Medical Device Regulation and Nanotechnologies

Determining the Role of Patient Safety Concerns in Policymaking

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Abstract

Balancing acceptable risks and early release of products for new treatments in patient care with the rights of patients and the rights of stakeholders—device makers and regulators—is a complex task. With the rapid technological innovations of the last two decades, providing a balanced voice to all participants is essential, but a sense of urgency depends on which side of the aisle one is sitting: on the side of patients, surgeons, regulators, and device makers, or that of providers and scientific advisors. A review of the medical device political economy suggests why patient safety concerns are or should be kept alive throughout the entire regulatory cycle from clinical evaluation and pre-market checks to their final use in a huge variety of clinical settings around the globe. The key issue for nano-enhanced devices now is whether the uncertainties and perceived risks can be reduced through more stringent regulatory requirements

and proactive measures without stifling innovation and development of new treatments for patients.

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Introduction

Balancing acceptable risks and early release of products for new treatments in patient care with the rights of patients and the rights of stakeholders—device makers and regulators—is a complex task. With the rapid technological innovations of the last two decades, providing a balanced voice to all participants is essential, but a sense of urgency depends on which side of the aisle one is sitting: on the side of patients, surgeons, regulators, and device makers, or that of providers and scientific advisors. A review of the medical device political economy suggests why patient safety concerns are or should be kept alive throughout the entire regulatory cycle from clinical evaluation and pre-market checks to their final use in a huge variety of clinical settings around the globe. The key issue for nano-enhanced devices now is whether the uncertainties and perceived risks can be reduced through more stringent regulatory requirements and proactive measures without stifling innovation and development of new treatments for patients.

Risk regulation takes into account product types: diagnostics (IVDs) and medical devices, as well as nanopharmaceuticals and nanodevices. Some 8,000 different types of medical devices have been sold on the world market (United States International Trade Commission 2007), but so far only 125 medical devices or diagnostic tests use nanotechnology and were in pre-clinical,

clinical, and commercial development in mid-2006 (Missios 2009). Each type reflects different product characteristics, legal foundations, and historical origin in the pharmaceutical regime, while diagnostic devices and nanopharmaceuticals remain largely under the drug framework. Experience with medical devices accumulated over the last twenty years can provide precious lessons for nanomedical regulation. Yet, while the wide range of medical device regulations can provide a model for the regulation of new nanotechnology innovations, nanotechnology is sufficiently different from biotechnology that existing medical device regulations cannot properly recognize the higher level of risk of these advancements.

This article discusses the European Union (EU) medical device regulation and the myths and facts of patient safety concerns in risk regulation. Special attention is paid to new product development that uses nanotechnologies.[1] When used in medical devices, nanotechnology and nanomedicine seek to improve diagnostic and therapeutic patient monitoring, as well as rehabilitative possibilities in health care. This objective has not changed much from biotechnology predecessors to the nano-era, but the materials being used have changed significantly. Since the 1960s, every decade has seen an explosion of innovative developments ranging from imaging equipment to nanomedicine. Patients everywhere have much to gain from further technological-medical advances. But regulation faces a dilemma in this field: the public has limited knowledge about and interests in these advances, yet wants the best and latest application of new technologies in medicine when sick (Naidu 2009).

The analysis focuses on the EU regulatory framework for medical devices, which covers a diversity of medical devices and diagnostic products, including devices with nano-scale components (such as biomaterials, combination products (drug/device), and diagnostic products), and not on innovative processes occurring within distinct scientific disciplines, micro-

applications, and diagnostic innovations. Empirical illustrations from the American and global experiences highlight key problematics: sometimes misguided guidance for risk regulation borrowed from drug regulation, no up-to-date expertise, ghostwriting by industry-sponsored authors, and a severe shortage of experienced scientists, as well as unsettling conflict of interest issues involving device-maker-physician relations and scientific advice-giving to an agency that cannot afford or cannot hire in-house expertise because it may be a budget victim (Brizmohun and Sharma 2009; Brizmohun 2009; Demske 2008; Zuckerman 2008; Eaton and Kennedy 2007; Greenberg 2007;).[2] Dependence on extramural advice rises in proportion to the speed of new and emerging technologies (Altenstetter 2009). Finally, implementation deficits remain among the most intractable problematics because even when policymakers get medical device risk regulation scientifically and politically correct, they may face challenges securing implementation on the ground. No matter how the U.S. and the EU eventually address problem-solving in the future, the key question in both cases is whether the existing methods of risk assessment, risk management, and market approval are sufficient or, alternatively, require a more prescriptive approach to medical device risk-regulation in the era of nanotechnology.

The analysis draws on a governance perspective.[3] This perspective is useful not only for identifying the stakeholders involved in EU regulatory policy-making, but also for exploring what happens after rules and procedures are written into law and after EU directives are transposed into national law. Institutional arrangements do mediate the implementation process and hence influence the role of patient safety in regulatory practice. The relationship between patient safety and market access, trade, and profits is complex – conceptually, analytically, and empirically. Policy actors operate in centralized governmental and non-governmental arenas at several levels and in highly diffused and decentralized patient care settings. A governance

perspective includes interaction between public, private, and sometimes even corporatist actors, and is not limited to national developments. Rather, the concept of transnational governance is increasingly used to describe what is happening at the international, transnational, and national levels (Grande and Pauly 2007; Pierre and Peters 2004, 2000). The pathway to markets and profits and the one to safe medical devices are fundamentally different and unfold under different conditions in the context of the political economy of a country, region, or in the global economy. Yet, the lines between these two poles are blurred through multiple crossover operations.

The article proceeds in several steps and is organized into two parts, each with several sections. Part I will provide a broader lens with which to think about and examine the medical technology regulatory framework against the background of both global developments in the medical technology field and the criteria of an effective regulatory regime as seen from a public health perspective. Part II focuses on the three medical device-specific directives that have formed the core of medical device regulation since the early 1990s: the Active Implantable Medical Device Directive of 1990 (AIMDD, 90/385/EEC), the Medical Devices Directive of 1993 (MDD, 93/42/EEC, as amended), and the In Vitro Diagnostic Directive of 1998 (IVD, 89/79/EC). These directives provide the lens with which to analyze, assess, and regulate medical devices for their potential risks to human health from the early 1990s onward. The discussion will explore the extent to which the organization of the core regulatory framework for medical devices has changed from the early 1990s to the present, and how it might need to be revised and modified for the era of nanotechnology and nanomedicine for the twenty-first century. This analysis will revisit what has been learned about medical device regulatory governance at the EU level and in the member states since the early and mid-1990s, including experiences with

implementation of adverse event reporting and medical vigilance in select member states over time.

