patients and will need to limit its restrictive measures to what is strictly necessary.

## 5.2 Measure outside the harmonised fields

Member State are competent for the definition of their health policy and for the organisation and delivery of health services and medical care.

In this context, Belgium could take various measures in order to monitor the distribution and use of high risks medical devices and implants and to improve the scientific knowledge of these products after their placing on the market. To obtain this, a specific level of expertise and training of persons involved in the distribution and use of medical devices could be demanded.

Moreover, it appears that access to relevant information on medical devices is a central element. This information should enable to have **better knowledge of the product.** In addition, it must allow to assess the risks that will, where appropriate, justify special protective measures. Ultimately, access to the relevant **information and data is the central element to allow the patient to make an informed choice and to the health professional to make a reasoned choice.** Indeed, the “informed” consent of the patient assumes that the doctor himself is fully and effectively informed about the advantages and disadvantages of the proposed treatment. The extent of information available to the health care professional will therefore also be a central element to measure its responsibility.

Member States however do not enjoy total freedom to intervene even on aspects that are not covered by the Directive 93/42. They do not have the obligation to respect the notification requirement in the Directive. They still however need to respect the principle of free movement of goods and

services and derogations to these principle need to be justified, necessary and proportional (Article 36 TFEU).

In addition, Belgium has to consider principles such as the therapeutic freedom and the choice of the patient.

### 5.2.1 Restrictions on the distribution of medical devices

Belgium can regulate the distribution, promotion and delivery of medical devices after their placing on the market / putting into service. Classical principles applicable to the restrictions on the free movement of goods and precautionary principle will still apply.

In this regard, Belgium has already implemented various measures (mentioned under section 4.1).

The Belgian legislative framework allows further improvement or measure to be taken:

#### 1. Conditions for the distribution, validation, reception and/or release of medical devices

Article 10bis § 5 of the Royal decree dated 18 march 1999 states that:

*“Concerning operations preceding the “putting into service” of medical devices, the competent Ministers may, for devices falling within their competence, **lay down conditions for their distribution, validation, reception and/or release.**”*

The competent Ministers could consider, on the basis of this article, laying down additional requirements with regard to the distribution, validation, reception and release of medical devices such as for instance:

- an obligation for the **distributors** of certain medical devices, to provide health care professionals (medical teams, pharmacists, ...) with certain (public) information before they can distribute their medical devices;
- an obligation for hospital pharmacists to document their choice for certain medical devices before their release;
- an obligation to appoint qualified staff for the distribution, validation, reception or release of medical devices



## 2. Additional restrictions regarding advertisement

Additional rules restricting the advertisement of medical devices, will need to be adopted by the King<sup>nnnnn</sup>.

### 5.2.2 *Restrictions on the use of medical devices and the performance of complicated surgeries to implant them*

A medical device is not only a health product. It forms also part of a treatment of a disease by a healthcare professional. Beyond product-related regulation, the other face of the treatment - **the therapeutic use of the product - can therefore be an alternative route to also achieve a guided introduction of medical devices.**

#### 5.2.2.1 *Possibility*

In addition to this “product oriented” approach, Belgium should regulate the medical practice linked to these devices.

The **promotion of reference centres is often proposed**. This solution has been implemented in various countries, including Belgium, for the treatment of rare diseases.

The **possibility to appoint reference centres already exists in Belgian law**. Indeed, the Hospitals Act was modified in 2002 by the law of 14 January 2002 which introduced the possibility to designate a hospital as a ‘centre of reference’ (article 14 of the Hospitals Act).

In the parliamentary discussions preceding the adoption of this provision, the Legislator underlined that the **primarily rational for reference centres was the quality of health care**. This provision could perfectly be met when the implantation of certain medical devices poses high risk for the patients and when the concentration of expertise protects public health. When the use or implantation of certain medical devices requires very specific skills, the quality of health care can justify the (transitional) limitation to expertise

centres. It must be justified however, on a case by case basis, that the implantation or use specifically requires certain skill or precautions.

The measure must be necessary and justified but also need to be proportionate. In this regard, the limitation to expertise centres should be limited in duration. Another means to reinforce proportionality would be, where possible, to organize “shared care networks”: if the treatment can be divided between reference centres and other health care facilities or, if the treatment can be performed under the supervision of a reference centre,

The KCE recently issued a report on the treatment of rare cancers encouraging the recognition of reference centres<sup>oooo</sup>. The promotion of reference centres is also promoted by the government in the governmental agreement declaration<sup>ppppp</sup>. Article 14 of the Hospitals Act was recently implemented by two royal decrees with regard to “rare diseases”<sup>qqqqq</sup>.

