



Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform

Report of a policy conference of the European Society of Cardiology[†]

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The European Commission announced in 2008 that a fundamental revision of the medical device directives is being considered in order to clarify and strengthen the current legal framework. The system for testing and approving devices in Europe was established >20 years ago as a 'New Approach' to a previously little-regulated industry. It is recognized by many that the regulatory system has not kept pace with technological advances and changing patterns of medical practice. New legislation will be drafted during 2011, but medical experts have been little involved in this important process. This context makes it an opportune time for a professional association to advise from both clinical and academic perspectives about changes which should be made to improve the safety and efficacy of devices used in clinical practice and to develop more appropriate systems for their clinical evaluation and post-marketing surveillance. This report summarizes how medical devices are regulated and it reviews some serious clinical problems that have occurred with cardiovascular devices. Finally, it presents the main recommendations from a Policy Conference on the Clinical Evaluation of Cardiovascular Devices that was held at the European Heart House in January 2011.

Keywords Medical devices • European device directives • Recast of legislation • Premarket approval • Post-marketing surveillance

Introduction

A medical device is defined as 'any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human

beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease...'¹

The use and complexity of diagnostic and therapeutic devices is increasing, particularly in cardiovascular medicine, and expenditure on devices contributes significantly to the escalating costs of health care. The medical device sector in Europe has grown to >11 000 companies, which employ more than half a million people and have

[†]This report presents a summary and the consensus conclusions from the Policy Conference organized by the European Society of Cardiology (ESC) and held at the European Heart House on 27–28 January 2011. It does not necessarily reflect the opinions of individual participants.

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[‡]The list of participants are given in the appendix section. Anker SD, Auricchio A, Bailey S, Bonhoeffer P, Borggrefe M, Brodin L-Å, Bruining N, Buser P, Butchart E, Calle Gordo J, Cleland J, Danchin N, Daubert JC, Degertekin M, Demade I, Denjoy N, Derumeaux G, Di Mario C, Dickstein K, Dudek D, Estes NA, Farb A, Flotats A, Fraser AG, Gueret P, Israel C, James S, Kautzner J, Komajda M, Krucoff MW, Lombardi M, Marwick T, Mioulet M, O'Kelly S, Perrone-Filardi P, Rosano G, Rosenhek R, Sabate M, Smith SC, Swahn E, Tavazzi L, Van de Werf F, van der Velde E, van Herwerden L, Vardas PE, Voigt J-U, Weaver D and Wilmshurst P.

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combined annual sales of >€72 billion.² Estimates of the total number of medical devices range upwards from 200 000. There is a clear need for safety and performance to be established before new medical devices are approved but there is a fundamental tension between providing high-level clinical evidence and promoting innovation. Rational practice with minimal inappropriate use is in the interests of patients and providers, and clinical safety must come first.

It can be argued that the manufacturers of devices used in medicine have the same ethical responsibilities to the individual patient, as have those companies which manufacture and sell drugs. Many principles of regulatory approval are similar—such as an evaluation of risks and benefits—but the processes by which devices and drugs are governed within Europe vary greatly.

The European Medicines Agency (EMA) was established in 1995. Its main responsibility is the protection of public health through the scientific evaluation and supervision of medicines. Companies can submit a single application to the EMA for authorization by the European Commission (EC) and marketing throughout Europe. The Committee for Medicinal Products for Human Use is responsible for conducting the initial assessment of medicines for which an European Union (EU)-wide marketing authorization is sought; it has a Cardiovascular Working Party. The EMA is also responsible for pharmacovigilance and for coordinating national authorities. It works with a network of >4500 European experts. In general, proof of safety and clinical efficacy is required from randomized trials before a new drug can be introduced. The manufacturer of a generic version of an existing drug must produce a virtually identical compound 'with the same qualitative and quantitative composition in active substance(s)', 'the same pharmaceutical form', and demonstrated 'bioequivalence to the reference product',³ before it can be marketed.

The regulation of medical devices is the responsibility of the 27 Member States of the EU, each of which has its own national 'competent authority'. Many national authorities have combined responsibilities for overseeing both drugs and devices, but there is no single, common European agency for assessing devices; the main role of the EC is advisory. For approval, manufacturers must satisfy the relevant 'essential requirements' of safety and performance but they do not always need to establish that their medical device has an impact on clinical outcomes, even if it is a completely new technology. If an equivalent device does exist, then a new device once approved can be marketed as an alternative without the manufacturer being required to prove in head-to-head comparisons that its clinical effectiveness is similar.

The system for testing and approving devices in Europe was established >20 years ago as a 'New Approach' to a previously little-regulated industry. It is recognized by many that the regulatory system has not kept pace with technological advances and changing patterns of medical practice. In 2008, the EC announced that a fundamental revision is being considered,⁴ in order to clarify and strengthen the current legal framework. Producing one common document from many existing texts will also simplify the legislation and meet a commitment of the Treaty of Lisbon which came into force in December 2009. The recast will be a joint decision for the Council of Ministers and the European Parliament, on the basis of a proposal adopted by the College of

Commissioners and drafted by the Cosmetics and Medical Devices Unit of the EC, which moved in 2010 from being part of the Directorate General for Enterprise and Industry (DG ENTR) to the Directorate General for Health and Consumer Affairs (DG SANCO).

This context makes it an opportune time for the medical profession to advise from both clinical and academic perspectives about changes which should be made to improve the safety and efficacy of devices used in clinical practice and to develop more appropriate systems for their clinical evaluation and post-marketing surveillance (PMS).

Background: current regulations

European Union

Rules relating to the safety and performance of medical devices were harmonized in the EU in the 1990s, with the adoption of directives concerning Active Implantable Medical Devices (1990),⁵ other Medical Devices (1993),⁶ and *In Vitro* Diagnostic Medical Devices (1998).⁷ These three main directives have been transposed into the national laws of EU Member States. After the EC decided in 2005 that the medical device directives needed revision,⁸ they were supplemented in 2007 by a modifying directive which introduced new essential requirements and recommendations concerning clinical evaluation and vigilance,¹ and in 2009 by an amendment concerning common technical specifications for *in vitro* diagnostic medical devices.⁹ This main legal framework is complemented by non-binding guidance (called MEDDEV documents)^{10–12} including consensus statements and interpretative documents which aim to ensure uniform application of the relevant provisions of the directives within the EU. The system is shared by another five countries in the European Economic Area (EEA) and the European Free Trade Association (EFTA) with which the EC has signed a free trade agreement.

Devices are assigned to four groups according to risk¹³ and these relate to different levels of testing and evidence that are needed before they are approved. For low-risk cardiovascular devices in Class I, ranging from stethoscopes to cooling jackets for patients who have suffered a cardiac arrest, generally little evaluation is needed before the device is placed on the market; the manufacturer is allowed to self-declare conformity with the essential requirements, affix a CE mark, and register its product with a competent authority. Class IIa includes devices for monitoring blood pressure, and diagnostic equipment for magnetic resonance imaging, ultrasound scanning, and nuclear studies using gamma cameras or positron emission tomography. Class IIb includes other diagnostic radiology equipment such as X-ray machines. Class III, the highest risk group, includes invasive or implantable devices such as coronary stents, prosthetic heart valves, pacemakers, implantable defibrillators, and devices and leads for resynchronization therapy.

Any manufacturer wishing to obtain approval to market a new device in a medium- or high-risk group (classes IIa, IIb, III)¹³ must undergo a 'conformity assessment procedure' involving one or more Notified Bodies (NBs). The manufacturer must demonstrate safety and conformity with the legal requirements contained in the

first annexes of the three directives. To do this, the manufacturer may refer to relevant technical standards such as those from the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC).¹⁴ In most instances, these mirror the standards from the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). Effective performance of the device for its intended purpose (as claimed by the manufacturer) needs to be demonstrated. The precise definition of the designated task of any device, therefore, is a key decision for each manufacturer. It can be argued that this process encourages the manufacturer to keep its claims for a device as simple as possible.

