

# A game with rules in the making – how the high probability of waiting games in nanomedicine is being mitigated through distributed regulation and responsible innovation

Joel D'Silva<sup>a\*</sup>, Douglas K.R. Robinson<sup>b,c</sup> and Clare Shelley-Egan<sup>a</sup>

<sup>a</sup>*Law and Regulation Group, Department of Public Administration, University of Twente, The Netherlands;*

<sup>b</sup>*TEQNODE Limited (SARL), Paris, France;* <sup>c</sup>*MINES Paristech, CGS- center for management science, Paris, France*

The potential benefits of nanotechnologies in healthcare are widely expected to be enormous and a considerable amount of investment is already pouring into public research in this area. These high expectations of benefits are coupled with uncertainty surrounding the potential risks of the prospective products containing nanomaterials, in addition to concerns about the adequacy of regulatory oversight. These challenges add another level of uncertainty for those deciding to invest in nanotechnology R&D and threaten to impede product development and commercialisation. Nanotechnology in healthcare (often labelled as nanomedicine) presents a situation where waiting games are a strong possibility; however, waiting games have been avoided (so far) through the unlocking of the dominant regulation regime. This paper describes how an innovation impasse in nanomedicine could have ensued if the traditional wait and watch strategies of legislators and regulators had been followed. We describe how waiting games were avoided through the opening up and distribution of regulatory approaches.

**Keywords:** regulation; responsible development; nanotechnology; nanomedicine; definitions; waiting games

## Introduction

Nanotechnologies are predicted to have an impact on almost every aspect of society; however, there is increasing concern that they will also bring unforeseen human and environmental health and safety risks (Van Calster, Bowman, and D'Silva 2011, 85; Parandian, Rip, and te Kulve 2012, in this issue). As government, industry and scientists race to determine and evaluate the potential risks posed by some aspects of nanotechnologies – particularly free engineered nanoparticles – there have been increasing calls for governments and other stakeholders to evaluate the adequacy

---

\*Corresponding author. Email: joel.dsilva@telenet.be

of current regulatory regimes for the various current and future applications of the technology (Van Calster, Bowman, and D'Silva 2011, 86; Hodge et al. 2010; Maynard et al. 2010). These include calls for new legislation (Davies 2006) up to a moratorium on development until adequate regulation can be assured (see, ETC 2006, 2010).

Nanomaterial standards, regulations and occupational health issues are still in flux. Nanomaterials are an extremely complex issue because of the wide variety of materials and properties at the nanoscale, the limited knowledge of toxicity of nanomaterials on living systems and their transport in living and environmental systems and the lack of harmonised standards or guidance for nanomaterial production. In Europe, where the precautionary principle is prominent, this lack of clarity is currently seen as the biggest bottleneck to nano-enabled innovations.

Innovation actors widely recognise that a clear regulatory landscape is essential to enable strategic decision making (Bergeson and Auer 2011) in its simplest form: to invest in or stay out of the innovation avenues which are opening up. The experience with genetically modified organisms (GMOs) in particular, in addition to regulatory failures such as those around asbestos, has led to several debates on how regulatory structures for nanotechnology should be developed and how the interplay between new product development and regulation should evolve.<sup>1</sup> However, increasing the specificity of legislation and regulation at an early stage in the emergence of a new technological field is not easy, nor is it necessarily desirable as often, 'in order to design and implement a legal system able to cope with rapid changes in technology, a broader perspective is generally required' (Moses 2007).

The regulatory environment for new technologies in general can be said to comprise 'a fluid, evolving collection of inter-related and overlapping measures, with jurisdictions at local, national and international levels' (Faulkner et al. 2004).

There is hence a dilemma, as described by Moses (2007, 248): The emphasis on broadness and fluidity has to be balanced with real-time co-evolution of regulatory frameworks. If this balance is not in place, four potential problems may arise according to Moses (2007):

1. There will be a failure in developing oversight approaches and appropriate legal restrictions and precautions to control risks associated with new technologies;
2. There will be high uncertainty in the application of existing frameworks to new technologies;
3. Existing rules might under or over-regulate the technology; and finally,
4. There is the potential for the new technology to make existing rules obsolete (see also, Marchant et al. 2009a,b).

Thus there is a dilemma to resolve in regulating new technologies and also an associated 'wicked' problem which may lead to an innovation impasse and waiting games.