**Medical practitioners should not be subjected to any regulatory restrictions while choosing the means to diagnose or treat their patients.** This freedom is essentially recognized under articles 11 and 12 of the Royal Nr. 78 of 10 November 1967. This freedom implies however that the medical practitioner is responsible for his choices. The medical practitioner will indeed be liable if, amongst various possibilities, he chooses a method or a mean that would not have been chosen by any other normally prudent and diligent doctor, placed in the same circumstances. If the medical practitioner is aware of a predictable damage, he must do everything to control the risk, or at least to reduce it to the maximum extent compatible with the therapeutic objective pursued<sup>rrrrr</sup>. **This freedom does not prevent the public authorities to adopt public health measures were appropriate.** The Constitutional Court expressly recognized, in the context of PET-scanners limitation, that the Legislator has a very broad margin of appreciation to meet the requirement of optimal healthcaresssss.

<sup>nnnnn</sup> Article 9, § 4 of the Law of 25 March 1964 on medicines.

<sup>oooo</sup> KCE report 219Bs, 2014, “Organisation des soins pour les adultes avec un cancer rare ou complexe ».

<sup>ppppp</sup> *Doc. Parl.*, Ch., 2014-2015, n°54- 0020/001, p. 89.

<sup>qqqqq</sup> Arrêté royal du 25 avril 2014 fixant les caractéristiques pour la désignation de centres de référence " maladies rares ", appelés " centres d'expertise ", dans

les fonctions " maladies rares " agréées et arrêté royal du 25 avril 2014 rendant certaines dispositions de la loi coordonnée du 10 juillet 2008 sur les hôpitaux et autres établissements de soins applicables aux centres de référence " Maladies rares ", également appelés " centres d'expertise " ;

<sup>rrrrr</sup> See judgment of the Court of first instance of Brussels 23/01/2007.

<sup>sssss</sup> Constitutional Court. n° 165/2003, 17 December 2003, B.5.2..



To that extent, we believe that it can be **useful to implement reference centres**. These centres would be designated based on (necessarily) multiple criteria concerning not only the doctors involved, but also the whole teams and the infrastructure put in place. This to avoid competition between hospitals and a "medical mercato". The experience gained by the team with the proposed technology must be a central criterium to take into account. It should be noted that, in view of the free movement of health care professionals, this experience can partly be acquired beyond the Belgian borders. The sharing of experience and the training offered to other teams can also be taken into account. Conversely, geographic criteria will only be considered within the strict limits of a medical need for rapid interventions.

The participation of the approved team in studies in the medical field for which the device is used can be taken into consideration as a selection criteria. Rather than developing experience on a specific technique or surgery, the appointed centres would develop a deep knowledge on the whole treatment or disease.

In return for this designation, centres of reference could be required to collect specific data and, where appropriate, to make these data available to the authorities and to allow, if supported by evidence, the expansion of the treatment. The effective training of colleagues from other health-care institutions could be also included in the obligation package of these centres.

In any case, such criteria must be scalable. Restrictions must be temporary to provide the time to identify a real risk or to share the knowledge, or even to find a trivialization of the intervention and, therefore, the need to "exit" from the system of reference centres.

In conclusion the method to select the centers should comply with the principle that the following fundamental rights must be protected:

- Economic rights (to work and provide services)
- Therapeutic freedom
- Patient's choice

However exceptions to these principles are possible if they are:

- Justified (the objective is legitimate)
- Necessary
- Proportionate (the less restrictive means were chosen)

The intended measures are aiming at reducing a "health" risk. The selection criteria to define the reference centers authorized to use certain medical devices should therefore primarily be health-related (scientific justification):

Therefore the limitation should be justified by a health reason (not linked to the product itself but to the associated expertise, experience, specialism etc.) – the use of the medical device requires e.g.:

- a specific experience,
- a specific team,
- a multidisciplinary environment,
- a deep knowledge of the product,
- etc.

Where concentration of expertise is necessary to meet these requirements, one should however chose the highest reasonable/possible number of centers (taking into account the ratio between the needs of the patients and the volume of required experience, knowledge, teams, etc.). However, if experience is required, a high dilution by a too high number of centers might disqualify the criterion.

The proposed measure should be double-checked taking into account that there are no better means (less detrimental) to meet the same objective.

Possible criteria likely to meet these requirement are for instance: experience of the doctors and medical teams, involvement of the team in research, etc. The geographical criteria will possibly be used if one can link it to the quality of care (the patient need to be treated near to his place of living, etc.).

The collection of data and obligation to train other specialists will not as such be a selection criteria but a means to ensure proportionality.