The clinical data used for CE marking may be a critical evaluation of the relevant scientific literature currently available relating to the design characteristics, intended purpose, safety, and performance of a device, when it is demonstrated to be equivalent to another device which already complies with relevant essential requirements and for which there are data. Alternatively, the manufacturer may present a critical evaluation of the results of all reported clinical investigations that have addressed residual safety concerns.^{10,15} For devices in Class III, the manufacturer must conduct some human clinical investigations, but it is not compulsory that these are randomized clinical trials.

Notified Bodies

A medical device company is free to approach any NB in Europe that has been designated for the respective 'conformity assessment procedure' (Figure 1). This process has given rise to suspicions that companies may go 'forum shopping' to select the NB that will conduct the least burdensome or the fastest review, but no systematic audit of the NBs has been published. Since 1985, a NB

has been any organization designated to assess if manufactured products conform with the requirements of any EU new approach directive; the website of the Enterprise and Industry Directorate-General listed 2271 NBs in January 2011. Of these, 74 were approved to evaluate medical devices, including some organizations located outside the EU;¹⁶ several NBs have been approved to evaluate all medical devices. Most NBs are independent commercial organizations, and they are supported in part by the fees paid by device companies. Notified Bodies are designated, monitored, and audited by the competent authorities of the member state in which they are based.

The duties of a NB are to review the technical dossier submitted by the manufacturer, to assess the manufacturer's quality management system, and to evaluate any evidence that has been submitted from laboratory, animal, and clinical studies. The manufacturer submits a sample of the device under review, and the NB may conduct direct testing especially if it is an active medical device. The NB may also visit the manufacturer to inspect the production process and quality control. If these tests are judged satisfactory, then the NB issues a certificate (which is valid for a maximum of 5 years before renewal) and the manufacturer can affix the CE mark (Figure 1). Thereafter, the device can be marketed throughout the EU.

Some NBs also function as national standards institutes and their division with this responsibility may participate in writing ISO standards. In addition, national competent authorities have specified that NBs, as part of their contract, should participate in the vigilance (or PMS) of medical devices, in which case they receive reports of adverse incidents. Reports are also transmitted together with the proposed 'Field Safety Corrective Action' (FSCA) by the manufacturer to the competent authority which is responsible for

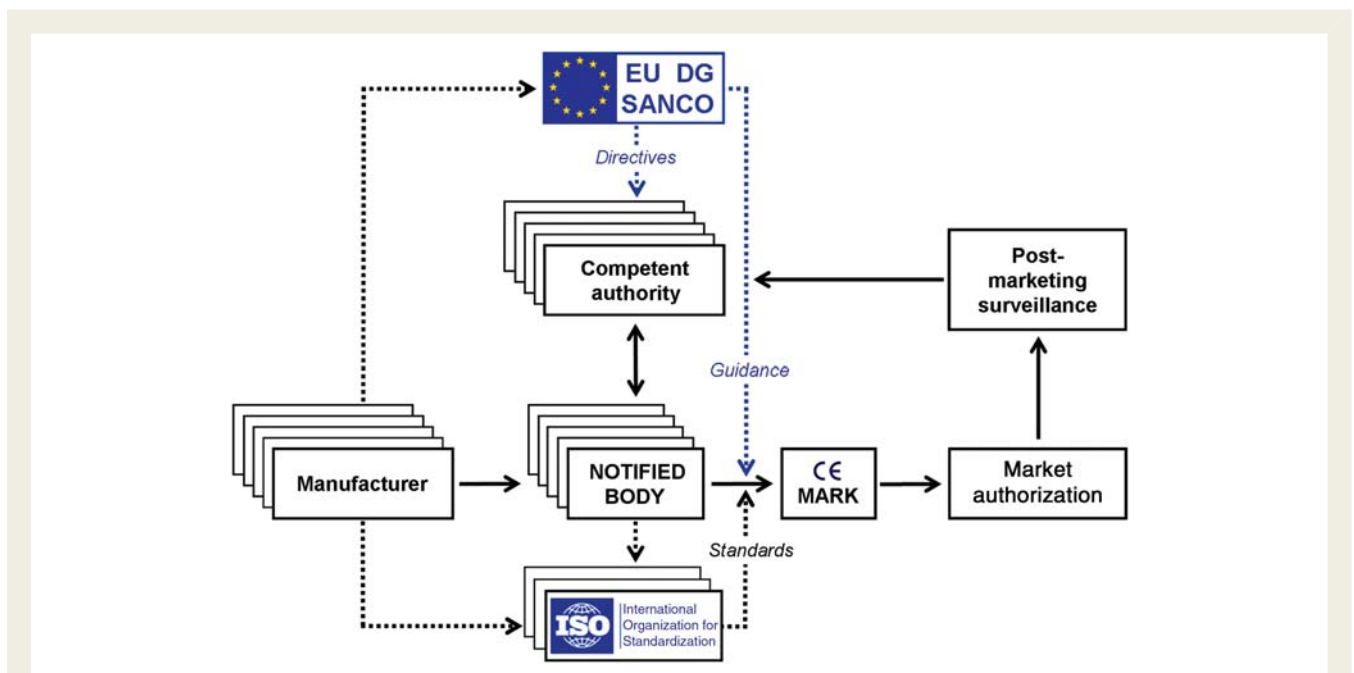


Figure 1 Summary of the major steps in the current regulatory framework for approving medical devices in Europe. Solid lines denote formal requirements; dotted lines represent guidance or advice. DG SANCO = Directorate General for Health and Consumer Affairs.

their review. If a device needs to be removed from the market, it is the responsibility of the NB to suspend its certificate.

Coordination

The Committee on Medical Devices, organized by the EC and composed of representatives of the Member States, has specific regulatory powers for the device directives. Policy is coordinated by the Medical Devices Experts Group (MDEG) which is said to 'encompass all stakeholders'.¹⁷ Its members include representatives from trade federations, CEN, CENELEC, NBs, and patients' organizations. There are currently no members from European medical associations, although the EC states that they have previously been invited.

The Notified Bodies group (NB-MED) and the Notified Bodies Operation Group (NBOG) were established by the EC to improve cooperation and performance of the NBs with the competent authorities in the medical devices sector.

The European Databank on Medical Devices (Eudamed) was created in 1998 to allow Member States to strengthen PMS by exchanging information about adverse events related to the use of medical devices. Reporting will become mandatory from May 2011.¹⁸ Competent authorities will have rapid access to the database which will include names of registered manufacturers, data relating to certificates, and reports from vigilance procedures with the findings of clinical investigations. The European Databank on Medical Devices will implement the Global Medical Device Nomenclature (GMDN) code; there is also a GMDN Agency, established under the auspices of CEN. There is no plan to open the contents of Eudamed to the public.

The USA

In the USA, the evaluation and approval of medical devices is the responsibility of the Food and Drug Administration (FDA) through its Center for Devices and Radiological Health (CDRH), which has a Division of Cardiovascular Devices. As in Europe, devices are categorized by risk into three classes, and higher levels of evidence including clinical evidence are required for approval of devices in Class III. In addition to internal regulatory review by FDA personnel, advice is often sought from external, independent experts through well-established Medical Devices Advisory Committees (including a Circulatory System Devices Advisory Panel),¹⁹ for example, for first-of-a-kind devices and for devices that are expected to have a broad impact on public health. This provides a transparent mechanism for public review of issues relating to the approval of complex devices.