Part I Locating Patient Safety Concerns in a Broader Context

The arguments presented in Part I proceed in several steps designed to establish the broader context bearing on the regulation of medical devices. I begin by unpacking the concept of patient safety and then placing it in the context of recent global developments. Finally, I draw on recent experiences in the U.S. to underscore the kind of challenges that may be in store for EU and national policymakers.

Unpacking the Concept of Patient Safety

The term "patient safety" is a multifaceted concept shaped by policy, politics, and law, as well as by regulatory science and institutions (Eaton and Kennedy 2007; Cooper 2006; Vincent 2006; Cohen and Hanf 2004; Marlin-Bennett 2004; Institute of Medicine 2001a, 2001b, 2000). As a concept, patient safety provides an analytical framework that helps describe the extent to which regulatory governance and policymaking in the medical device sector is an effective regulatory system designed to achieve patient safety. The most comprehensive definition of patient safety is provided by the Institute of Medicine in its study *Responsible Research. A Systems Approach to Protecting Research Participants* (2001b), and it identifies the areas in which protection functions are necessary to ensure the safety of participants. The National Quality Forum in health care in the U.S. has recently been criticized for relying too much on legal approaches (Figueroa and Staton 2009; Buris 2008; Halpern 2008; Hoflund and Farquhar 2008). When it comes to patient safety, law tends to only deal with the tip of the iceberg (RAJ Devices 2009; RAJ Devices 2008a).

As summarized in Table 1 below, in 2003 the criteria supporting an effective medical device regulatory system were established by the World Health Organization (WHO) and the Pan American Health Association in cooperation with the U.S. Food and Drug Administration (FDA). These guiding principles set a "gold standard" for an effective regulatory system by setting the minimum requirements and principles that ideally should be reflected in regulatory governance.[4] The litmus test of an effective medical technology framework is two-pronged: first, are these ideas and tools institutionalized in EU governance and policymaking, and second, are they operative in grassroots-level structures responsible for adverse events reporting and medical vigilance in the twenty seven nation-states? Setting principles is the easier of two tasks; finding the appropriate mechanisms (*structure* and *process*) for implementation is more complex and fraught with obstacles.

[Table 1 Guiding Principles for an Effective Medical Devices Regulatory Program] about here

Decision makers face considerable uncertainties. One way to minimize such uncertainties is to recognize risks and potential harm *ex ante* before the technologies reach the market. Due to the nature of the products and clinical trials of medical technologies, the most valuable patient safety information is obtained from medical vigilance and adverse reporting *ex post.* In theory and practice, this information can help minimize the uncertainties surrounding medical technology regulation and ensure that patients and doctors have a voice, that their rights are protected under the respective regulatory framework in each society, and that they have a seat at

the negotiating table. Regulators are known to largely rely on reactive strategies to deal with medical errors and vigilance reports, to sit on indispensable information and data, and to control respective regulatory databases that are confidential and closed. Information on recalls and discovered risks is shared with regulators in foreign countries but is not available to researchers, let alone doctors, the public, or patients. Further roadblocks range from not sharing the results of clinical trials (negative or positive) with the public to hiring lawyers to help deliberately obstruct investigations or delay the investigation process. The evidence is compelling; as a result of out of court settlements or court rulings, heavy fines seem to be the only means by which device makers render information they otherwise prefer to keep under cover (Demske 2008; Chatterji et al. 2008..[5]

An OECD study (2007) reveals that while "patient safety data systems are on the agenda at the local, regional, national and international level… they are not on the agenda for all countries and not all levels listed." Moreover, "the information agenda is not considered from a patient perspective in most countries" (19). Only a few countries and few professional subspecialties run patient data registries. The study concludes by stating that "landmark studies on medical practice and on rates of medical errors in countries such as the U.S., Australia, Canada, the UK and others…have shown, virtually universally, that gaps in patient safety in terms of adverse events, complications of care or surgeries and medical errors occur at very similar rates across countries" (11). Furthermore, "currently, virtually no country in the OECD has a uniform or official vehicle for incorporating patient reports of adverse events into their regulator patient safety data systems" (8).

Global Regulation and Patient Safety Concerns

The increasing importance of global developments impacting upon transnational and national medical device regulatory policy and governance requires a broader perspective (Meidinger 2009; Zach and Bier 2009; Epps 2008; Hodge, Bowman and Ludlow 2007; Mordini 2007). Two opposing objectives in medical device regulation are competing for attention: patient safety, on one extreme, and access to new markets, trade, and profits on the other. By stepping back to look at the "big picture," we are reminded of these two objectives as the most salient driving forces of technological-medical innovations and as a response to medical device regulation over the last decades (Mattli and Woods 2009; Drezner 2007; Fuchs 2007; Grande and Pauly 2007; Blank 1995; Burns 2005; Kruger 2005; West 2007).

Some ubiquitous, yet prevalent medical devices, such as shoulder, knee, hip, and implanted heart valves, are frequently not always of high quality and fail to last as long as patients and doctors expect. Indeed, high-risk medical device recalls are as frequent as drug recalls. Over the years, a consensus among the global stakeholders—regulatory authorities and industry—has emerged, indicating that efforts toward global harmonization will serve the objectives of "enhancing patient safety and increasing access to safe, effective and clinically beneficial medical technologies around the world" (Global Harmonization Task Force (GHTF), "[R]ealizing the value of technology" (GHTF 2009) quality, safety and performance, and efficacy are also repeatedly cited in numerous sources and GHTF guiding documents as the gold standard of good medical device regulation (GHTF 2009, 2007, 2006.[6] Catch phrases such as "patient safety," "patient and public health," and "design for patient safety in a global model" (the logos of the 2009 and 2007 conferences) permeate the regulatory discourse and framework, and there is a definite push for early market availability of new treatments and devices to benefit patients around the globe. Whether these intentions translate into patient safety—and what form

it will take—is one of the more important questions concerning risk regulation and its implementation throughout the life cycle of a product. At first glance, these logos appear to be a guiding principle shaping global regulatory affairs in the medical device sector.

Considering the voluntary participation and informal collaboration in the GHTF,[7] one would be inclined to believe that only rigorous risk-based and science-driven methods guide the review and the decisions medical device market approvals. The approval process also has elements of a standard public relations game, however, where medical-device industry representatives lobby in all corridors of political authority, influencing the debates, negotiations, and final outcomes regarding the entire range of regulatory issues, including patient safety. If regulators and device-makers share a strong patient safety concern, why are advanced countries in Europe and North America—to name but two regions—unable and/or unwilling to address patient safety issues more aggressively (Ludgate 2009; Institute of Medicine 2000, 2001a, and 2001b, 2000)?