Where those scientific criteria (protection of public health/quality of care) offer a possibility/need to choose between several equally efficient centers, additional criteria need to be identified: this sub-selection should be based on objective and verifiable criteria.

- To that extent, the competent authorities can also pursue other goals (financing of health care, etc.). In this context geographical criteria or rotation system could eventually be used but they still will need to be justified, necessary and proportionate.



- Any other criteria might be chosen, provided however that those criteria are non-exclusive (meaning that at some point in time every center who meets the criteria could have statistically similar possibilities to be selected).

#### 5.2.2.2 Knowledge transfer

If the treatment offers an added value for the patients and should be used outside of the reference centres, training should be provided to colleagues. The benefits of an intervention often vary considerably due to the user interference and expertise.<sup>38</sup> *“There is often a ‘learning curve’ associated with the use of medical devices, particularly in the case of complex high-tech devices, and a need for technical training and support. This may have a major impact on the benefits for the intended patients or individuals or their health outcomes. **User interference** becomes even more crucial when a medical device is applied in a wider population than it was originally evaluated in, emphasising the need for extensive postmarketing surveillance.”*<sup>38</sup> Having an explicit approach for this knowledge transfer is desirable.

#### 5.2.3 Increase HCP’s obligations

On basis of the voluntary Covenant applied in The Netherlands, one could require HCP’s (doctors and/or hospital) to justify the implantation / use of « *novel devices, devices for which a novel technology is being used, devices belonging to a category of devices with increased serious incident rates or devices for which significant discrepancies in the conformity assessment by different notified bodies have been identified in respect of substantially similar devices* » (See EC proposal) and to keep specific records of these justifications internally. In case of incident, the patient could rely on this to sue the hospital or medical team.

Given the obligation to inform the patient of the existence of alternatives and the need to provide complete information, one could also expressly provide that in case of such use, **the informed consent of the patient include the justification for the use of a new or specific medical device** (modification of the law on patient’s rights). In reality, this is not a change as such. Any health professional must, in the present state of the law on patient’s rights, advice on the risks and benefits of his therapeutic choices. In pursuit of the basic principles mentioned by the Council of the European Union almost 10

years ago, the patient is the actor of his health care. This right expressly included in the Act on the patients’ rights of 22 August 2002, must essentially be reminded.

It should be noted in this regard that information and knowledge are intimately linked.

By the application of aforementioned Article 30 of the Law on hospitals, as it requires a personal obligation for hospitals to ensure compliance with the law on patients’ rights, the obligation of information – and therefore to obtain the relevant information – also relies on health care institutions. This may induce a strengthened commercial **pressure that the HCP and care institutions can exert on suppliers of implants to obtain – for actual use – data on the efficacy and effectiveness** of products.

Therefore, recalling the obligation for doctors to inform patients and their responsibility in this regard is part of the solution. As a result, they will have to demand sufficient data from the manufacturer of the device to cover their responsibility. In doing so, firms will, likewise, be encouraged to provide data and to be bring to the HCP elements to better understand the effectiveness of the products they implant. **Insofar as this falls within the correct and full application of the law on patients’ rights, this does not pose new constraints.** Such a measure allows to meet the need for access to information without crimping the freedom of Meddev producers, but by making use of their commercial freedom to inform (or not) their customers.

Nevertheless, in order to strengthen the effectiveness of this right, this **obligation to provide information could be rephrased**: it could be clarified that for some devices (a list would be established by the King) the practitioner should specifically **explain to the patient** – and document this in his medical records – **the reason for the choice of an innovative treatment comparing to existing alternatives**. Strengthen the information obligation for doctors should meet the requirement of necessity and proportionality. This requirement would not be particularly difficult to meet for doctors.

This obligation could be merely recalled in an administrative guideline, implemented by a specific and mandatory administrative document.

Eventually, one could implement an additional **obligation for HCP’s to anonymise and notify the implantation/use in advance and fully justify the use of this medical device** (benefits for the patients and comparison



with alternative products) to a public body. The aim of this notification would be to measure and evaluate the adequacy of the treatment:

- If this is justified and the risk is acceptable: the practitioner may implant / use
- If this is too risky: implantation / use must be supervised by a qualified practitioner working in a reference centre

Such measures are therefore also graduated. To the extent where the obligation to (usefully) inform the patient of the therapeutic options and to keep a well-documented record of the patient that already exist currently, the measure might be implemented by an informative circular to the attention of health care providers.

If, however a more specific measure must be considered, it can be done by means of an amendment of the Act on the rights of the patient, providing the possibility for the King to designate products or classes of products requiring the communication of more complete information to the patient. Such a measure poses no particular difficulties.