Low-risk devices (class I) are approved by registration, after compliance with general controls such as regulations for good manufacturing practice. More complex, moderate-risk devices (class II) require additional special controls, such as specific labeling, compliance with requirements in guidance documents, device tracking, and design controls. The regulatory pathway for class II products is through the Premarket Notification ['510(k)'] programme, which is the pathway through which most medical devices are marketed. A manufacturer submits a 'premarket notification' asserting that their new device is substantially equivalent (i.e. at least as safe and effective) as one ('the predicate') that is already legally on the market. If the FDA determines that the

information and performance testing demonstrate that this is the case, then the device can be marketed in the USA. Ten to 15% of 510(k) submissions require data from human clinical studies to supplement preclinical testing.

High-risk devices (class III) follow the regulatory pathway for premarket approval (PMA). This requires a comprehensive evaluation including bench testing, preclinical animal studies, and clinical data, so that the device demonstrates a reasonable assurance of safety and effectiveness. The term 'effectiveness' means that the device will provide clinically significant benefits, and thus evaluation focuses on clinical outcomes such as a reduction in symptoms or adverse events. In contrast, 'performance' (a standard EU regulatory parameter) focuses on a device's mechanism of action such as enlargement of the arterial lumen or enhanced myocardial blood flow. Clinical data for a PMA are typically obtained from feasibility studies followed by a larger, 'pivotal' trial. In order to conduct a clinical trial in the USA to assess the safety and effectiveness of a 'significant risk' device and thereby provide evidence that will support a PMA or 510(k), the sponsor must obtain FDA approval of an Investigational Device Exemption (IDE).

In general, regulatory reviews by the FDA incorporate more detailed technical standards and requirements for clinical evaluation of devices than occurs in Europe, and they are more rigorous. Preclinical testing plays a more important role, with questions regarding long-term durability and local and systemic histopathological responses being addressed in bench and animal studies. Since the FDA requires adequate preclinical safety data before the initiation of human trials, there may be a lag of several years after the introduction of some devices for clinical use within Europe before they are used in patients in the USA. Many US companies first get approval for their new medical devices in the EU and then use 'OUS' (outside the USA) data relating to safety and effectiveness to support the initiation of a pivotal IDE study at US study sites.

In a recent decision, the US Supreme Court judged that the manufacturer of a medical device could not be sued by a patient on the basis of alleged defects relating to its safety because the device had received PMA from the FDA.²⁰ The consequences of this decision are still unclear; for example, it is uncertain if it may encourage manufacturers to submit more detailed claims for devices when applying for regulatory approval.

For permanently implanted class III devices such as coronary stents and devices for occluding intracardiac shunts, the FDA typically requires 5 years of clinical follow-up. Post-approval clinical studies that collect and report real-world outcomes associated with the use of novel devices are also commonly required. The FDA has had a policy of 'global transparency' since 1994 and all medical device reports (MDRs) concerning significant adverse events are available on the Internet.

United States and OUS device manufacturers can meet with FDA staff at multiple times during the development of a device, through the CDRH's Pre-Submission Program. These informal meetings are particularly useful for the sponsors and the FDA to reach consensus on preclinical device testing, key elements of IDE clinical trials, and requirements for PMA submissions. The 510(k) program has been reviewed by the Institute of Medicine²¹ and it is being reviewed by the FDA. Recommendations which

will aim to raise standards by incorporating more scientific advice and objective appraisal are expected in the near future.²²

International comparisons

The clinical safety and efficacy of a medical device is less likely to vary between countries when it is used for the same indication in patients with the same condition, than may occur with drugs that are metabolized, but it may be affected by the experience of the physician. Nonetheless, from a clinical perspective, substantial variations in requirements for its approval may be illogical. Although there is no international legal basis for coordinating the scrutiny of medical devices, a voluntary collaboration between the national regulatory authorities in Europe, Japan, Australia, the USA, and Canada was established in 1992, called the Global Harmonization Task Force (GHTF). Its objective is to share experience between competent authorities of their varying approaches to the regulation and control of medical devices and to encourage convergence towards common essential principles of their evaluation. The GHTF has a study group on clinical safety and performance which has published recommendations concerning clinical evaluation (2007),²³ clinical investigation of devices before approval (2010),²⁴ and clinical follow-up studies (2010).²⁵ The vice-chair of each GHTF committee has come from industry.

The organization and membership of the GHTF are being reviewed.²⁶ It has been noted that uniform implementation of the recommended common models of governance has not been achieved. Since a meeting in February 2011, the regulators have announced that they will seek a regulator-led group with the task of increasing coordination and harmonization. Not just industry, but healthcare professional groups, academics, and consumers will be consulted as appropriate.

Two other international collaborations of regulatory authorities, the Asian Harmonization Working Party (AHWP) whose >20 members include China and India, and the Latin American Harmonization Working Party (LAHWP), work in conjunction with the GHTF.

The Technical Committees of ISO produce international standards for medical devices.²⁷ TC210 on quality management is coordinating its work with the GHTF. TC194 (biological evaluation of medical devices) publishes ISO Standard 14 155 concerning clinical investigations of medical devices.²⁸

Whether or not a device is used or its use is reimbursed after its safety, and clinical performance or efficacy, have been established, depends on national health-care systems and varies according to local circumstances. Availability may be influenced by decisions taken by national bodies responsible for health technology assessment; 34 such agencies from countries within the EU, EEA, and EFTA, collaborate through the European Network for Health Technology Assessment (EUnetHTA) to share knowledge and promote good practice in their methods and processes.²⁹ There is overlap between these bodies and the regulatory authorities, since the core model for health technology assessment lists criteria that include safety and clinical effectiveness.³⁰

The World Health Organization has published two important papers concerning medical devices—a global overview of regulations, in 2003,³¹ and most recently, in 2010, a call for improving access to medical devices in poorer nations.³² The common framework for medical device regulations mentions safety, performance,

and vigilance, but not clinical trials.³¹ In 2007, the World Health Assembly noted the need to expand expertise in medical devices, and it called for regional guidelines on regulatory practices 'to ensure the quality, safety and efficacy of medical devices and where appropriate participation in international harmonization'.³³ It organized the first global forum on medical devices, in 2010. The strategic plan of WHO includes the objective 'to ensure improved access, quality and use of medical products and technologies'.³⁴

Europe, the USA and Japan account for 89% of the world market for medical devices.² This is likely to change, but at present, countries with minimal resources to purchase devices probably have similarly scarce resources to evaluate them. Proper evaluation could reasonably be a responsibility of those countries with a disproportionate share per capita of the use of devices. One of the four principles of the current EU strategy for health is to offer 'sustained collective leadership in global health... by sharing its values, experience and expertise...'.³⁵

Lessons from clinical experience

Medical devices have been hugely beneficial for countless patients, but some well-publicized failures of cardiovascular devices causing clinical problems have prompted concerns about the adequacy of current standards for evaluation before approval. There have also been examples of the rapid clinical uptake of devices that were later proved to be ineffective or harmful. Examples are discussed below, and possible contributory factors relating to regulatory processes are listed in *Table 1*.