How can the paradoxical message gathered from the GHTF sources be explained?[8] On the one hand, we learn that goals of global regulation include "the early availability of new treatments to patients around the globe" and new market availability. We also learn that the U.S. and the EU continue to follow their distinctive approach to the regulation of medical devices while participating in and pressing for harmonizing certain rules and procedures, although they primarily focus on manufacture, distribution, nomenclature, and uniform medical device identifiers. On the other hand, global regulatory activities are ongoing and have an impact far beyond the GHTF. Asian, Latin American, and other countries are busy setting up their own regulatory frameworks, imitating and emulating regulatory requirements and practices either from the U.S., the EU, or the GHTF model, which incorporates elements of both. Is safety being

pursued? Or is a level playing field for trade with medical devices and mutual recognition of national regulation the ultimate objective?

By default and intention, patient safety is not at the heart of regulatory activities at the global level. Nor does the record on implementation in most countries show a full commitment to patient safety as a shared responsibility of manufacturers, distributors, vendors, regulators, clinicians/users, and patients (Cheng 2007, 2003; Cheng and Fahlgren 2006). In reality, stakeholders are not evenly committed to patient safety. Yet industry representatives and members of the medical technology policy community would have consumers believe that the medical technology framework in the EU is "sound" (N&ET Working Group 2007; European Commission 2003a and 2003b). This is why it is important to distinguish between regulatory governance at the global and EU levels: namely, regulatory processes, participants, and the underlying power structure.

Learning from U.S. Experiences

In recent years, the FDA, a longtime leader in risk regulation and a trendsetter for global enforcement standards, has lost credibility when it comes to effectively regulating the entire lifespan of a product—from design to implantation into a patient. Accused of being "captured" by industry interests and the most powerful device companies, people doubt seriously whether the rigorous scientific reviews preceding product approval are indeed risk-based or are instead driven by politics, market ideology, and strong lobbying (General Accounting Office 2009a, 2009b, 2009c; RAJ Devices 2008b).

While the FDA has historically enjoyed the status of an autonomous regulatory agency, the recent move toward "agencification," through slimming down of the public sector by meting

out regulatory functions from a ministry of health, is a fairly recent trend in Europe and other regions. Regulatory policymaking that is politically, organizationally, and professionally divorced from healthcare policymaking raises serious questions as to whether patient safety can be secured and whether public health structures have a voice in regulatory governance. Are doctors, nurses, and hospitals doing a satisfactory job monitoring risks to patients and reporting adverse events? The argument that we need not concern ourselves as long as little is known (according to the 2007 OECD study) ignores the ever-increasing risks patients face (Institute of Medicine 2001a, 2000). The dependence on fees to carry out day-to-day operations in the interest of public health has significantly increased the FDA's dependence on device-makers and has led to a neglect of auditing outsourced manufacturing and clinical research sites. The implication of outsourcing for the quality of final products is recognized as being serious (Wilkinson 2010; Kahan 2009; See Barnett Educational Services 2005, for a collection of interviews with relevant officials in the United States, European Union and the United Kingdom). If "direct control" (Peters and Wright 1996) is coupled with the ubiquitous request for "least burdensome regulation," at some point the bottom line will be drawn between burdening the industry and providing a sense of security to the public (within the constraints that zero risks cannot be guaranteed), and formalized in law and procedures. Yet, it is doubtful that uniform regulations (understood in law as one-size-fits-all) actually match the wide spectrum of highly differentiated medical devices and that law can raise patient safety.

Risk regulation is shaped by regulatory science and experience. The science may be robust and sound but does relevant information exposing potential harm to patients actually reach doctors and patients? Typically, the FDA receives information about medical device complaints from competitors, subjects in clinical trials, or employees of device-makers (US

Department of Health and Human Services, FDA, Center for Devices and Radiological Health 2006). Complaints also come from within the FDA and/or other agencies (Demske 2008). While much information is available, the information is hardly accessible to outsiders like patients.

Part II Revisiting the EU Medical Technology Framework

Part II begins with a brief historical overview. Drawing on a governance perspective, I reconstruct the formal structural elements specific to medical device governance, starting with the Commission and outlining its internal coordination mechanisms. I then move on to cover policymaking by committees and scientific policymaking. Finally, I explore the language of risk regulation and identify the most important building blocks of medical device regulation, as these were institutionalized by the *new approach* to harmonization and technical standardization after 1987.

Since 1990, the EU has enacted nine directives, with the AIMDD (90/385/EEC), the MDD (93/42/EEC)—both as amended by the IVDD (89/79/EC) and further amended by the 2007/47/EC (discussed below) and representing the core of the legal framework—and six modifying and/or implementing directives (Altenstetter 2008; Young 2006; Hodges 2004; Egan 2002; Chai 2000).[9] Fifteen years later the *new and global approach* is the EU's export model to global regulation. EU law consolidated twelve highly fragmented, uneven, and diverse national regulatory laws and practices of twelve EU member states into a uniform regime for medical devices EU-wide. Today, the EU framework covers twenty-seven member states, but it operates within the context of very different traditions of public law and administrative law that make convergence to occur in implementation complex if not impossible (Beaumont, Lyons, and Walker 2002; Barnard and Scott 2002). Although the EU has also completed mutual recognition

agreements with other countries outside its borders[10] and the European Court of Justice (ECJ) has established mutual recognition as a legal principle, very little consensus concerning public health and healthcare issues has been achieved among the member states.

EU Medical Device Governance: Process and Structure

The EU medical device regime rests on a governance structure that has undergone several mutations since the early 1990s. The essence of the initial architecture is characterized by a floor set by Community legislation and a ceiling set by the Treaty, while leaving member states considerable leeway to pursue their own policies. Despite decentralized strategies and measures secured by the subsidiarity principle (enshrined in the Treaty of Maastricht of 1993, also known as the Treaty of the European Union [TEU], which amended the 1958 treaty for the first time) there is a certain hierarchy of EU law and procedures over national laws and procedures, but the governance mechanisms originally established have combined centralized and decentralized actions both in formulating policy at the EU level and implementing risk regulation of medical devices in the member states. Over sixty commercial certification authorities (in legal terms, notified bodies) certify manufacturers' compliance with the Essential Requirements (ERs)[11] and grant *Conformité Européenne* (CE) marking as proof of compliance with EU directives and requirements for technical and clinical standards. With this classic co-regulation instrument in place (rather than self-regulation or direct government regulation), the responsibilities of the national competent authorities are limited to oversight and monitoring functions.

The core of EU medical device governance rests in the shift of jurisdictional powers over medical devices upwards to EU institutions and away from the nation-state, embodied in the mandate removing tariff and non-tariff barriers and quantitative restrictions to free trade and

undistorted competition (Kohler-Koch and Rittberger 2007; Scharpf 1999). The institutional and structural dimensions of "network governance" (Benz 2009) in the medical device sector are reflected in distinct configurations, as discussed below. Decision-making by committees has been a key feature characterizing policymaking in the EU since the start of the European Economic Community (EEC, 1958), and it began to take on a more concrete shape in the 1960s and 1970s (Christiansen and Larsson 2007; Joerges 1999; Joerges and Voss 1999). But the real changes came with the creation of the Single Market in 1987. Ten years later, the Treaty of Amsterdam (1997) institutionalized a more diversified pattern, and the Commission was asked to justify all internal market proposals with scientific evidence (Art. 100[3]).