The determination by the King of a list of products or classes of products subject to such a measure may be more difficult: it is necessary to ensure that the determination of the list of devices concerned is based on criteria of necessity and proportionality. In this regard, it will be important to document the risk associated with this type of product.

If a prior authorization for implantation is implemented, the implantation risk should be sufficiently documented to justify this restriction to doctor's therapeutic freedom. Specifically, the King should be able to identify that this prior authorisation is not unnecessarily restrictive or, in other words, that a mere information does not prevent the risk. It should be noted, however, that such a measure is less restrictive than a general market access restriction (as it would be e.g. a safeguard measure within the meaning of the Directives on medical devices).

The HCP's obligation will however be meaningless if they have no access to the relevant information on devices. In order to inform the patient, HCP's should at least have access to the following information:

- Study design and summary report of the study results that led to the CE marking

- Incident rates and detailed information about e.g. adverse events, rehospitalizations, etc.

#### *5.2.4 Improve the use of registries and reinforce post marketing surveillance*

Mandatory and systematic use of medical devices specific registries could still be improved.

At this stage, the new implant registry set up by the Law of 15 December 2013 is a traceability tool. It was not aimed to contain more specific information to be used as a scientific analysis tool. In some countries where the registries are handled by public or private bodies in charge of a public missions, these registries can be used as scientific knowledge development tools.

If registers are well designed and used, they can help to improve the knowledge on the use of certain devices. In this regard, it is important to provide records which include both devices used for research purposes (the first three phases in the IDEAL framework, see 5.2.5) and those used for strictly therapeutic purposes (the long-term follow-up in the IDEAL framework).

Mandatory and systematic use of certain registries could be enforced in a law and in the royal decree on medical devices. This could be done on the basis of actual registries used by the reimbursement authorities or the new implant registry.

However, it should also be checked if the registries can answer the open research questions. Registries can be useful for long-term surveillance and postmarketing surveillance, but as all study designs, they have their pros and cons. One of the advantages is that registry data reflects the use of devices in the real-world setting and can contain data on large numbers of patients. Such studies are thus very useful to gather data on rare and long-term outcomes (see 5.2.5). On the other hand, the main disadvantage of a registry is that there is no control group. Such studies will have problems to demonstrate the benefit for the patient in comparison to other alternative interventions. Non-randomised studies are more prone to bias due to differences in demographic and clinical characteristics between the groups being compared and the main challenge of such non-randomised study may



be to correct for such biases to reach valid (unbiased) conclusions about the benefits of device use.<sup>38</sup>

When discussing whether a registry is the appropriate research design, one should question a.o. which evidence is needed and which study design may be used to answer this question. It should be avoided that registries are set up without any final goal. It may be expected that healthcare providers are not very happy with investing their time in filling in registries of which its usefulness may be questioned, and vice versa.

### 5.2.5 The IDEAL framework: no surgical innovation without evaluation

The value of both RCTs and registries, for different purposes, is also reflected in the IDEAL framework (<http://www.ideal-collaboration.net/>). This framework developed by a.o. surgeons, researchers and methodologists, describes the stages in the development and assessment of surgical innovations. IDEAL stands for: idea, development, exploration, assessment and long-term study (see Table 1):<sup>39</sup>

- Idea/proof of concept: when (a) surgeon(s) try out a procedure for the first time.

*“At this stage, research ethics approval is not appropriate, although full and clear informed consent is an ethical obligation for competent patients. **All new procedures should be reported automatically, whether successful or not. It is perhaps even more important to report adverse events and failures than successes, to avoid their repetition in the future. Hospitals need to be informed; however, surgeons should also report the new procedures in an online register available to all surgeons. ... These reports should contain clear anonymous details of the patient, their condition, the rationale and background for use of the procedure, exactly what was done, and adequate details of relevant outcomes.**”*

- Development: if early reports suggest benefits → early adopters may take up the innovation.

*“Involves the planned use of a procedure in an initial small group of patients (rarely more than 30 and sometimes less than ten) **to support experience with its first use and often to refine or modify the precise technique. ... we recommend that protocols for***

***prospective development studies are registered before patient recruitment begins, describing patient selection principles, operative methods, and outcomes to be measured. Protocols should be registered beyond the surgeon’s institution and should undergo some form of ethical approval. ... Learning curves are also an important issue in this phase, and clear sequential outcome reporting of all cases should be done, without omissions. Ethical considerations require that all reasonable precautions are taken to avoid harm to patients during the learning curve, including, when possible, mentoring.**”*

- Exploration/learning: understanding potential benefits and harms.
 