### **Wicked problems that may lead to waiting games**

As much of the potential of nanotechnologies lies in the future, regulation is also expected to tackle anticipated issues, as Kearnes and Rip (2009) observe: 'The primary uncertainty regarding the trajectory of nanotechnology and its possible risks and broader societal consequences have given rise to the proposition that policymakers and regulators need to identify frameworks of governance that are adaptive and anticipatory, yet which recognise the limits of prediction' (Kearnes and Rip 2009, 97). The discussion of the governance of the associated risks of nanotechnology is running in parallel with the development of the technology and the associated products themselves. Thus,

there are also uncertainties regarding the form that the regulatory framework will eventually take and when it might emerge. For potentially radical innovation fields, this uncertainty can be extremely high and thus is a major factor in innovation actors' assessments as to whether to invest resources in the particular field.

The combined force of these uncertainties leads to a 'wicked' situation (Rittel and Webber 1973): Investing in development at an early stage presents a risk in terms of one or more of the uncertainties mentioned, while waiting to use nanotechnologies is also a risk in terms of lost opportunities. Thus innovation actors are faced with a problem which is difficult to resolve. One potential resolution is a 'waiting game' as defined in the editorial of this special issue 'Innovation waiting games occur over and above the strategies of individual actors. They are self-reinforcing mechanisms which can lead to a situation of innovation stalemate or stagnation, even if there is general acceptance that innovation is necessary' (Robinson, Le Masson, and Weil 2012). In a waiting game, actors wait for others to reduce uncertainties before they invest in innovation pathways (Robinson, Le Masson, and Weil 2011; Agogu , Le Masson, and Robinson 2012).

However, given the huge opportunities the commercialisation of innovations from nanotechnologies offers to business (innovation actors), there is pressure to (at least partially) resolve this problem. This, in turn, generates pressure for anticipatory governance because innovation actors will be less willing to move until there is greater clarity with regard to the regulatory landscape. However, on *their* side, regulators are caught between regulating too early, which is likely to stifle innovation, and regulating too late, which could result in a failure to have measures in place to provide safe and fair technology development and diffusion. For this reason, the traditional wait and watch strategies of legislation developers are insufficient.

This situation can be described as a tension: on the one hand, an announced desire (demand) for more targeted legislation and regulation from those stakeholders involved in the development and uptake of the emerging technology, and on the other hand, recognition by those who define and implement (supply) legislation and regulation that broadness is desirable and a complex entanglement of measures is required to be able to provide for an evolving field.

Given this high level of uncertainty for both developers and regulators, one might reasonably expect a static situation in which waiting games abound.

This paper shows that the situation is more dynamic and has shifted from wait and watch strategies to proactive (and distributed) discourse on different forms of regulation. More specifically, for the case of nanotechnology for healthcare (nanomedicine), this paper shows that a waiting game is not (yet) taking place because the wicked situation is allayed (but not circumvented) by the mix of regulation/governance activities distributed across many stakeholders and many arenas.

In section I, we outline key elements of the regulatory landscape, which are important for nanotechnology more broadly, such as definitions, standards and voluntary codes. We follow, in section II, with a more specific look at nanomedicine, where nanomaterials (manifest as supply chains for the value chains in healthcare innovation) are entering the healthcare sector.

### **I. An account of regulatory approaches, their effects and shortcomings**

Contemporary regulation is increasingly being viewed as much broader than simply 'command and control' or 'black letter law' (Brownsword 2010), covering multiple disciplines, 'decentralised' to a greater degree, and crossing a number of sectors. Beyond the formalised processes of Parliament or Congress, industry and civil society also regulate. According to Braithwaite et al. (2007, 3) regulation,

... can be conceived as that large subset of governance that is about steering the flow of events and behaviour, as opposed to providing and distributing. Of course when regulators regulate, they often steer the providing and distributing that regulated actors undertake as well.

While regulation may often be perceived as a way to minimise or manage risk of harm, it may also be used to encourage a particular type of activity in order to promote economic interests or innovation (Ludlow, Bowman, and Kirk 2009). Indeed, regulation is a key element of the 'responsible development of nanotechnology', which explicitly aims at enabling the development and commercialisation of nanotechnologies. In the remainder of this section, we will outline the general forms of regulation, starting with the role of standards and definitions.