Regulatory Governance and the Commission

The Commission sits at the apex of EU governance, but it should not be thought of as a single hierarchical institutional framework. Instead, it relies on multiple and interconnected organizational layers within the Commission, between the Commission and member state officials, and among officials and staff within the member states. To the extent that biotechnology was the paradigm for the first and second generations of biomaterials, combination products, and IVD-products, it is necessary to ask how the Commission handled policy issues related to biotechnology, and what kinds of coordination mechanisms have been in place within the Commission since the AIMDD was adopted in 1990 and a draft for the MDD readied while the draft IVDD was being disconnected from the MDD.

In the aftermath of several scandals involving public health issues and in response to pressures by the European Parliament and some European publics, the Commission created two interdepartmental coordination committees: the Biotechnology Steering Committee (1984) and

the Biotechnology Inter-services Committee (1985). They were replaced by the Biotechnology Coordinating Committee in 1990, which, with minor modifications, continues to the present day (Pollack and Shaffer 2005; Patterson 2000). The 2000 mandate of the Biotechnology Coordinating Committee, including the development of internal guidelines on broad issues to do with biotechnology such as how to combine the "horizontal" and the product-by-product approach without creating excessive burdens for industry, has implications for medical device regulation and for coordinating biotech- and nanotech-related issues within the Commission. Given the heterogeneity of medical devices, scientific advice and recommendations always needed to be gathered from a wide range of scientific and technical knowledge and expertise. Specialization tends to intensify decision-making by committees.

Regulatory Policymaking by Committees

Decision-making by committees in the medical device field has always operated on several layers within EU governance and broadly fits the description provided earlier by Tömmel and Verdun (2009), who argue that "hierarchy is based on a weaker institutional structure whereas negotiations, competition, and cooperation are embedded into a more organized and formalized institutional framework" (300). In the medical device sector we find multiple regulatory groups, working groups, subcommittees, and *ad hoc* groups bringing together representatives of the Commission, member state authorities, industry, and notified bodies.[12] They deal with the whole range of risk-related issues of medical devices, and, depending on the group, membership is limited to the respective officeholders within each group. Until recently, the missing piece has been a lack of consumer/patient interest representation.

Two standing committees—the Committee on Medical Devices, which routinely serves as a regulatory committee, and the Committee on Standards and Technical Regulation—constitute a first layer within a loose hierarchy. Members of the committees are the representatives of national administrations and Commission services. The European Commission chairs the meeting, sets the agenda, and submits proposals for discussion. If no agreement is reached, the next step is the Council or, ultimately, a procedure before the Court of Justice (Hodges 2005, 2004). The pros and cons, opportunities and constraints, as well as the fundamental logic behind the so-called comitology system, have been the subject of controversial debates and in-depth analysis by experts in law and political science (Joerges 1999; Joerges and Vos 1999 and contributors).

Since 2002 the Medical Device Expert Group (MDEG), chaired by the European Commission, has evolved into an umbrella group coordinating and overseeing the work of all other groups. The membership of MDEG consists of representatives of the Commission, competent authorities, and notified bodies. In-house procedures (1999/468/EC) allow for the splitting up of an MDEG meeting into a formal and an informal part. In the informal part, input from all participants is solicited. Once the meetings are declared closed, the committee functions as the regulatory committee attended by Commission representatives and national officials.

The MDEG solicits and receives feedback from many networked expert groups, including the Notified Bodies Operations Group (NBOG) and the Market Surveillance Operations Group (MSOG). MDEG, NBOG, and MSOG work in cooperation with the Commission on the development of non-binding guiding documents (archived under Medical Device guide or interpretation text, widely referred to as MEDDEVs as amended). Not all expert groups were formed in the initial phases of the emerging EU medical device regime in the early

1990s. A Classification Working Group was established in 1996, followed by the Drug/Device Issue Group and the Medical Vigilance Group in February 1998. In 2000 the NBOG and the MSOG were set up in response to widespread criticism aimed at both notified bodies and competent authorities for not living up to their respective responsibilities. Members of the groups include the Commission and nominees from the member state competent authorities, which are now organized into a Competent Authority Group. NBOG meetings (held twice a year) are chaired by a competent authority of a member state while the Commission serves as host. In addition, experts work through the IVD Technical Group, a Working Group on Clinical Investigations and Evaluation (CIE, which is the EU mirror committee to GHTF SG 5 on the global level), and an Electronic Labeling Working Group in addition to the New & Emerging Technologies Group (N&ET), a European Databank for Medical Devices Working Group (referred to as EUDAMED Working Group), and the Notified Body Medical Devices Group (referred to as NB-MED). Within this governance structure, N&ET is in charge of addressing nanotechnology and its potential risks. As argued by Tömmel and Verdun (2009), these groups are indeed "embedded into a more organized and formalized institutional framework" (300). Examples in particular include the Competent Authority Group, the Compliance and Enforcement Group (COEN), and the Notified Body Operations Group, which are closed to outside representation (Brizmohun and Sharma 2009).

The Commission chairs MDEG, Vigilance WG, Classification and Borderline WG, an Electronic Labeling WG, and EUDAMED WG. Coordination among the member state competent authorities is reflected in chair responsibilities: Ireland chairs the COEN Working Group, Germany the NBOG, and France both the IVD Technical Group and the Working Group

on Clinical Investigation and Evaluation (CIE). The competent authority of the Netherlands chairs the N&ET Group and Notified Bodies (NL) the NB-MED.

Scientific Policymaking, 1990-2009

A formalized scientific structure serving in an advisory function was not created until 1997. The Scientific Steering Committee (SSC) was reorganized in 2004, and again in 2009. Today, the European Commission solicits scientific advice from these scientific committees: the Scientific Committee on Medicinal Products and Medical Devices, established within the European Medicines Agency (EMA) in London (until 2004 the European Medicinal Evaluation Agency); the Scientific Committee on Consumer Products (SCCP); the Scientific Committee on Health and Environmental Risks (SCHER); and the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR). Since 2007, the latter has become a focal point for nanotechnology and nano-enhanced materials, and has questioned the appropriateness of the methods used for assessing risks (N&ET Working Group Report 2007). On behalf of the EU, SCENIHR now is cooperating with the GHTF, which only two years ago considered nanotechnology regulation a low priority. Due to the fact that nano-relevant issues are device-specific, rather than specific to types of medical devices, we have to leave it at that. A final group essential to the *new and global approach* and risk regulation includes the transnational standards committees that set scientific and technical standards through delegation by the Commission to standard setting bodies: the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC).