*“Exploration occurs **once the procedure has been described and the main technical aspects worked out.**”* In this phase, *“prospective research databases are valuable. These carefully planned, **prospective but uncontrolled clinical studies** could run as parallel additions to smaller feasibility or explanatory randomised clinical trials that might be appropriate at this stage (see Table 1). These uncontrolled studies could also be an integral preparatory stage for a major randomised trial”*
- Assessment: Is this technique better than established methods in terms of clinical efficacy and cost-effectiveness?
 

*“this stage aims to **assess effectiveness against current standards.** ... The key issue is to decide which is the best feasible comparator for the new procedure. **Randomised trials should be the default option in this stage,** but trials of surgical techniques are sometimes unnecessary,<sup>40</sup> sometimes not feasible, and sometimes might need adaptations or additional features. ... Most operations, however, are smaller advances prone to overoptimistic assessment by their developers and, therefore, need controlled randomised studies, when possible. ... randomised trials may not be feasible for ethical or pragmatic reasons, such as recruitment difficulties. In these cases, alternative designs are necessary.”*



- Long-term study/surveillance:

*“In this stage, established procedures are assessed for **rare and long-term outcomes**, and for variations in outcome. ... differences in selection criteria or in the quality of surgery or aftercare may become apparent through unexpected outcome variation between study centres. The **typical study design is a registry**. ... The value of this type of study depends on its representativeness; therefore, only key outcomes and relevant information should be obtained to encourage complete data entry.”*

*“The main focus of outcome evaluation will change with the stages, from the possibility of the intervention to the refinement and standardisation of technical details, to the potential for benefit and harm, to comparison with current practice, and finally to quality control, with outcomes focusing on long-term benefit and harms.”<sup>39</sup> There is no precise timepoint to indicate when an ‘innovation’ goes from one phase to another. However, before being widely used, a formal scientific evaluation of an innovation in comparison to existing alternatives in an appropriate research design is recommended. The IDEAL framework also stresses the **importance of “transparent reporting** of research protocol and context, and of ethical approvals to register research initiatives before patient enrolment, and to report outcomes in peer-reviewed publications. ... A lot of data for innovation (especially unsuccessful innovation) are simply not recorded at present, condemning failed innovations to be repeated by others.”<sup>39</sup>*



Table 1 – Stages of surgical innovation

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; complete information for non-RCT participants	Description; audit; regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); disease based (diagnostic)	RCT with or without additions/modifications; alternative designs	Registry; routine database (eg, SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle-term and long-term outcomes; patient-centred (reported) outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video <sup>6</sup>	Tissue engineered vessels <sup>7</sup>	Italian D2 gastrectomy study <sup>8</sup>	Swedish obese patients study <sup>9</sup>	UK national adult cardiac surgical database <sup>10</sup>

RCT= randomised controlled trial. SCOAP= Surgical Clinical Outcomes Assessment Programme. STS= Society of Thoracic Surgeons. NSQIP= National Surgical Quality Improvement Program. NOTES= natural orifice transluminal endoscopic surgery.

Source: McCulloch et al., *Lancet*, 2009<sup>39</sup>



### 5.2.6 Selection of the appropriate research design

There is no unified European regulation that imposes any specific study design. Therefore, the sponsor (where applicable) is free to determine the study design he/she finds appropriate. Ethics committees can possibly dispute the choice of a study design for the studies conducted in Belgium.

Where authorities would require one to study some elements regarding to a specific device, those authorities would therefore need to evaluate, on a case-by-case basis (or at least for specific categories), what study design is most appropriate. Further measures could therefore be implemented:

#### The Dutch example

The Dutch Royal academy of sciences has issued a report on the exploration of new technologies.<sup>38</sup> We quote from this interesting report.

*“The **committee takes the view that regardless of the type of device, evidence of some form of benefit to be gained from using the device should be addressed.** The committee has therefore introduced the overarching principle that actually drives the evaluation and regulation of any health care intervention, including medical devices: To **generate and accumulate evidence that the use of a device is not only safe but also has benefits**, preferably added benefits beyond existing care, for the health or health care of the intended individuals, patients, professionals or for society at large.”*

*“**How much evidence, however, and what form it should take may differ according to the device’s risk classification and its life cycle phase:** is it a breakthrough device that is ready for a first-in-man study, or is it the fifteenth version of a device that already has a CE marking and whose precursors are regularly being used in health care [and which already has proven its benefit to the patient]?”*

Concerning the study design, *“there is **no one-size-fits-all approach** in the realm of medical device evaluations, simply because of the wide variety of medical devices available.”* *“The challenge is thus to identify the type of*