### *(a) The role of standards and definitions*

The application of regulatory approaches (be they governmental, civil-based or mixed) also requires regulators to be able to say definitively that an object is a nanomaterial or nano-object (so it can fit into the remit of the regulation). The production and availability of well-characterised and controlled nanotechnology products depends on the availability of documentary standards for terminology, nomenclature, measurement and characterisation (Miles 2007, 344; Violet 2010). In the case of standards, most will have to be anticipatory since many nanotechnological developments still lie in the future. There are two major hurdles to overcome: a lack of sufficient scientific and technological knowledge and differences in the way the standards may be developed. Despite these hurdles, standards are necessary to facilitate the inter-operability of nanoscale devices and systems. Taxonomy standards will also be needed to ensure that everyone involved in the field is speaking the same language (Rashba et al. 2004, 192; Hunt 2004).

Another important element in the scope of regulating nanotechnologies is its very definition. Definitions are important from a regulatory perspective as 'they assist in establishing the subject matter and scope of what is to be regulated' (Bowman, D'Silva, and Van Calster 2010, 115; Williams 2010, 109–11). However, considering the complexities associated with nanoscience and the differing opinions on various definitions, this has not been an easy task. To date, there is no internationally recognised and accepted definition of a 'nanomaterial' even though several definitions have been discussed and proposed by national authorities, scientific committees, international organisations, and other bodies (Bowman, D'Silva, and Van Calster 2010; D'Silva 2011; D'Silva and Bowman 2010). For example, the European Union's (EU) recast Cosmetics Regulation<sup>2</sup> introduced a definition of a 'nanomaterial' (Article 2, 1(k)) and the attempted Novel Foods Recast.<sup>3</sup>

Further, in October 2011, the European Commission (EC) adopted a recommendation on the definition of a nanomaterial (European Commission 2011). The adopted definition is however not without its critics. For example, the European Environmental Bureau (EEB 2011) expressed disappointment that the definition was too narrow, while according to the European Association for the Co-ordination of Consumer Representation in Standardisation (ANEC), the use of such a definition may lead to a large number of products escaping regulation (ANEC 2011). Moreover, the European Chemical Industry Council (CEFIC) stated that the definition is too broad, and that it would add an 'unnecessary burden' as well as legal uncertainty for companies (CEFIC 2011).

However, with regard to developments in terms of standards and definitions, the question remains: Will these have any immediate impact on industry or do other parts of the regulatory puzzle have to fall into place before there is better knowledge about how nanomaterials will be regulated in the future (Chemical Watch 2011)? This question points to the importance of the reduction of waiting games in the (partial) resolution of the wicked situation.

**(b) Regulation by government and its limitations**

Nanotechnologies are not emerging in a vacuum; they are emerging in incumbent research disciplines, incumbent industrial sectors and, therefore, are emerging within existing regulatory frameworks such as various Acts, Regulations and Directives:

These traditional state-based “command and control” forms of regulation have considerable legitimacy with the public despite their perceived imperfections. Their compulsory nature, the appearance of strong accountability and higher certainty are all characteristics that appeal to voters. (Bowman 2010, 76)

However, as stated by Majone (1994, 81),

regulation cannot be achieved by simply passing a law, but in fact requires detailed knowledge of, and intimate involvement with, the regulated “activity”.

Therefore, while state-based regulation may provide clarity, the traditional form of regulation suffers from several shortcomings (Gunningham and Rees 1997; Vogel 2006). It is often touted as being slow, cumbersome, rigid and involving high transaction costs (Moran 1995; and Sinclair 1997), characteristics that are amplified in the context of a rapidly evolving field where the regulatory requirements are more dynamic and information is imperfect (Bowman 2010, 76). Given these general limitations, it is unsurprising that some commentators have suggested that in the short term, nano-specific legislation may not be the most appropriate or effective way to regulate the technology (see Bowman and Hodge 2008).

The *wicked situation* (described in the introduction) raises its head here: how to regulate such that innovation can be enabled while sufficient regulatory measures for a rapidly evolving field can be implemented?

Civil-based regulation may provide a partial solution to this wicked problem, although it does also have its limitations, as will be described in the following section.

**(c) Civil-based and self-regulation**

‘Soft law’ – or civil regulation – mechanisms are part of the regulatory continuum and include various voluntary codes of conduct, risk management frameworks and industry codes, as well as hybrid arrangements (Gunningham and Rees 1997; Vogel 2006). Importantly, ‘civil regulation extends regulatory authority “sideways” beyond the state to civil society and to non-state actors’, thereby removing the potential for legally binding standards<sup>4</sup> (Vogel 2006, 3). Voluntary forms of regulation are less resource intensive to develop and administer, have the ability to evolve and respond to the changing environment quicker than state-based regulation and provide breathing space for a nascent field of innovation. Given these features, one might reasonably expect that voluntary forms of regulation could provide a solution to the needs of both the technology developers (more context targeted regulation that can be implemented swiftly), provide an interim solution to allow the traditional wait and watch strategies of regulators to play out, and in the mean-time assuage the potential users of new products (and civil society in general) of concerns about quality and safety.