Heart valves

In 1980 (before the European device directives were adopted), Shiley, Inc., modified their Björk–Shiley Convexo–Concave heart valve by increasing its opening angle to 70°. The valve was withdrawn in 1983 after catastrophic failures had been observed that were caused by spontaneous fracture of the outlet strut that held the occluder in place.^{36,37} The increased risk was at least three-fold, compared with the previous design,³⁶ and the absolute risk was ~0.7%.³⁸ Detailed investigations traced the cause back to a change in the manufacturing process. Similar valve failure had occurred during the premarket trial of the valve but permission was given by the FDA for the valve to be exported from the US manufacturing site, as the first valve failure was believed to be an isolated case³⁹ and other available data suggested that it was safe and effective. Subsequently, mortality rates in patients with strut fracture of up to 84%⁴⁰ led to recommendations for patients in high-risk groups to undergo elective explantation and re-replacement.^{40,41} In retrospect, prolonged accelerated wear testing of the valve in a pulse duplicator might have revealed the problem, because detailed examination of explanted valves showed serious prefracture defects in 32% that increased with the duration of implantation.⁴² In the USA, the 70° valve was never approved by the FDA, and the 60° Convexo–Concave valve which had received FDA approval was withdrawn also due to strut fracture.

In 1997, the St Jude heart valve was modified by impregnating its sewing ring with silver, which has antibacterial properties *in vitro*. The new model of this valve, called the Silzone valve, was taken

Table 1 Some lessons learned from clinical experience of cardiovascular devices**Heart valves**

Animal models dissimilar from human, insufficiently predictive⁴⁵
 Inadequate bench testing of mechanical properties^{36,42}
 Incomplete assessment of fluid mechanical properties^{47,48}
 Approval of changes as iterative that proved to be substantial^{36,39,43,44}

Percutaneous coronary interventions

Clinical application of concept that was not proved^{60,66,80}
 Use of unblinded studies with significant placebo effect⁸⁰
 Over-reliance on composite end-points⁷¹
 Overuse of equivalence for CE marking without new pivotal trials^{57–60}
 Devices not taken off market when negative long-term outcome trials reported^{65,81}

Diagnostic imaging

No standard industry-wide phantoms for some imaging modalities
 No reporting of diagnostic accuracy and reproducibility by manufacturers
 No requirements for manufacturers to present normal values

Cardiovascular implantable electronic devices

Need for long-term registries conducted independently from industry^{106,118}
 Incomplete capture of clinical events by registries with voluntary reporting
 Need for rapid and open access to reports of device failures^{110,111}

Closure of patent foramen ovale

Early CE marking leading to rapid adoption before proven clinical benefit
 Failure by physicians to enrol patients in trials^{124,125}

off the market after the AVERT trial reported paraprosthetic regurgitation in 8.9% of patients at 2 years, compared with 1.1% in patients receiving the standard model.⁴³ The Silzone valve was also associated with a high incidence of valve thrombosis and thromboembolism.^{43,44} It has since been recognized that toxic biological properties of silver prevented normal tissue ingrowth and endothelialization of the sewing ring, but this problem had not been revealed by reports from a small preliminary animal study.⁴⁵ At the time of its recall, the manufacturer estimated that 36 000 Silzone valves had already been implanted.⁴⁶

In these cases, changes to the design of a valve had been approved without evidence from prospective clinical trials, on the basis that they were minor modifications. A third mechanical prosthesis, the Medtronic Parallel valve, was also withdrawn from the market after early incidents of thrombosis, in this case related to pockets of stasis. Valve thrombosis might have been predicted by fluid dynamic computational simulations and *in vitro* studies,^{47,48} before human implants, but the patterns of retrograde flow through the hinge pockets had not been studied. The Parallel valve was neither studied nor approved in the USA; it was evaluated in 16 European centres.

Gersh et al.⁴⁹ identified the need for common standards for evaluating heart valves and subsequent authors suggested alternatives to randomized trials.^{50,51} In 1994 the FDA responded by issuing 'objective performance criteria' for heart valves.⁵² More recently, experts have revised recommendations for the evaluation of valve performance and the reporting of complications.⁵³ Recommendations for reporting endpoints in clinical trials of transcatheter aortic valve implantation (TAVI) have also been published⁵⁴ and endorsed by the FDA.⁵⁵

Percutaneous interventions for coronary artery disease

The initial success rate of balloon coronary angioplasty was ~63%, and the procedure was first approved by the FDA after 60 patients had been treated for 6 months.⁵⁶ In early series, >10% of patients required emergency bypass surgery and there were many deaths. It would have been very difficult to get such approval, either in the USA or in Europe, if angioplasty had had to be tested against surgery while the technology was in its infancy. Early approval gave an impetus to technological developments in interventional cardiology and to many important randomized clinical trials in Europe, resulting in a highly effective treatment that reduces morbidity and mortality.⁵⁷ Nonetheless, several scores of coronary stents have received a CE mark and are available within Europe, in spite of the fact that only six drug-eluting stents have been proved to be effective by meeting primary clinical endpoints in pivotal trials.⁵⁷ Long-term results (≥ 5 years) are available for only three stents.⁵⁷ It has been recommended that market access should be based on efficacy⁵⁸ but many stents have been approved on the basis of technical equivalence rather than clinical outcomes. In some countries, reimbursement is limited to proved devices but in others, doctors may be asked to use cheaper stents even when proof is lacking.

It cannot be assumed that either bare metal or drug-eluting stents are all similar.^{58,59} For example, the Niroyal stent was gold plated in order to enhance its opacity on radiographic screening. It was given a CE mark in May 1999 without a pre-marketing clinical trial. A registry reported in 2000 that it gave excellent primary angiographic success rates, and event rates at 6 months were lower than reported in other series.⁶⁰ A randomized trial, however, showed a smaller minimal luminal diameter and a higher late loss.⁶¹ The adverse effects of gold plating were confirmed independently by other investigators.⁶²

Directional coronary atherectomy was evaluated between 1988 and 1990 under an IDE. The device was approved by the FDA in September 1990 on the basis of a primary success rate of 85%, although one or more major complications occurred in 4.9% of procedures and the restenosis rate at 6 months was 42%.⁶³ In the CAVEAT study, the new technique had a higher rate of early complications (11%) and it conferred no significant benefit over balloon angioplasty alone at 6 months.⁶⁴ One-year follow-up revealed an increase in mortality at 2.2% in the atherectomy group compared with 0.6% in controls.⁶⁵ The device was withdrawn from the market for commercial reasons rather than because of regulatory decisions. An estimated 177 000 patients were treated worldwide.⁶⁶

The first clinical use of intracoronary beta or gamma irradiation (brachytherapy) to prevent or treat restenosis after balloon angioplasty was reported from a Swiss pilot study of 15 patients in 1997.⁶⁷ The investigators obtained informed consent from their patients after the protocol had been approved by the hospital Ethics Committee, but there is no reference in their manuscript to regulatory issues or approval for use of a prototype device. A similar clinical pilot study of 23 patients was reported from the USA in 1998 by investigators who had obtained an IDE.⁶⁸ In early clinical trials, brachytherapy was reported to reduce restenosis within a stent but it increased stenosis at the stent margins by up to four-fold.^{69,70} After two more trials^{71,72} the FDA approved brachytherapy in 2001 for the treatment of in-stent restenosis, but with conditions because of reports of thrombosis particularly when anti-platelet treatment was discontinued.⁷³ By this time, small animal models had already revealed incomplete healing with poor endothelialization⁷⁴ and edge effects.⁷⁵ A registry of 1098 patients from 46 centres reported good results and showed considerable adoption of the new technique in Europe.⁷⁶ Further randomized controlled trials, however, confirmed that both the early and late results of brachytherapy were worse than standard therapy⁷⁷ or therapy with drug-eluting stents.^{78,79} This discrepancy between registries and randomized trials highlights the importance of independent PMS studies with centrally adjudicated and monitored adverse events.