*evidence and study approach that is required, given the specifics of the device (e.g. therapeutic or information-generating, invasive or non-invasive, requiring user interference/interpretation or not), its intended context, intended indication, and targeted individuals. However, **we strongly recommend maintaining a mental picture of the optimal randomised<sup>tttt</sup> comparative effectiveness study when designing or choosing any alternative research approaches**, to allow for valid inferences about the benefits/added benefits of device use for health or health care.”*

*“For many devices (e.g. prostheses, robots and implants), it is not possible to perform double-blind randomised studies.”* While a patient-blind trial may of course be impossible in many cases (e.g. surgical versus non-surgical approach), it can still be possible to blind an independent observer. A non-blinded observer for clear objective outcomes, like mortality or a re-hospitalisation, is of course also not a major problem. So it is correct that a double-blinded RCT is not always possible, but this does not exclude related alternatives which may minimize the risk of bias.

The Dutch report mentions numerous alternative study approaches which are also capable to answer the open research question (e.g. on efficacy/effectiveness), with their pros and cons).

- *“A **placebo or sham-controlled parallel randomised design** is the most traditional randomised design, and comes from the pharmaceutical domain. Sham or placebo-device interventions as comparison exist but are rare in device evaluations. ... a full placebo or sham-management control group can be **extremely difficult**. ... These trials deliver evidence in an environment that can be quite different from real-world, pragmatic use.”*
- *“A large-scale, long-term **pragmatic or comparative effectiveness randomised trial** compares the use of the device in question directly with the best alternative care in the right population, measuring all*

<sup>tttt</sup> *“Randomisation ensures that the groups being compared – one in which the device is used and one (or more) in which not the device but some alternative, comparative management (including placebo or sham management) is used – are created by random or chance splitting. Provided they are large enough,*

*the groups are ‘the same’ except for the device under study. All other modifying factors – the ‘confounders’ – are equally distributed across the comparison groups. Accordingly, any observed differences in benefits (and risks) between the groups can be assigned with a larger measure of likelihood to the actual difference in management, and thus to the device use.”<sup>38</sup>*

relevant outcomes over the long term and with use as it would be in everyday practice.

Pragmatic randomised trials are a specific and – for device evaluations – arguably the best form of a parallel RCT. The key feature of the pragmatic trial is that the comparison is not a placebo intervention (see below) but an alternative intervention, usually best current practice, with no restrictions on their application.

The pragmatic aspects of a trial may include, among others:

- the use of broad eligibility criteria to specifically select participants with heterogeneous characteristics, conform daily care;
- include a variety of practitioners with different expertise regarding the device use;
- include a variety of clinical settings; ...

Outcomes of pragmatic randomised trials are considered to have greater relevance for clinical practice and health policy makers.”

- **“Adaptive trials:** This novel approach is defined as ‘a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.’<sup>41</sup>

An example of the latter is that, based on observed benefits (or absence of benefits) in particular subgroups in the first series of randomised subjects, one continues the randomisation (or discontinues the trial) in those subgroups only.

The major advantage of adaptive trial designs is that they can suffice with considerably smaller sample sizes and are very efficient compared to typical randomised trials with fixed numbers of participants, thereby shortening the device evaluation process.

On the other hand, Trials may also be discontinued prematurely in error.”

- **expertise-based RCT:** this study design “randomises participants to clinicians with expertise in intervention A or clinicians with expertise in intervention B, and the clinicians perform only the procedure they are expert in.”<sup>42</sup>

In the end, “improved guidance in assessing the clinical benefit or added benefit of medical devices will lead to more clinical and statistically relevant data that can be used to inform CE-marking, uptake and reimbursement discussions.”<sup>38</sup>

The Dutch Order of Medical Specialists (OMS) and the Dutch Health Insurance Board (CvZ) issued guidelines for the safe introduction and use by professionals of new medical innovations in regular care. With this guideline, the ‘guided introduction’ of new techniques is regulated as much as possible by the healthcare providers themselves.

After completing only six steps, it is clear whether previous experiences with the new intervention exist, what the safety risks and financial risks may be, and how a plan e.g. for training and monitoring might look like. Hereafter we describe some of the main questions in this approach, which are relevant for this report. The questionnaire is much longer than what we present here and for full details, we refer to the report (in Dutch).<sup>uuuuu</sup>

Step 1: determine the **innovation class of the new intervention**

- Is this new intervention ‘experimental care’ that is not used in the Netherlands and for which (inter)national guidelines and evidence is not available?
  - if yes: refrain from local introduction and discuss approach with relevant scientific associations.

Step 2: determine the **added value of this new intervention**

- Is an evidence-based foundation available for the safety and efficacy of the new intervention? Is the added value compared to existing care (in hospital) sufficiently demonstrated?