Several features stand out. Decisions are taken by consensus in fairly informal and technocratic processes. Technocratic decision-making increases with the distance from the top

layers and is particularly true for the scientific advisory groups. Yet, science is conflict-prone and not objective to every community (Epps 2008). Scientists do not always agree on the best way of risk-regulation, the best scientific standards, and the best approach to ensure that scientific reasoning has its place in the policymaking process. If there are scientific conflicts, they may not only be disagreements over science but may also indicate broader political-ideological and professional conflicts. A scientist/advisor may also disagree for pragmatic reasons. A scientist with knowledge in a highly specialized field may abstain from having an opinion on a topic that requires yet another specialty. Scientists knowledgeable in nanotechnology are in short supply. Given that medical devices were addressed in three distinct directives roughly corresponding to three major product categories and industrial subsectors—active and non-active medical devices and in vitro diagnostic devices—additional, hypothetical scenarios of working groups in networked governance are imaginable. In addition, committee members meet behind closed doors, decide in secrecy, and are hardly accountable to any elected body (Dehousse 1999). Scientific issues are usually settled at this level and seldom, if ever, appear on the agenda of the Commission, the Council, or the European Parliament. Finally, in the initial years of EU medical device governance, reliance on scientific decision-making tended to privilege the larger member states perceived as having stronger scientific capacities (UK, France, Germany, and Italy). At that time, these four countries alone controlled forty votes out of the sixty-two needed for a qualified majority voting in the Council (Art. 148[2)] of the Amsterdam Treaty). In the in vitro diagnostic sector, the foremost leaders included the Germans and the French.

As this analysis has shown, over a span of twenty years innovations in governance occurred on two levels: within EU governance and national governance. On the EU level, the

directives prescribed policy and legal instruments that regulated medical devices under the medical technology framework. This, in part, disrupted the prior trajectory of medical device regulation subject to pharmaceutical regulation in those countries that regulated medical devices, while leaving the substance and essence of risk regulation to the various committee groups mentioned above. They produced a good number of soft instruments, such as the non-binding guiding documents (MEDDEVs), the NBOG, MSOG, and NB-Med documents, as well as a Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices (Medical Devices Expert Group). Actors operating in a more decentralized fashion include individual device makers, certification bodies, testing laboratories, etc.

Nanotechnology and Risk Regulation

Several observations are helpful to explore the evolution of medical device regulation in the European Union from the pre-nano to the nano era. The first consideration is that biomaterials emerged in several generations. While the first and second generations of biomaterials have been governed by the paradigm of biotechnology, the third or current generation of biomaterials explicitly addresses materials at the nanoscale and now is clustered around the concept of nanotechnology. Nanotechnology requires even more interdisciplinary effort than was previously true for medical technology regulation, as it involves knowledge from several disciplines: biomaterial and medical science, chemistry, physics, and biology. David Naidu (2009), a lawyer and partner in a U.S.-based law firm asks whether stricter regulatory controls are or should be in place "because of the *process* by which the product was created, or because the *product* itself has characteristics or qualities that render it potentially more risky to human health or the environment than products using other techniques?" (7). Third, he insists

that “the regulatory principles that were eventually approved for biotechnology are the same principles for nanotechnology today” (3). And, finally, nano-relevant risk issues tend to be product-specific and are not related to families of medical devices of, for example, implants, non-implants, powered or non-powered devices, and in-vitro diagnostic products, etc. This probably explains why the terms nanotechnology and nanomedicine are absent even in the most comprehensive and recent publications on the law and regulations of medical devices in the U.S. (Kahan 2009) and in the EU (O’Donnell 2009).

Risk regulation (covering risk assessment and management) has evolved in tandem with the revisions of the AIMDD and the MDD, as amended by the IVDD in 1998, and the regulation of advanced therapies as well as other adjustments of EU medical device governance to new developments. In the public arena, these issues have been debated in the language of biomaterials, combination products, and in-vitro diagnostics (Altenstetter 2008). Reference to nanotechnology and nanodevices are not found even in the most recent comprehensive study of the sector (Pammolli et al. 2005) or in earlier discussion documents (European Commission 1995). Nano-specific discussions within the EU governance system began in a methodologically systematic way only after 2004. The sale and use of nano-enhanced medicines and medical devices are expected to increase significantly by 2015 and will raise a host of governance, legal, and regulatory issues (Bauer and Lach 2008; Kelly and Bogaert 2008). This does not mean that risk regulation only started with an increasing awareness of risks associated with nanotechnology and nanoparticles; rather, it highlights how nanotechnology was considered under other existing, regulatory frameworks.

Invasiveness is one criteria for classifying medical devices. Experts expect improvements from nanotechnology for: catheters, endoscopes, needles for electro-stimulation, smart stents,

gene or cell transfection systems, syringes for less traumatic sampling, local delivery of therapeutic agents, and on-line monitoring sensors for detection of circulating molecules with low concentration. They also expect "improved instrumental biocompatibility, sustainable power supply, remote control and self-diagnostic capacity. Non-invasive medical devices like sensors for glucose monitoring, swallow able pills, or surface electrodes could also benefit from miniaturization and integration of several functions on a chip or on a device" (European Commission 2006, 15). However, it is also important to note that the average life span of a device is only eighteen months. Rather than an entirely different molecule, as in drugs, the method in medical device innovation usually involves an incremental change of one generation of, for example, an imaging unit or a heart valve. A good many of these devices existed in earlier versions and were subject to EU risk regulation.

Risk-related concerns are addressed in a number of formal and informal sources: Essential Requirements (ERs), comprehensive annexes to the directives (hard law), and guiding documents and interpretative documents referred to as MEDDEVs (non-binding or soft law, e.g., on reclassification of hip, knee, and shoulder implants), including occasional Commission guidance (e.g. on breast implants). Specifically, risk regulation of medical device rests on several building blocks that have evolved and been modified over the last twenty years, such as essential requirements, clinical evaluation, and risk analysis, including scientific/technical justification. [13] Risk concerns are also present in requirements for labeling, testing, processing, packaging, distribution, traceability and trackability, as well as related EN and ISO standards.

An integral part of risk assessment from the beginning, setting scientific standards for medical devices—in Class I (low risk), Class IIa and Class IIb (medium risk), and Class III (high risk)—is not static but has evolved over decades. For example, implants were upgraded to Class

III devices. Standards for clinical investigation and evaluation were tightened in the late 1990s and further tightened later. Now "[a]ll devices incorporating or consisting of particles, components or devices at the nanoscale are in Class III unless they are encapsulated or bound in such a manner that they cannot be released to the patient's organs, tissues, cells or molecules" (N&ET Working Group 2007, 6). A strictly regulated expansion of medical devices occurred with the submission of tissue-engineered products to regulation (discussed later).