The rationale proposed for laser myocardial revascularization was that creating multiple pits in ischaemic myocardium with a laser beam would promote the formation of collateral channels or new vessels. The concept was developed as a surgical technique and evolved towards percutaneous delivery. In an initial unblinded trial, 221 patients were randomized to laser or continued medical treatment.⁸⁰ Patients treated with laser revascularization had improved exercise tolerance at follow-up but more deaths than controls. The technique was used in a limited number of centres, mainly because of its cost, until a later blinded trial of 298 patients in which controls underwent a sham procedure, showed no functional benefit and increased early complications in laser-treated patients.⁸¹ Percutaneous laser revascularization was not approved by the FDA. Recent UK guidance concluded that it was ineffective, had unacceptable risks, and should not be used.⁸² Some laser systems are still commercially available, however, and occasionally used during surgery.

When detailed professional recommendations are produced, there is some evidence that these are taken up by regulators. The 2007 report of the Academic Research Consortium on clinical endpoints in coronary stent trials⁸³ was cited in regulatory guidance published by the EC in 2008.⁸⁴ An earlier expert document⁸⁵ and a more recent consensus conference on drug-eluting stents, both organized by the ESC, had no official status but established a useful model of dialogue between clinical investigators, regulators, and industry.⁵⁸ It was recommended that the EC should produce uniform standards in a guidance document⁵⁸ but this has not yet been done, perhaps because the EC does not have the authority or responsibility to commission such standards. Recent authors have advocated a balance between the more detailed assessment conducted by the FDA and the more rapid response to innovations that is possible in Europe.⁸⁶

Diagnostic imaging

Medical imaging has the highest growth rate within the health-care sector (~10% per year)^{87,88} but it may be the least supported by objective data—for example, only 4.8% of the recommendations included in guidelines for radionuclide imaging from the American College of Cardiology and the American Heart Association are supported by evidence from multiple randomized clinical trials⁸⁹ although these have been recommended as the desired method for establishing the clinical efficacy of diagnostic devices.⁹⁰

The hardware and software used by any company in an imaging system may be considered as intellectual property and protected by patents. If another company wishes to offer its customers equivalent diagnostic tools, it must produce its own (quite possibly unique) solutions to the engineering challenges, including decisions about how the raw signals are obtained, processed, and smoothed, as well as how they are displayed. There is a single industry standard for exporting images (digital images and communication in medicine—DICOM) that is coordinated by the Association of Electrical and Medical Imaging Equipment Manufacturers (NEMA) in the USA. DICOM is designed so that images from one machine can be viewed on other systems, but it has not been adapted for all new methods (such as real-time acquisition of 3D images) or fully applied by all manufacturers, and thus complete interoperability remains elusive.

It is increasingly apparent that detailed measurements obtained using the diagnostic equipment of one manufacturer may vary substantially from the same measurements obtained in the same patient by using a similar machine from a different manufacturer^{91,92} or by using a different imaging modality for the same purpose.^{93–97} In the PROSPECT trial, echocardiography was used to try to identify responders to cardiac resynchronization therapy (CRT); six different machines and more than six versions of software were used, from six companies, and the analyses were performed in three core laboratories.⁹⁸ Although the rationale for the study was logical, the results were negative, perhaps because of wide inter-centre and inter-machine variability in measurements.

Calls are now being made for more formal evaluation and regulation of imaging technologies, such as CT scanning⁹⁹ and magnetic resonance imaging. There is a need to consider the impact of ionizing radiation, especially when safe alternatives are available;¹⁰⁰ if 40-year-old subjects have CT coronary angiography, the risk that they may develop cancer has been estimated at 1 in 270 for women and 1 in 600 for men.¹⁰¹ With imaging, the greatest risk to patients may be inappropriate use by an inexperienced operator. Appropriateness criteria do not fill the gap in evidence since they represent the consensus view of experts as to which tests are reasonable for which indications, without guaranteeing that there is evidence of clinical impact. Evaluation of diagnostic strategies should compare all the alternative tests for any particular clinical question.¹⁰²

Cardiovascular implantable electronic devices

It was estimated in 2007 that almost 700 000 patients in western and central Europe had implanted pacemakers, another 90 000 implantable cardioverter-defibrillators (ICDs), and 60 000 CRT.¹⁰³ Many new

concepts and devices have been developed in Europe. Advanced and effective device therapy for arrhythmias and/or heart failure can transform lives, and reliability of individual devices can be 99%.¹⁰⁴ Nonetheless, these advanced technologies still have risks, and electronic devices need to be evaluated and monitored carefully.

Fracture of pacemaker leads and technical failures of pacemakers are a recognized and accepted complication, and the rate of replacement because of pacemaker malfunction is decreasing.¹⁰⁵ Long-term studies are needed to assess chronic lead performance¹⁰⁶ but it is unclear how these will be funded or who should organize them. Remote telemonitoring is now possible. As with diagnostic imaging, there may be differences between devices such as CRT which manufacturers offer as equivalent but which have different technical specifications or treatment algorithms.

There is less clear evidence that the risk of generator malfunction of an ICD is also declining.^{107,108} Problems such as battery depletion¹⁰⁴ if unexpected can occasionally result in death attributable to device failure.¹⁰⁹ Major clinical, ethical, and legal problems may arise, as in a case where a young patient died when his ICD malfunctioned; the unit had not been replaced, and the company had delayed giving any advice to physicians and patients although they had known for >2 years that there was a risk of technical failure.¹¹⁰ More recently, lawsuits have been filed against another company after it too delayed disclosing information, this time about lead fractures.¹¹¹ Failure rates for the Medtronic Sprint Fidelis lead have been estimated at 2.3% at 30 months, or 2.6 times the failure rate of a reference lead, and this fault can cause inappropriate shocks.¹¹²

It is difficult for physicians to know how to respond to advisory notices issued by companies when technical problems are discovered with a particular device, because the risk associated with replacement of a potentially faulty ICD device may be higher than its risk of failure.¹¹³ Even replacing faulty leads is associated with major complications in 7% of patients.¹¹⁴ One recommended approach is to offer elective replacement to device-dependent patients when the 'number needed to replace' (NNR) is <250.¹¹⁵

Automatic external defibrillators have been classified as class III devices because of their similarity to other devices in that class, but many reports of technical failures have been received by the FDA.¹¹⁶ A discussion paper proposed two options—either to reclassify them to class II or to increase the levels of proof and technical performance and reliability required to be demonstrated by manufacturers before these devices are approved;¹¹⁷ the Circulatory System Devices Panel of the FDA recently recommended the second option. Increased PMS has also been advocated¹¹⁸ although this may be difficult given the numbers of devices installed and their location in public places.

Closure of patent foramen ovale

The first use of a percutaneous device for closing a patent foramen ovale (PFO) was reported in 1992.¹¹⁹ At least 12 different PFO closure devices have received CE marking. Risks include pericardial effusion and tamponade, unsuccessful deployment, incomplete closure, device migration, thrombosis, and the development of atrial fibrillation.^{120,121}

Between 1999 and 2002, the FDA approved two PFO occluders as Humanitarian Use Devices, which means that a device has been

designed to treat a disease that occurs in fewer than 4000 people in the USA per year. The approved indication was limited to patients with *recurrent* cryptogenic stroke who had *failed* conventional drug therapy. Approval was granted through the regulatory pathway for Humanitarian Device Exemption (HDE), and it was based upon clinical experience in <100 patients with each device. After approval of the HDEs, it became apparent that many PFO occluders were being implanted off-label for patients with a *first* cryptogenic stroke who had *not* failed medical therapy. Enrolment in randomized IDE trials comparing device closure with medical therapy was exceedingly slow. A systematic review published in 2004 reconfirmed the need for randomized studies,¹²² but recruitment continued to lag because 'some physicians have concluded that the therapy is effective despite the lack of appropriate evidence'.¹²³ A re-analysis demonstrated that there were >4000 patients with cryptogenic stroke per year who might be candidates for PFO closure, and the two industry sponsors voluntarily withdrew their HDEs in 2006. Enrolment in studies remained slow despite more recommendations from FDA Advisory Panels and experts regarding the need for randomized trials, in 2007¹²⁴ and in 2009.¹²⁵