There are clear limitations of this perspective. Self-regulation in particular, is accused of serving the interests of industry above those of civil society (and their representatives) by having variable standards of enforcement and of lacking the accountability and legitimacy of government regulation (see Braithwaite 1993; Webb and Morrison 1996). A persistent criticism of industry led

self-regulation relates to inherent conflicts of interest: 'it seems to let the proverbial fox guard the hen-house' (Lin 2007, 111).

It can, however, be argued that 'an enlightened company might see that it is in their best interest to deliver safe products, since harming one's own customers is counterproductive to one's reputation and business as well as opens the company to possible litigation' (Lin 2007, 111). We return to these two perspectives later when we describe responsible development and innovation.

#### ***(d) Co-regulatory strategies***

Attempts have been made to overcome the limitations of civil-based regulation and self-regulation, with the instigation of co-regulatory strategies that aim to bring greater transparency to regulatory moves by industry by inviting companies to take part in voluntary reporting.

Evidence of co-regulation has already emerged – in consultation with industry and other stakeholders and voluntary reporting schemes or data stewardship programs have already been implemented (for example, Department of Environment Food and Rural Affairs 2006 (Defra); National Industrial Chemical Notification and Assessment Scheme 2007, 2008; Environment Protection Agency 2008 (EPA)). However, according to Marchant et al. (2010), such schemes may not bring broad industry participation, and sufficient data submission to aid regulators in risk assessments, reinforcing the concern of public stakeholders of the reduced government involvement (which would provide greater credibility in the eyes of civil society).

The ongoing challenge for various stakeholders will be acquiring an acceptable balance between the different regulatory approaches. This is likely to be dependent in part on; the state of scientific knowledge (and its rate of evolution), the degree of legitimacy attached to any one approach, the jurisdiction in which it is employed, and the way in which benefits and risks of particular areas are perceived within those jurisdictions (Ludlow, Bowman, and Kirk 2009).

Another related point is what does all this mean for another important stakeholder: the insurance industry? With several customers working in a range of industries, many of whom are investing heavily in nanotechnology, the insurance industry also faces challenges relating to novelty, uncertainty, emerging risks and limited available data. According to Epprecht, 'this parallelism makes it tempting to believe that the insurance industry can play a quasi-regulatory role or act as a judge where there are conflicting interests' (2010, 169).

Furthermore, the regulatory goal 'can only be achieved with the aid of insurance when risks are, first of all, measurable, acceptable and affordable; that is, if the prerequisites of insurability are met' (Epprecht 2010, 170). A liable party can hence meet much of its obligations by transferring the associated financial burden to a risk carrier such as an insurer (Epprecht 2010, 170). The role of insurance companies in the governance mix for nanotechnologies has been visible since the mid-2000s (for example, Swiss Re, see Robinson 2009a).

#### ***(e) The rise of 'responsible development' of nanotechnology***

The need to achieve this regulatory balance lies at the heart of policy innovations in the governance of nanotechnology, which, taken together, form what Kearnes and Rip (2009) term the 'emerging governance landscape of nanotechnology'. This emerging landscape includes various initiatives aimed at enabling the development and commercialisation of nanotechnologies, in addition to the development of regulatory approaches and civil-based and self-regulation, other forms of soft law, mechanisms for the study of ethical and societal aspects,<sup>5</sup> and public deliberation and voluntary codes on responsible development. These initiatives have culminated in a

discourse of ‘responsible development’, which has become a new feature in science policy programmes.

The notion of the ‘responsible development’ of nanotechnology refers to ‘responsibility’ as a general governance framework for development. The voluntary EC Code of Conduct for Responsible Nanosciences and Nanotechnologies Research<sup>6</sup> is illustrative of the move towards this kind of framework.