National competent authorities began to discuss risks associated with nanotechnology in July 2004. The issue was taken up by the MDEG in October 2004. A Working Group on New and Emerging Technologies was formed in 2004, meeting several times in 2005 and 2006 (European Commission 2005, 2006). As stated in the Executive Summary (2006), this platform "is an industry-led consortium, bringing together the key European stakeholders in the sector" (1). The members in the platform are the leading American and European globally operating device makers, who have much to gain or lose from regulation. More recently, the N&ET Working Group published the *Report on Nanotechnology to the Medical Devices Expert Group* in 2007. The results of an ongoing Commission consultation on nanotech safety, launched in April 2009, may be known in the future.

It would be premature to comment in depth on the possible organizational changes that a discussion on nanotechnology and nanomedicine may produce in the next few years, though a brief discussion of pending changes is included below. No matter what will be proposed and where the sources of innovative ideas may come from—domestic or international—realistically, one should expect they will be framed in such a way that they can be enforced and implemented within the existing multi-tiered medical device governance system, relevant committees, and working groups with representation of industry and science. Only the future will tell how an

explicit recognition of the risks derived from nanotechnology and nanomedicine might transform the regulatory framework and clinical practice, and why such transformation should be welcomed, not obstructed.

Domestic Implementation and Compliance

Patient safety requires more than good intentions. The proof is in the pudding, namely implementation in the national arena and compliance at the "shop floor" of notified bodies, companies, hospitals, and other stakeholders The rules governing implementation in the member states remain a composite of EU directives, ECJ rulings and case law, EU-generated soft guidance, feedback from NBOGs on borderline and classification issues, consensus statements, interpretation documents, new approach standards, new and emerging technologies, and vigilance reports. Risk regulation and patient safety issues depend on such technical details. While these documents are valid for EU-based processes, they in particular provide guidance for implementation in the member states along the direction of established standard operating procedures (SOPs), routines and practices embedded in the historical trajectory of government, and public administration in each member state.

EU regulatory governance and multi-level policymaking on medical devices is characterized by a deliberate separation of policymaking from implementation (broadly speaking). Through a confluence of ECJ rulings on "direct effect" and "supremacy" of European law over national law, the three directives established a hierarchy by law and procedures and the *new approach* or co-regulation. In the member states, compliance, enforcement, and implementation rely on legacies of national regulation within the governmental and public administrative systems, and on the respective organization of the medical and scientific

professions within each society, as well as on a body of case law on medical devices (Hodges 2004; Beaumont, Lyons, and Walker 2002). The member states chose to support EU-wide regulation of medical devices, as long as they remained in charge of all oversight, monitoring, compliance, and implementation functions, along with control over the health protection scheme, health professions, and the delivery of health care. Member states have certainly taken advantage of having such extensive control over such functions. With each enlargement from the EU12 to the EU15 in 1995, EU25 in 2004, and then to the EU27 in 2007, the domestic implementation universe has become increasingly more diverse and complex. The "Swiss cheese-like model of implementation" (metaphor adapted from Cooper's image of a Swiss-Cheese Model of Patient Safety) applies in particular to the conduct of clinical trials and accident reporting. Well-documented data recently published by the Commission highlights the severity of adverse event reporting and medical vigilance in the delivery of health care in the EU member states. (Altenstetter 2008; Dahlkamp, Ludwig, and Schmid 2008).[14]

Restructuring the EU Medical Technology Framework

As mentioned earlier, a strictly regulated expansion of medical devices occurred with the submission of tissue-engineered products to regulation (Faulkner et al. 2003; Kent and Faulkner 2002). Unlike the previous AIMDD, MDD and IVDD, gene, cell- and tissue-based therapies, commonly referred to as advanced therapies, and borderline products were subject to a Regulation and to the pharmaceutical regime. The European Medicines Agency in London—the EU-level enforcement agency for the centralized procedure for pharmaceutical market licensing—received powers over these new products. Classification by risk category is suspended for these products and replaced by a product-by-product risk management approach.

This move away from the medical technology framework introduced considerable legal, institutional, and procedural variations within the EU medical-device specific framework and across the medical device and drug sectors. A survey of domestic implementation reveals more variation than the field of medical devices. For example, Ireland and the Netherlands only required an import license; Austria, Germany, Finland, and Belgium treated them as medicinal products; Spain, the UK, and Sweden took a case-by-case approach, classifying them as medical device or pharmaceutical. In France, Spain, and Belgium tissue banks played an important role (Altenstetter and Permanand 2007).

Implementation deficits are longstanding and indeed structural and institutional. They were identified in 2002 when the MDEG wrote the first ten-year review of the EU medical device framework. At that time, the legal framework was found to be sound and appropriate (European Commission 2003a, 2003b), yet implementation in the member states was not. Lessons are being learned from past problems in implementation. The emergence and work of the various working groups, and notably the report of the Working Group on New and Emerging Technologies in Medical Devices (N&ET Working Group 2007), are reflected in the new Directive (2007/47/EC). The new Directive (2007/47/EC) (amending directives 90/385/EEC, 93/42/EEC, and 98/8/EC) is the first significant overhaul of the MDD. It came into force on March 21, 2010.

The changes target three areas: the *essential requirements* which medical devices must satisfy in order to be lawfully placed on the market, the corresponding *conformity assessment procedures* and the *classification of devices* (European Commission 2009a). There also will be new rules for medical device software. Issues on borderline products (those that straddle two regulatory frameworks such as drugs and medical devices) remain. And though these issues are

very different from those involved in advanced therapies, they are equally relevant for nanomedical regulation. Klümper and Vollebregt (2009) ask: "where does a medical device oend and the network or other software begins?" (4-5). A medical device or an accessory to a medical device is subject to the directive and will require CE-marking for software.

These changes are significant and are designed to repair institutional and structural weaknesses found along all stages of a medical device life cycle and along the continuum of enforcing and implementing EU directives. Though not obvious at first glance, they do foster patient safety concerns by imposing more stringent requirements on clinical investigation, evaluation, and proof of clinical evidence, covering devices from Class I through Class III,[15] and requiring higher safety standards and uniform assessments throughout the EU. For the first time, the revised Directive (2007/47/EC) imposes the requirements that appropriate expertise for evaluating the most critical and innovative medical devices (mostly Class III devices) must be available. This requirement may present a serious dilemma for nanomedical regulation and nano-specific instruments of implementation due to a scarcity of in-house and out-of-house expertise and staff trained in nanotechnology and nanomedicine (N&ET Working Group 2007). Despite this dilemma, these measures are designed to coordinate adverse incident reporting on behalf of EU citizens by reducing risks and providing a safer environment for patients across Europe. With free mobility of European citizens and patients across national borders, patient safety concerns slowly but surely landed on the Commission's agenda (European Commission 2008b. Plans for revising the medical device framework further are under way, and specific provisions are expected to materialize in 2012 (European Commission 2008a). In January 2009, the Commission presented a proposal for a council recommendation on patient safety, including the prevention and control of healthcare associated infections (Commission 2009b).