Two trials have been completed. The MIST study in patients with a PFO and migraine, published in 2008,¹²⁶ and the CLOSURE-1 study in patients with a PFO and cryptogenic stroke,¹²⁷ reported in 2010¹²⁸ but not yet published, both found PFO closure to be no better than medical treatment. Unfortunately, the procedure is already so 'established' that many clinicians remain unconvinced.^{129–131} No PFO closure device has been approved in the USA, but many devices continue to be implanted in Europe; a recent report from a single centre included 825 patients.¹³²

The case for reform

Clinical problems relating to failures of medical devices have led to mounting concerns over shortcomings in regulatory processes and calls for their reform, both in Europe and in North America.^{133–143} Most detailed studies have been performed in the USA; for example, more class III devices are approved by the FDA on 510(k) exemptions than by full clinical evaluation,¹³⁶ only 27% of clinical studies used to support premarket applications for cardiovascular devices were randomized,¹³⁵ and most devices which are recalled had been approved without detailed evaluation.¹⁴² Unfortunately, the lack of information from the many competent authorities and NBs means that no comparable analyses are available for Europe. Nonetheless, several major issues can be identified.

(1) Complexity of the legislative framework

The main Directives of the EU have been amended several times and supplemented by various implementing measures and interpretative documents. It is difficult for inexperienced health-care professionals to understand fully this large body of texts. Algorithms can be used to determine the probable class of a device¹³ but there is no website that can be visited to confirm how a particular medical device has been classified or to review the evidence on which it has been approved. There are substantial variations between the transposition measures and additional requirements that some Member States have adopted⁴ because of the lack of

Table 2 Extracts from European and international recommendations concerning the clinical evaluation of medical devices

European Commission Directive 90/385/EEC; Annexes 1 and 7	The purpose of clinical investigation is to verify that, under normal conditions of use, the performances of the device comply with those . . . intended by the manufacturer . . . in such a way that their use does not compromise the clinical condition or safety of patients ⁵
NB-MED/2.7/Rec3; Evaluation of clinical data; Section 4.1	The manufacturer is required by the Directive to perform a risk analysis . . . From the results of the risk analysis, the manufacturer lays out how each risk is addressed and decides on the acceptability of risks when weighed against the intended benefits ¹⁴⁵
European Commission MEDDEV 2.7.1; Annex X, Section 1.1	The objectives of a clinical investigation must be to verify a positive benefit/risk profile of the device for the indications and limitations of use as specified by the manufacturer ¹⁰
Global Harmonization Task Force (2010); Study Group 5; Clinical investigations	Clinical investigations are necessary to provide the data not available through other sources (such as literature or preclinical testing) required to demonstrate compliance with the relevant Essential Principles (including safety, clinical performance and acceptability of risk/benefit ratio associated with its use) ²⁴
ISO 14971 (2007); Medical devices—application of risk management to medical devices	This International Standard specifies a process through which the manufacturer of a medical device can identify hazards associated with a medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of that control For each risk management plan the manufacturer should choose appropriate risk acceptability criteria ²⁷
ISO 14155 (2011); Clinical investigation of medical devices for human subjects—good clinical practice	The clinical evaluation includes an assessment and analysis of clinical data concerning safety or performance of the investigational device . . . The evaluation shall be relevant to the intended purpose of the investigational device and the proposed method of use. It shall be designed . . . to ensure that the results . . . have clinical relevance and scientific validity ²⁸

detailed guidance at the EU level. The current system is criticized because there is reputed to be insufficient standardization and uniformity of performance across the NBs. There is no convincing clinical or public health argument why class III devices should be regulated in Europe by a fragmented system when a unified system is used to evaluate drugs.

(2) Regulatory gaps and need to clarify boundaries

Some new technologies are not regulated by the existing texts. Examples include electronic medical records (currently the object of a European concerted action to ensure inter-operability between Member States), software tools for supporting clinical decisions, and automated methods of quantifying diagnostic imaging. Inadequate security of a computerized database, a software malfunction, or an erroneous measurement could all have adverse clinical consequences for an individual patient. Incorporation of medical devices into IT networks in the clinical environment has been recognized as a less regulated area, and so a new standard has been developed.¹⁴⁴ It is sometimes unclear which devices fall under which directive; special measures are required for devices that have both mechanical, and biological or pharmaceutical, components ('borderline' products).

There appears to be overlap and therefore some imprecision about the responsibilities of NBs, competent authorities, and health technology assessment: all three can consider clinical evidence.

(3) Weakness of the clinical data requirements

The European guidance that is available about the clinical evaluation of medical devices, mostly concerns good clinical practices and the methodology of clinical trials—in other words, it is

rather vague (*Table 2*). New ISO standards specify in detail how clinical studies of devices should be performed,²⁸ but they do not specify the possibly more important question of when they are required. The GHTF Study Group 5 has stipulated that human clinical trials should address residual safety concerns that cannot be resolved through pre-clinical testing or by evaluating existing clinical data. Specific criteria including standards applied by the NBs are not readily available and particular essential requirements for the clinical evaluation of individual types of devices are not published in EU guidance. Thus it is often unclear when there is a need for observational or randomized clinical studies, and decisions may be inconsistent. In most cases, it seems to be left to the manufacturer to evaluate potential risks and decide which clinical data will be sufficient for an application to a NB for CE marking (see *Table 2*). There is overuse of equivalence as the basis for approval,⁵⁷ for example when a non-inferiority clinical trial with good statistical power has not been performed.

Medical devices often undergo serial changes, appropriately, as manufacturing processes evolve and the device is refined or new facilities and tools are added. Such step-by-step 'iterative' changes are offered by the device companies as minor modifications and they may be approved without repeating the process of clinical or regulatory evaluation. At some point, however, a sequence of iterative changes must represent a real change in the device and re-evaluation may be clinically important.

It has been argued that registry studies conducted for the further clinical evaluation of diagnostic and therapeutic devices after regulatory approval has been obtained, are the main control point for medical devices.¹⁴⁶ In general, these studies have been conducted by industry. The manufacturer designs a

plan for PMS and proposes this to its NB; if the manufacturer then also selects the participating centres, there is a significant risk of bias. New methods for automatically monitoring large registries can identify even low-frequency risks.^{147,148}

(4) Accountability of the Notified Bodies

Given the large number of NBs, it may be difficult to ensure that they have comparable and high levels of specialist expertise, but this is desirable for all NBs that review clinical data produced by manufacturers in order to assess conformity of class III devices. The claims for a device made by its manufacturer and the evaluation of any particular device by any particular NB are not publicly available. If approval of a new device has been granted on the basis of equivalence, it is not reported which data the manufacturer submitted in order to demonstrate that its new device performs the same task as other devices which have previously been given a certificate and CE mark. It is inappropriate that responsibility for approving PMS belongs to the NBs rather than the competent authorities; the complexity and largely sporadic nature of communications regarding FSCAs makes this unsatisfactory. When a NB receives fees from companies whose devices it assesses, there may be a conflict of interest.

There is no publicly available list of medical devices in Europe. Each NB or competent authority may have its own list but there is currently no formal system for these lists to be shared or for them to be made available for consultation by patients or health-care professionals.