<sup>uuuuu</sup> Dutch guidelines for the safe introduction and use by professionals of new medical innovations: Short version of the 6-steps plan: <http://kims.orde.nl/assets/structured-files/downloads/Stappenplan%20Nieuwe%20Interventies%20def.pdf>

Full report of the 6-steps plan: <http://kims.orde.nl/assets/structured-files/downloads/Leidraad%20Nieuwe%20interventies%20in%20de%20klinische%20praktijk%20def.pdf>



→ If yes, motivate this. If not sufficient supporting evidence is available, consider introduction in a research setting in consultation with the scientific association.

Step 3: determine the **risk class** based on safety, organisational issues, budget impact and financial risks

- Are the healthcare providers currently sufficiently trained/educated to apply this intervention safely? To what extent is additional training/education necessary to achieve this? How is the use monitored and are relevant characteristics registered? How are complications handled? Is there a CE marking? How are patients informed? How is this new intervention financed?
  - This will determine whether the introduction risks are low, average or high and whether the healthcare providers are capable of introducing the new intervention in a safe manner.

Step 4: determine the **general risk class** of the new intervention

- Based on 1) the safety risks associated with the introduction of the new intervention (low/average/high) and 2) The organisational risks, budget impact and financial risks (low/average/high)
  - introduce an appropriate prospective risk inventory

Step 5: develop an **introduction plan**

- Develop a training protocol and a framework for data registration and monitoring. Also inform the relevant involved stakeholders (including the Board of Directors) about the start and way of introducing the new intervention and about when progress will be discussed.

Step 6: **evaluate the outcomes**

- The introduction of new interventions should be evaluated over time (e.g. after 6 and 12 months), based on the gathered information on safety and effectiveness. The central question is whether the use of the new intervention can be maintained, should be adjusted, or even should be stopped.

This system enquires the health care practitioner to reflect on the justification of the use of a high-risk device and whether he can provide the appropriate environment to perform the procedure. This measure could/should already lead to a restriction of the number of non-evidence based high-risk medical devices and a proper selection of centres using it.

This system could indirectly force the manufacturers to be more transparent and provide the results of their studies. How else can a specialist explain to a patient that a particular intervention could be considered? Mentioning the device has a CE label is not sufficient. If the manufacturer does not provide clear information to the physician, the physician can not be well informed, nor inform his patient. If specialists do not follow the guidelines and provide full information, then they increase their liability.

This self-regulating system also provides the advantage that it acts quickly on the introduction of new devices since it is the user of the new devices that has to notify its use (if they follow the guidelines). This contrasts with government initiated horizon scanning activities, where setting up and maintaining a list of products for which there is not (yet) enough evidence might be difficult and often comes too late.

### 5.3 Final remark

The various measures proposed are all partial. They answer different parts of the issue. Their direct effect is sometimes less important than their induced effect. We believe that these measures should be seen as a whole to increase knowledge of the devices in question in order to, ultimately, set, on the basis of this knowledge, enlightened health and reimbursement policies



## ■ REFERENCES

1. Hulstaert F, Neyt M, Vinck I, Stordeur S, Huić M, Sauerland S, et al. The pre-market clinical evaluation of innovative high-risk medical devices. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. KCE Report 158C
2. Food and Drug Administration (FDA), Department of health and human services. Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US. May, 2012.
3. Van de Voorde C, Van den Heede K, Obyn C, Quentin W, Geissler A, Wittenbecher F, et al. Conceptual framework for the reform of the Belgian hospital payment system. Brussels: Belgian Health Care Knowledge Centre (KCE); 2014. Health Services Research (HSR)
4. Vinck I, Neyt M, Thiry N, Louagie M, Ghinet D, Cleemput I, et al. An evaluation procedure for the emerging medical technologies [In Dutch: Een procedure voor de beoordeling van nieuwe medische hulpmiddelen]. Brussels: Belgian Health Care Knowledge Centre (KCE); 2006. Health Technology Assessment (HTA) KCE reports 44A
5. Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. *BMJ*. 1999;319(7211):652-3.
6. Hines JZ, Lurie P, Yu E, Wolfe S. Left to their own devices: breakdowns in United States medical device premarket review. *PLoS Med*. 2010;7(7):e1000280.
7. Jefferys DB. The regulation of medical devices and the role of the Medical Devices Agency. *Br J Clin Pharmacol*. 2001;52(3):229-35.
8. Cohen D, Billingsley M. Europeans are left to their own devices. *BMJ*. 2011;342:d2748.
9. Heneghan C, Thompson M, Billingsley M, Cohen D. Medical-device recalls in the UK and the device-regulation process: retrospective review of safety notices and alerts. *BMJ Open*. 2011;1(1):e000155.
10. Thompson M, Heneghan C, Billingsley M, Cohen D. Medical device recalls and transparency in the UK. *BMJ*. 2011;342:d2973.
11. Roszek B, de Bruijn A, Pot J, van Drongelen A. Assessment of technical documentation of Class III medical devices. National Institute for Public Health and the Environment, The Netherlands (RIVM); 2010. Report 360050021/2010 Available from: [www.rivm.nl](http://www.rivm.nl)