The Code advocates a ‘general culture of responsibility (...) in view of challenges and opportunities that may be raised in the future and that we cannot at present foresee’ (European Commission 2008). Developers of nanotechnology are invited to contribute actively to the responsible development of nanotechnology, as is explicitly set out in the following definition of responsible development:

... [Responsible development of nanotechnology] implies a commitment to develop and use technology to help meet the most pressing human and societal needs, while making every reasonable effort to anticipate and mitigate adverse implications or unintended consequences. (Committee to Review the National Nanotechnology Initiative, National Research Council 2006)

Although ‘responsible development’ is not operationalised and there are no specific, dedicated activities associated with it, developers none the less feel pressurised to respond. In the regulatory domain, this is visible in the introduction of innovative regulatory mechanisms aimed at enabling safe and beneficial innovation. The use of these regulatory initiatives, along with the emergence of a discourse of responsible development, is constructed as a strategic response to the uncertainties that underlie current nanotechnology development. Importantly, current debates about the governance and regulation of nanotechnology are viewed as a test case of how to regulate early in development in order to provide a secure regulatory footing to enable the (responsible) development of nanotechnology (Kearnes and Rip 2009).

A recurrent debate in the discussion of regulation for nanotechnology centres on whether existing regulatory frameworks are sufficient for the regulation of nanotechnologies. Early debate was initiated by strong precautionary approaches and calls for moratoria on the use of nanomaterials in laboratory settings and on their release into the environment. Important to note, is that non-regulatory actors provided a demand for regulatory action at a relatively early stage in the emergence of nanotechnology. The Royal Society/Royal Academy of Engineering report (2004) emphasised the importance of regulatory reviews regarding the sufficiency of existing regulatory frameworks. The existence of regulatory gaps led to the establishment of voluntary reporting schemes – designed to build a knowledge base for the use of engineered nanoparticles and materials – such as the UK Department of Environment, Food and Rural Affairs (Defra) ‘Voluntary Reporting Scheme for Engineered Nanoscale Materials’ and the US Environmental Protection Agency’s Stewardship programme of voluntary reporting on nanotechnology-enabled products.

By July 2008, only nine companies had registered with the Defra scheme and the EPA had received four submissions under the basic programme (and commitments from 12 additional companies), whilst no company has agreed to participate in the in-depth programme. The disappointing response to both schemes demonstrates that regulation of nanotechnology is not just a matter of a new government initiative. It is prepared through actors moving in new directions. Such actors can include firms that realise that they need to proceed cautiously and perhaps assure credibility by being more transparent. Regulatory actors can recognise that there are opportunities for regulatory action but do not know how exactly to proceed. The combination of the two creates a situation where soft law can be envisaged (Shelley-Egan 2011). Indeed, soft law forms

of voluntary regulation did emerge, in particular the corporate partnership established in 2005 between DuPont and Environmental Defense to produce a nano risk framework<sup>7</sup> aimed at evaluating and addressing potential environmental, health and safety risks of nanomaterials across the entire life cycle of the materials. Soft law approaches have also been taken up in voluntary codes on responsible development such as the Responsible NanoCode developed by the Royal Society, Insight Investment and the Nanotechnology Industries Association which aims to stimulate organisations involved in the research, development, manufacturing and retailing of products using nanotechnologies to 'consider all aspects of their involvement with nanotechnologies, including the broader social and ethical issues' (Responsible Nanotechnologies Code. Consultation Draft 2007). Approaches to 'responsible' development of nanotechnology have also gained traction in industry, as is visible in the proliferation of soft law approaches such as a Code of Conduct for nanotechnology (BASF), public position statements on nanotechnologies (DSM and GSK) and a 'Nano Guideline' (Evonik). In these initiatives, responsible development is generally articulated in terms of environmental, health and safety issues, risk assessment and risk management. There is also some reference to dialogue with society (BASF and DSM) in such initiatives.

These activities related to responsible development as making every reasonable effort to anticipate and mitigate adverse implications or unintended consequences, allay waiting games by offering arenas in which key elements of best practice for the responsible development of nanotechnologies can be negotiated and debated. Indeed Bowman and Hodge (2008) note that no one single mechanism provides the perfect regulatory solution. Instead, they predict that, given the heterogeneous nature of nanotechnology, 'individual regulatory mechanisms will exist within a broader matrix, most of which will involve public and private-sector participation and cooperation of varying degrees' (Bowman and Hodge 2008, 479; D'Silva and Van Calster 2010). Their observation highlights the centrality of *distributed responsibility in nanotechnology regulation*. Responsibility for the development and use of nanotechnology is distributed across myriad stakeholders. There is no longer one central regulating actor; regulatory and governance initiatives are spread out across various actors. Thus the process of the governance of the responsible development of nanotechnology will include 'many visible hands' (Rip and Groen 2001), rather than one invisible hand steering the development. While such distributed regulation may invite questions about the legitimacy and effectiveness of regulation, it has also led to active engagement with the 'wicked' problem of regulating too early, which is likely to stifle innovation, and regulating too late, which could result in a failure to have measures in place to provide safe and fair technology development and diffusion.