(5) Insufficient use of expert medical advice

Concerns have been expressed that there is dialogue between manufacturers and regulatory authorities but academic clinicians are rarely involved.¹⁴⁹ The organizations responsible for setting standards, such as CENELEC and IEC, use a large network of experts, but their activities are supported and partly funded by industry. National competent authorities and NBs have their own advisers. The Medical Devices Unit of the EC takes advice from trade organizations, and individual scientists and clinical researchers serve as members of its scientific committee. No partnerships have yet been established with professional medical associations at a European level, but the EC is open to participation by all stakeholders. The EC is not involved in individual clinical evaluations or approvals of particular devices (which are the responsibility of member states and NBs) and so there is no coordinated system for obtaining detailed professional advice concerning new high-risk devices.

Balancing innovation and regulation

One of the three main objectives of the strategy for health of the EU from 2008 to 2013 (published by the EC as a white paper in 2007) is to support new technologies 'which have the potential to revolutionise healthcare and health systems'.³⁵ Eighty per cent of the companies in the medical device sector in the EU are small and medium enterprises (SMEs)² and so encouraging the growth of this sector has been a foremost objective of the

EC, particularly when the Medical Devices Unit was part of DG ENTR. The health strategy also states, however, that new technologies 'must be evaluated properly, including for cost-effectiveness and equity' and it affirms as a fundamental principle that 'health policy must be based on the best scientific evidence derived from sound data and information, and relevant research.' For medical devices, it is not clear that this happens at the EU level.

A key initiative of the Europe 2020 Strategy announced by the EC in 2010 is the 'Innovation Union'. One important objective is to promote research and development of new medicines, treatments, and diagnostic tools to improve quality of life for the elderly.¹⁵⁰ The document includes a general proposal to remove barriers to bring ideas to market, but concerning the objective of healthy ageing there are also specific statements relating to the need to improve rules for clinical trials and testing of new medicines by the EMA, and to ensure interoperability and the setting of standards and reference specifications for new equipment.

Reconciling these priorities—economic sustainability and clinical scrutiny—will be a key challenge for the planned recast of the European medical device directives. Two seemingly conflicting objectives—to streamline and to enhance the legislation—were recognized in the public consultation that the Commission initiated in 2008 to seek advice from expert groups and 'stakeholders' on topics such as the clinical evaluation of devices, vigilance, market surveillance, and transparency.¹⁵¹ The 92 replies from industry almost unanimously rejected the proposal to expand the role of EMA in order to create a new European medical devices agency, whereas there was considerable support for this concept in 41 replies from professional associations, academics, and patients.¹⁵²

The argument is made, usually by industry, that tighter requirements for clinical testing of devices before approval would stifle innovation and delay the availability to clinicians of useful new tools for diagnosing or treating their patients. This ignores the fact that some innovations are led by advances in technology ('solutions seeking applications') rather than being produced in response to identified clinical needs. Many physicians—for example, interventional cardiologists—also want to have early access to new devices and think that medical progress would be compromised and their patients might be disadvantaged if regulatory approval would take longer, but being at the forefront of technological advances also implies responsibilities to ensure that new treatments are safe and effective.

The typical product cycle of a medical device is much shorter than for a drug. The clinical value of an implantable or diagnostic device may be influenced by other factors, such as the expertise of the operator. It is reasonable that regulatory systems should reflect these differences. Classical clinical trials are not always possible or appropriate, but public health safety must always be assured by studies to establish a favourable risk/benefit ratio. Support for innovation^{153,140} in appropriate cases could be counterbalanced by more rigorous PMS.

A premature conclusion that a device is effective can result in more harm than good, whereas a premature decision that a device is ineffective may deprive patients of useful treatment. If there is any 'residual safety concern' then further clinical evaluation should always be the priority.

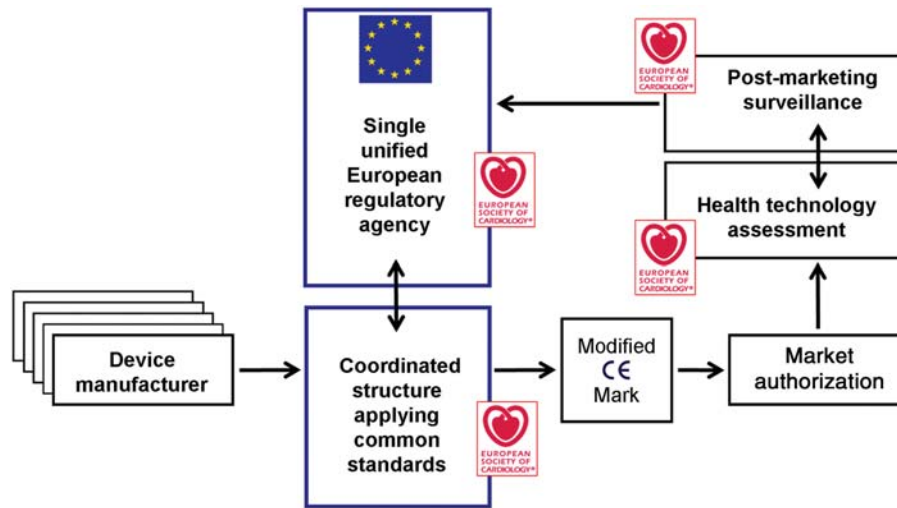


Figure 2 Recommended structure for approving and monitoring medical devices, based on a single European agency overseeing detailed European standards, assessed by a technical division or by a small number of coordinated Notified Bodies who award a medical CE mark, followed by integrated health technology assessment and post-marketing surveillance. Clinical experts from professional medical associations should contribute at many stages, as exemplified by the ESC logo.

Recommendations

The Policy Conference strongly supported the plan for a substantial recast of the Device Directives. This is an opportunity to reconsider the optimal governance of medical devices, going back to basic principles. It is essential that evidence of clinical efficacy as well as safety and technical performance is established before approval of any devices whose use may be associated with more than trivial risks.

(1) There should be a single, coordinated European system to oversee the evaluation and approval of medical devices

There should be integration and harmonization of processes between the competent authorities so that they apply uniform and higher standards. The most efficient way to achieve this would be the creation of a single regulatory authority in the EU (Figure 2); it could be a medical devices division of EMA or a new body, but its structure is less important than its function. There should be close collaboration between agencies conducting PMS and those responsible for health technology assessment, as well as increased international collaboration.

(2) The NBs should be reorganized as an integrated structure

The NBs should be reformed, with expertise concerning particular types of devices concentrated in single centres (for uncommon, high-risk devices) or only a few centres (for large categories). The regulatory authorities should direct applications for assessment of devices to the appropriate specialist NB(s). There should be closer supervision and coordination of the NBs to ensure that they have a single, high standard of excellence, experience, and competence. Options would be for the divisions of NBs

that assess medical devices to become the technical division of a new European medical devices agency, or they could remain decentralized while operating within an integrated system.

The use of the CE mark for medical devices should be reviewed as its meaning is often misunderstood. It may be interpreted by clinicians and patients as meaning that clinical effectiveness has been established, for example from clinical trials, whereas it simply implies conformity with essential requirements including an acceptable risk/benefit ratio. For implantable devices, a modified system should be considered, that indicates the level of clinical evidence established by trials.

(3) The classification of each type of device should be based on a detailed evaluation of risks

A risk-based classification is essential. This is the foundation of the current system of regulatory approval, but not all devices within each class have similar levels of clinical risk. Actual risks should be reflected in the clinical evidence required for a submission. For example, diagnostic imaging devices which use ionizing radiation or contrast agents have increased risks compared with safe alternatives such as ultrasound. The class of each new device should be considered separately and not determined by the manufacturer. International concordance of classifications is important.

Risk will be influenced by the population in which a device is used and so clinical indications should be considered when risk is being estimated. The system should be adaptable so that new devices can be considered promptly when they are introduced, before their long-term risks can be known. Also, the system should not restrict the application of devices in special groups such as children, when the devices meet technical standards but limited numbers of patients might make it difficult ever to collect detailed information about risks.