Summary and Concluding Comments

In this article, I have focused on global regulatory developments and the EU medical technology regulatory framework as it developed from the early 1990s to the present by highlighting the sometimes contradictory information on patient safety concerns and the role they play in regulatory policymaking. The separation of myth from fact is unclear, depending on the observer's perspective. For this observer, it involves assessing the actual workings of regulatory governance with a two-edged emphasis on the process and the actors, on the one hand and, the underlying power structure of the "troika of the medical-industrial complex"—regulators, business interests and scientific communities—on the other.

In sum, law and regulation are good at specifying what needs to be done. But they cannot explain nor predict how implementation will actually work in the nexus of EU-member states relations. A governance perspective extended to domestic implementation can or should help identify pitfalls and erroneous assumptions about what is feasible given certain conditions in the member states, but it cannot guarantee successful implementation. While companies can be expected to comply, since continued access to the market is in their interest, and while surgeons may follow best practice identified by professional peers and accepted as legitimate, it is patients who ultimately face the real challenge of what is an acceptable risk and what is not. No matter how well scientists assess nano-related risks or how EU policymakers modify the existing medical technology framework, a new risk policy needs to be addressed and developed with planning for implementation in mind. There cannot be any opt-out of patient safety. What distinguishes nanotechnology and nano-enhanced medical products from the previous

generations of biomaterials is the greater degree of uncertainty, which sets the agenda for a new risk policy.

From a patient safety perspective, a first and compelling myth relates to the implied motivation of device makers and regulators to cooperate at the global level and how far they would go to achieve certain regulatory objectives (mostly, pre-market measures). While device makers may proclaim their motivations are rooted in patient safety concerns, doubts are raised when they avoid other regulatory objectives, such as those in post-market surveillance. Similar doubts in motivation occur when questioning whether the founding countries of the GHTF ever intended to give up their national tool kits for regulating medical technologies and securing patient safety.

Over the last sixteen years, regulators from advanced countries and representatives of globally operating device companies have participated in the activities of the GHTF, investing time and resources to come up with consensus documents providing non-binding guidance for national stakeholders. Of particular importance to nanopharmaceuticals and combination products that use nanomaterials is whether the GHTF ever will serve in a role similar to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for pharmaceuticals whose decisions are accepted as binding by the stakeholders. By contrast, it was not the intention of the GHTF founding members to transfer significant powers to the GHTF in order to develop binding technical guidelines on medical devices in the future. In addition, nanodevices received attention from the GHTF only two years ago. Why the reluctance of the GHTF members not to transfer significant powers to the GHTF in comparison to the ICH? In large part, the answer lies in the diverse nature of medical technologies and the influence and power of the related networks of vested interests,

including the huge transaction costs involved if such a decision would require that either the EU or the U.S. consider giving up its distinctive approach.

A second myth from a patient's perspective concerns the implementation of voluntary guidance documents at the global level, as well as the implementation of EU directives, the MEDDEVs, and other guidance documents by actors in the national arena. There is an assumption that this guidance is self-executing. Neither the transposed directives nor guidance documents will be enforced unless the actors in the implementation arena are willing to follow them. The third of these myths is the expectation that patient safety can be achieved by regulation alone. Patient safety at the delivery end of regulatory policy is not solely the result of regulatory science and sound regulatory governance. Patient safety results from the interaction of multiple implementing agents and, above all, from the quality of monitoring the reporting of adverse incidence and medical vigilance and in proper responses. Patient safety depends on the value orientations of the actors and societal preferences, and three communities can make a difference: the regulators over the delivery of care and professions, healthcare administrators, and scientific clinicians, including practitioners.

In the EU, the free-movement rules and the specific design of the three directives, from their start in 1990 and to later amendments, systematically favored trade, competition, and industrial policy over public health and patient safety. Risk regulation, as originally conceived, drafted, and adopted did not and could not prioritize public health and patient safety concerns. This was in part because of an absence of political will among the initial drafters and their political allies, and minimal public health advocacy at the European level in the initial years.

The governance of the EU medical technology framework showcases not only an interesting alternative governance model to the models prevailing in the U.S., Japan, and other

advanced countries but also to regulatory ideas and remedies of risk regulation being discussed in the GHTF and international organizations (e.g. the World Health Organization, the World Trade Organization, and the World Bank). Despite the institutional and structural weaknesses not allowing the representation of public health and patient voices in regulatory governance, the separation of EU regulatory policymaking from domestic implementation offers opportunities for patient safety. Broadly, evidence suggests that EU regulation has worked in favor of higher thresholds of personal patient safety, public health, and clinical standards. This is true in the member states endowed with the necessary resources, the expertise, and organizational and clinical capacities. This is not the case in all member states. For the device industry, this multi-jurisdictional construction provides space for competition for quality and price, trade, and profits while leaving space wide open for medical innovations and the various disciplines involved in the development of medical technologies. European patients in general have benefited from higher quality, safety, and performance standards (rather than efficacy) in those member states where regulation of medical devices did not exist prior to EU regulation. On an EU average, the two-tiered system has provided individual patients faster access to new treatments than, for example, in the U.S. and Japan. In Europe, this is due in large part to the respective health protection schemes and public health programs that provide safeguards for patient safety and patient rights in most, albeit not all member states rather than medical device regulation per se. Finally, the two-tiered jurisdictional construction and multilayered medical technology governance in the EU offer opportunities to the stakeholders and the related policy communities to address the major challenges involved in medical device risk regulation and solve them at the EU or, most likely, at the member-state level. The challenges for nanomedical regulation in the future are even greater and more complex to secure and assess than patient safety in medical

device applications. Nanomedical regulation inherits the strengths and weaknesses of the EU medical technology framework and implementation with often broken chains of implementation and “Swiss-cheese”-type holes. A few member states are likely to live up to the challenges.

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Laws of the Member States Relating to Active Implantable Medical Devices, Council Directive 93/42/EEC Concerning Medical Devices, and Directive 98/8/EC Concerning the Placing of Biocidal Products on the Market.