12. Challoner D. Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years. Institute of Medicine; November 15, 2011.
13. Challoner D. letter to Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process. July 20, 2011.
14. Zuckerman DM, Brown P, Nissen SE. Medical device recalls and the FDA approval process. *Arch Intern Med.* 2011;171(11):1006-11.
15. Kramer DB, Xu S, Kesselheim AS. How does medical device regulation perform in the United States and the European union? A systematic review. *PLoS Med.* 2012;9(7):e1001276.
16. Gollaher DL, Goodall S. Competitiveness and regulation: the FDA and the future of America's biomedical industry. Boston Consulting Group; 2011 February. Available from: <http://www.bcg.com/documents/file72060.pdf>
17. Basu S, Hassenplug JC. Patient access to medical devices--a comparison of U.S. and European review processes. *N Engl J Med.* 2012;367(6):485-8.
18. Bakris GL, Townsend RR, Liu M, Cohen SA, D'Agostino R, Flack JM, et al. Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. *J Am Coll Cardiol.* 2014;64(11):1071-8.
19. EUnetHTA WP5 Joint Action 2 Strand B. Renal denervation systems for treatment-resistant hypertension: Pilot rapid assessment of other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment.
20. Sciruba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med.* 2010;363(13):1233-44.
21. Van Brabandt H, Neyt M. Endobronchial valves in the treatment of severe pulmonary emphysema: a rapid Health Technology Assessment. Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. Health Technology Assessment (HTA) KCE reports 114C
22. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* 2011;365(11):993-1003.
23. Bose A, Hartmann M, Henkes H, Liu HM, Teng MM, Szikora I, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. *Stroke.* 2007;38(5):1531-7.
24. Gartenberg AJ, Peleg A, Dhruva SS, Redberg RF. Presumed safe no more: lessons from the Wingspan saga on regulation of devices. *BMJ.* 2014;348:g93.
25. Neyt M, Van Brabandt H, Van de Sande S, Devriese S. Health Technology Assessment. Transcatheter Aortic Valve Implantation (TAVI): a Health Technology Assessment Update. Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. Health Technology Assessment (HTA) KCE Reports 163C
26. Van Brabandt H, Neyt M, Devos C. Catheter ablation of atrial fibrillation. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2012. KCE Report 184C
27. Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. *BMJ Open.* 2012;2(3).
28. Van Brabandt H, Neyt M, Devos C. Effectiveness of catheter ablation of atrial fibrillation in Belgian practice: a cohort analysis on administrative data. *Europace.* 2013;15(5):663-8.
29. Neyt M, Van Brabandt H, Devos C. The cost-utility of catheter ablation of atrial fibrillation: a systematic review and critical appraisal of economic evaluations. *BMC Cardiovasc Disord.* 2013;13:78.
30. Cohen D. How a fake hip showed up failings in European device regulation. *BMJ.* 2012;345:e7090.
31. McCulloch P. The EU's system for regulating medical devices. *BMJ.* 2012;345:e7126.
32. Cohen D. Manufacturers offered helping hand with EU approval. *BMJ.* 2012;345:e7225.



33. Cohen D. Notified bodies: are they fit for purpose? *BMJ*. 2012;345:e7177.
34. Cohen D. Faulty hip implant shows up failings of EU regulation. *BMJ*. 2012;345:e7163.
35. Kmietowicz Z, Cohen D. Device licensing bodies sometimes put business before safety, an investigation finds. *BMJ*. 2012;345:e7138.
36. Heneghan C. The saga of Poly Implant Prothese breast implants. *BMJ*. 2012;344:e306.
37. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33(19):2451-96.
38. KNAW. Evaluation of new technology in health care: In need of guidance for relevant evidence. Amsterdam: Koninklijke Nederlandse Akademie van Wetenschappen; 2014.
39. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet*. 2009;374(9695):1105-12.
40. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ*. 2007;334(7589):349-51.
41. U.S. Food and Drug Administration. Draft Guidance for Industry: adaptive design clinical trials for drugs and biologics. Available from:  
<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>
42. Devereaux PJ, Bhandari M, Clarke M, Montori VM, Cook DJ, Yusuf S, et al. Need for expertise based randomised controlled trials. *BMJ*. 2005;330(7482):88.