Risk assessments should be undertaken for health information technology.

(4) Product standards should be developed for each category of medical device in class II and class III

There is a need for specific standards concerning not just the technical design and performance but also the clinical performance and evaluation and requirements for PMS, of each type of device in class II and class III. Where these do not already exist, they should be developed, perhaps on an international basis. Recommendations should include requirements for clinical evaluation including numbers of patients to be studied, and guidance when clinical trials are needed to demonstrate an impact on clinical outcomes. These requirements should be binding on manufacturers. The design of trials may vary according to the class of a device, risk/benefit ratios, and the characteristics of the patients in whom it is used. There should be fewer approvals of new 'me-too' devices on the basis of equivalence, and standards should define when this would be acceptable. Approval for the use of a device should include a statement of its clinical indications.

Clinical evaluation should be extended to diagnostic imaging. Standards should determine acceptable limits of performance against imaging phantoms (test objects) and when feasible, acceptable levels of diagnostic accuracy.

Standards should be produced independently, without involvement by the organizations responsible for assessing conformity of devices. Manufacturers or members of trade associations can advise or participate as technical experts but they should not have responsibility for writing or approving standards. The EU or national competent authorities should fund the production of detailed standards.

(5) Expert professional advice is required

Professional associations such as the European Society of Cardiology are key stakeholders in developing policy concerning medical devices, as they represent networks of physicians who develop, use, and evaluate devices in daily clinical practice, and who understand and practise different methods of clinical assessment. Obtaining expert advice, for example from (bio)materials scientists, physicists, engineers, academic specialists, practising physicians, and nurses, should be an integral part of the regulatory process. Such independent advisers should be involved in setting standards, reviewing decisions about approval of new class III devices, defining clinical indications, performing health technology assessment, and designing and conducting programmes for PMS (Figure 2). Representatives with appropriate training and experience should be nominated by major medical associations in Europe to be members of the main advisory committees.

It is important that the experience and opinions of patients who use devices or who have received implantable devices should also be obtained and considered.

(6) Adequate transparency is essential

Legislation enacted by the European Parliament in 2001 on freedom of information enshrined the right of access of European citizens to documents of the EC and its agencies.¹⁵⁴ There are

compelling clinical reasons why transparency should be extended to documents relating to the approval of medical devices.

Currently, it is difficult for physicians to identify the class of any particular device or to obtain its essential requirements as evaluated by the NBs. Technical standards such as those produced by ISO can only be consulted by purchasing the documents. For medical devices, such information should be freely available in the public domain.

The content of dossiers prepared by companies when submitting their devices for approval, apart from any manufacturing details that are protected intellectual property, should be disclosed to physicians so that they can know the technical performance of the devices that they use. They should be able to review comparisons of the performance of devices within the same category.

Patients should be able to obtain information such as reports of malfunctioning devices, preferably together with professional advice from physicians.¹⁵⁵

(7) The concept of conditional approval of a medical device, pending further clinical evaluation, should be developed

When a new device is developed that represents a major technical advance and an important new option for treatment, then early approval may be appropriate as long as initial clinical safety and efficacy have been established and the clinical benefits from its use are likely to outweigh any anticipated risks. There would still be a need, however, for larger, longer, or randomized clinical studies to be performed. In such circumstances, CE marking might be awarded for a limited period (such as 2 or 3 years), conditional on the manufacturer reporting back to the regulatory authority before the expiry of that time period with the results of any further clinical studies that have been specified as the condition of approval. If new evidence is not submitted, then permission for continued marketing of the device would be withdrawn. The new category could be called 'Conditional Approval of a Device, pending clinical trial'. For diagnostic imaging, a similar concept has been described as 'coverage with evidence development'.¹⁵⁶ This proposal is not the same as an IDE, because the device could be CE marked while the manufacturer is mandated to undertake specific clinical research studies in addition to PMS.

The current directives already allow for compassionate use and investigational device approval, but this is granted by a national competent authority and not at the European level.

(8) Outcome studies after device implantation should be undertaken as a partnership between physicians, companies, and regulators

Post-marketing surveillance should be initiated by the manufacturer but PMS should not be the sole responsibility of industry. Follow-up studies should be proposed and coordinated by regulatory agencies or HTA bodies with the assistance of independent experts from professional scientific associations (such as the ESC¹⁵⁵). Funding for such studies might vary, from manufacturers to the EU itself, depending on the scope of information being gathered and its relevance to a specific device or to public health. These studies should evaluate the characteristics of patients undergoing diagnostic or therapeutic procedures using devices including

off-label applications, document immediate complications, and study medium and long-term outcomes including instances of device failure. To ensure that data are representative, outcomes should be collected from centres in all Member States that reflect different types and volumes of practice and the full range of complexity of clinical cases. Protocols and case record forms (CRFs) should be discussed and validated by academic experts, regulators, and companies. The database should not be the property of industry, and the main results should be freely available. A collaboration between EU regulatory bodies, the FDA, and scientific associations would allow coordination of reporting systems and more complete evaluation of safety issues related to newly marketed devices. This will complement the sharing of reports of adverse events and clinical alerts that is being developed by Eudamed.

(9) Limits to iterative changes should be defined

Detailed standards for each type of device should specify which modifications could reasonably be described as minor, and which others would warrant complete resubmission for approval as a new device. For example, if any modification has been submitted for a new patent, or if the materials used to make a device have been changed, then a *de novo* application should be required.

(10) Regulatory systems should retain flexibility for special circumstances

The system of regulatory approval should allow prototype or innovative devices to be approved for use in special circumstances when urgent clinical needs can only be met by their deployment. A common European equivalent of the HDE is required.

Special consideration might also be given to categories of medical device that are important but used so infrequently that they are not economically viable. Continuing clinical availability of 'orphan devices' might be supported by a grant from a common fund—for example, if a device is 'last in class'.

It may be difficult for devices used in paediatric cardiology to meet the standards and levels of clinical evidence required for devices used in adults, if numbers of patients are small or if devices are customized for each patient. Off-label use is common. Approval on the basis of limited evidence might then need to be balanced by more strict requirements for careful and complete PMS.¹⁵⁷

(11) Manufacturers should be responsible for the clinical evaluation of all class II and class III devices

Companies that manufacture any class II or class III devices should be responsible for initiating independently monitored clinical studies of their devices, including randomized controlled trials when these are required according to new standards, and also for supporting PMS. Researchers should have full access to the results of any clinical study so that they can conduct an independent statistical analysis, and the results should be published whether they are negative or positive. Clinical trials evaluating medical devices should be registered in a central database.¹⁵⁸ Depending on the class of device, companies should also train medical and nursing staff in the correct and safe use of their devices.

(12) Physicians should understand and engage with the regulatory systems for medical devices

Physicians have a responsibility to practice evidence-based medicine when using devices, and they should encourage their patients to participate in clinical trials when these are required, especially when there is equipoise. Physicians are keen to adopt new devices early but not as keen to undertake systematic monitoring afterwards; they should contribute routinely to PMS as this may be the only means by which unsuspected problems are discovered. It is the duty of physicians to report any failure of a device. Consideration could be given in the case of high-risk devices to making participation in PMS mandatory, as a requirement either for continued access to the device for their patients or to reimbursement of the hospital for its use. Professional societies should promote interest in the evaluation of innovative medical devices, through continuing medical education.

It is unethical for any physician to accept payment from a medical device company for the use of its device. If physicians have any financial interest in a device, they should disclose this information when reporting its performance or seeking consent for its use.

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Appendix

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