Table 1 Guiding Principles for an Effective Medical Device Regulatory Program

1. The primary goal is to protect public health and safety.
2. A regulatory system should ensure that valuable new technologies are made available to the clinical community and to patients and consumers expeditiously while preventing unsafe or ineffective devices from reaching the market.
3. Regulatory decisions must be based on strong and clear science, free of external influences and consistent with the directives of law.
4. As the guarantor of public health, enforcement of the law must be vigorously, fairly and uniformly carried out and appropriate regulatory and legal actions taken against violators.
5. Government-prescribed rules and procedures must be clearly articulated for those who must comply with them.... In other words, the specific rules promulgated by governments should be "transparent." Statutory, regulatory and scientific requirements must be clearly stated so industry will be fully aware of what is expected—that is, no "moving targets."
6. Assuring medical device safety entails more than the functioning of the device itself; it requires oversight of the use of medical devices.
7. Information on product risks must be openly communicated with health professionals and consumers.
8. Countries instituting medical device programs should be cognizant of ongoing international harmonization effects so as to preclude regulatory controls that conflict with actual harmonized rules and guidelines or with the spirit and goals on international harmonization.

Source: Eccleston, Robert C. 2001. *A Model Regulatory Program for Medical Devices: An International Guide.* Washington, D.C.: PAHO, WHO in cooperation with United States Food and Drug Administration. 3-6..

[1] "Nanotechnology is the design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanoscale" (N&ET Working Group 2007, 3).

[2] For more information on the financial relationship between the medical device industry and physicians, see the testimony of Gregory E. Demske, 2008. Demske is the Assistant Inspector General for Legal Affairs in the Office of Inspector General of the Department of Health and Human Services.

[3] EU governance and policymaking on medical devices and domestic implementation share many of the characteristics of governance identified by the contributors to *Innovative Governance in the European Union* (Tömmel and Verdun 2009). Drawn from cross-case policy sector comparisons, the lead scholar Ingeborg Tõmmel argues, "[T]he term governance has two dimensions: On the one hand, it refers to a process; on the other hand, it refers to the underlying regulatory structure. Governance as a process encompasses various modes of coordination, whereas governance in its structural dimension refers to the actors involved in the process and thus to an institutional setting underlying and shaping its various forms" (Tömmel and Verdun 2009, 12).

[4] Developing guiding principles is relatively easy when compared to putting the vital structural elements in place. Domestic politics, the political economy, and the historical legacy unique to each country explain why this is the case.

[5] In 2008 and 2009 not a week went by without the serious print media reporting on lawsuits, out-of-court settlements, investigations by the Justice Department, the Exchange and Security Commission, etc. See Demske (2008, 4-7); Dentzer (2008); Chatterji et al. (2008) for specific details.

[6] See www.ghtf.org for more information on the status of GHTF Documents.

[7] Representatives of regulatory authorities from the U.S. FDA, the EU, Canada, Australia, and Japan and leading device companies have been coming together in annual GHTF meetings, a voluntary international body established in 1993 with the goal of developing harmonized practices.

[8] Harmonized definitions are agreed upon for the essential requirements (ERs), how to perform a conformity assessment, what the essential principles of the manufacturing, including quality system, should look like, and what the principles of classifications and a uniform device identifier (UDI-Database) should be. They also have agreed on a global medical device nomenclature (GMDN). The UDI is expected to be approved by the relevant bodies in the EU in 2011. This is an extraordinary achievement considering the complex differences separating interested parties and stakeholders.

[9] Article 189 of the EEC Treaty outlines four instruments of EEC/EU regulatory power which vary in terms of their binding nature: regulations, directives, decisions, and recommendations. *Regulations* are binding directly on member states, individuals, or firms. *Directives* must be transposed in their entirety into national law leaving implementation to national governments and administrations. *Decisions* are binding upon specific parties. *Recommendations* are non-binding, "soft" instruments.

[10] Mutual recognition agreements between the EU and several countries are in effect, including Australia (OEJC L 229 of 17/08/98), New Zealand (OJEC L 229 of 17/08/98), the U.S. (OJEC L 31 of 4/02/99), Canada (OCEJ L 280 of 16/10/98), Israel (OJEC 263 of 9/10/99), Japan (OJEC L 284 of 29.10/2001), and Switzerland (OJEC L 114 of 30/04/2002).

[11] Since 1998 essential requirements (ERs) have specified the conditions for pre-market and post-market controls, including mandated adverse event reporting and medical vigilance. Conformity with ERs is the only valid basis for assessing quality, safety, and performance, which is slowly being complemented by attention to efficacy (i.e., effectiveness of treatment) and CE-marking. ERs are very relevant for patient safety issues and play a more important role in risk regulation for medical devices than for pharmaceuticals. Analysis reveals whether patient safety concerns are written into the MEDDEVs and provide guidance for manufacturers to follow. IVD products must meet specified technical and clinical standards for diagnosis and therapy. Common Technical Specifications (CTSs) exist for *in-vitro* diagnostic products (Commission Decision 2002/364/EC – OJ L 131/ 16.05.2002 and Commission Decision 2009/108/EC –OJ L 39/ 10.02.2009). ERs exist for chemical, physical, and biological properties, infection, and microbial contamination; construction and environmental properties; devices with measuring function; protection against radiation; requirements for medical devices connected to or equipped with an energy source (including electromagnetic compatibility); and information to be supplied by the manufacturer.

[12] From the industry-side network governance includes: the Medical Technologies Industry in Europe (EUCOMED), the European Coordination of the Radiological and Electromedical Industry (COCIR), the European Association of Authorized Representatives (EAAR), the European Diagnostic Manufacturers Association (EDMA), the European Hearing Instrument Manufacturing Association (EHIMA), the European Federation of Precision Mechanical and Optical Industries (EUROM), the European Industrial Federation committee on Medical Technology (EUROM VI), the European Contact lens and lens care industry's association (EUROMCONTACT) and, finally, the Federation of European Dental Industry (FIDE). Representatives of EUCOMED (European industry) and AdvaMed (US industry) keep in contact with each other through a so-called "virtual association of associations" with no secretariat or formal membership list but they do meet twice a year to exchange ideas about pricing and reimbursement. Lately, EUCOMED presents itself as the "Voice of the medical technology industry in Europe."

[13] Other risk activities are addressed in several activities: the scope, field of applications, definitions; classification; conformity assessment procedures; notified bodies; market surveillance; vigilance and adverse event reporting.

[14] Any interpretation, beyond the sheer numbers compiled and published by a regulatory agency, is limited by the history of regulation, a prevailing normative frame, and the maturity of the respective reporting system, if any exists, as well as the presence or absence of a "patient safety culture" in each country. For example, in 1998, the incidence rate of reporting in Germany was 1,134 cases. This figure was strikingly lower than for France (4,182 and rising) and the UK (6,298 and rising) (See Altenstetter 2008, 195-99). The low reporting in Germany (which rose from 1,134 to 4,646 by 2008) had little to do with superior quality of care or higher patient safety levels; it had everything to do with the legal requirements that only manufacturers were held to report incidents. It also displayed a hands-off stance of the regulatory agency rather than a "patient safety culture" (Dahlkamp, Ludwig, and Schmid 2008, 48-52).

[15] To clarify, these classes should not be confused with the three risk classes used in U.S. regulation.