## II. Nanomedicine and forms and effects of its regulation

Nanotechnology for healthcare generally involves the engineering, design, fabrication and application of drugs and medical devices that are about 1–100 nm in size or incorporate nanomaterials of this size into their structure (this is, however, not a standard definition). While it is expected that nanomedicine will radically change the health care sector, it is also predicted to challenge existing perceptions, dynamics and standards relating to ethics, patient and environmental safety and governance (D'Silva and Bowman 2011; D'Silva and Van Calster 2009; Marchant et al. 2009a,b; Wagner et al. 2006; Royal Society 2004).

In addition to the potential risks associated with nanomedical products themselves, a number of commentators have raised concerns about the potential occupational and environmental risks associated with the manufacture and disposal of nanomedicines, drugs and devices (Linkov, Satterstrom and Corey 2008; Marchant et al. 2009a,b). Regulators are increasingly faced with the



need to regulate nanomedicine, while knowledge gaps,<sup>8</sup> questions of expertise and definitional issues all pose crucial challenges (Chowdhury 2010, 135; D'Silva and Van Calster 2009). As in many other areas, there are no specific laws pertaining to nanomedicine in the European Union (EU), nor indeed in any other jurisdiction, at this time; this however does not mean that nanomedicine is 'unregulated' (D'Silva and Bowman forthcoming). Rather, such products are being regulated under existing legislation on medicinal products and devices, tissue engineering and other advanced therapies.

Before we go deeper into the current, and evolving regulatory landscape for nanomedicine, we introduce nanomedicine itself and the actors that are covered by this umbrella term.

### ***Introduction to nanomedicine and actors***

Many studies of nanotechnology governance look at the enabling nanotechnologies (mostly nanomaterials) themselves to explore the risks, regulation and standards for nanomaterials. Another approach is to look at the potential application envisioned in the future, and to speculate on the governance arrangements that will be needed to mitigate the risks, and promote the benefits, of nano-enabled products. Such anticipation and speculation on Nanomedicine futures is important if anticipatory forms of regulation (the opposite of wait and watch regulatory strategies) are to take place.

Studies of innovation show that there is a *translation* of promising technoscience into products in society. The translation occurs at the level of industries in particular sectors, in (usually) stabilised configurations of actors involved in adding value in the conversion of the original technology into a workable device/product that is embedded in society. The concept often used to describe this consecutive up-valuing of a material or technological device is the value chain model.<sup>9</sup>

In Figure 1 we provide a schematic for nanomaterials for healthcare (or better the nanomedicine value chains). Nanomaterial supply chains feed into three broad medical innovation chains: pharmaceutical, implants, and medical devices. The diagram illustrates that there are multiple and diverse actor types. On the left hand side of the diagram, there is the nanomaterial research community working on all sorts of materials. Also connected to this we see nanomaterial manufacturers who translate the technology knowledge into industrial production capabilities. Nanomaterial regulation, legislation, health and safety issues, as well as financing are located in the framing conditions that shape and direct the field of nanomaterials R&D. In the previous section, we described the spread of regulatory activities and processes that are involved in this 'pure nano' part of the nanomedicine value chain.

In providing anticipatory regulation (as opposed to wait and watch regulatory strategies) a clear picture of what are the collective expectations is necessary,<sup>10</sup> along with articulation of actual activities in nanomedicine. For nanomedicine, forums for coordinated expectation building across the medical innovation value chain have been initiated early. We argue that these co-ordinated articulation processes provide a half-way measure between dispersed and fragmented innovation pathway projections, and what Bakker and Budde (2012, in this issue) have termed as collective expectations. They allow innovators to align, to a certain extent, and provide scenarios for regulators (both legislator actors; and those involved in codes of conduct and other forms of soft law).

Figure 1 is actually a scheme of a potential collection of value chains for nanomedicine. For nanomedicine breakthroughs to succeed, actor realignment from laboratory to products and applications is necessary. Realignment is easier to achieve where the actors are known, their relationships functioning, regulation is largely unambiguous, and the technology field is well understood. The nano-hype has brought with it high expectations in the field of nanomedicine,

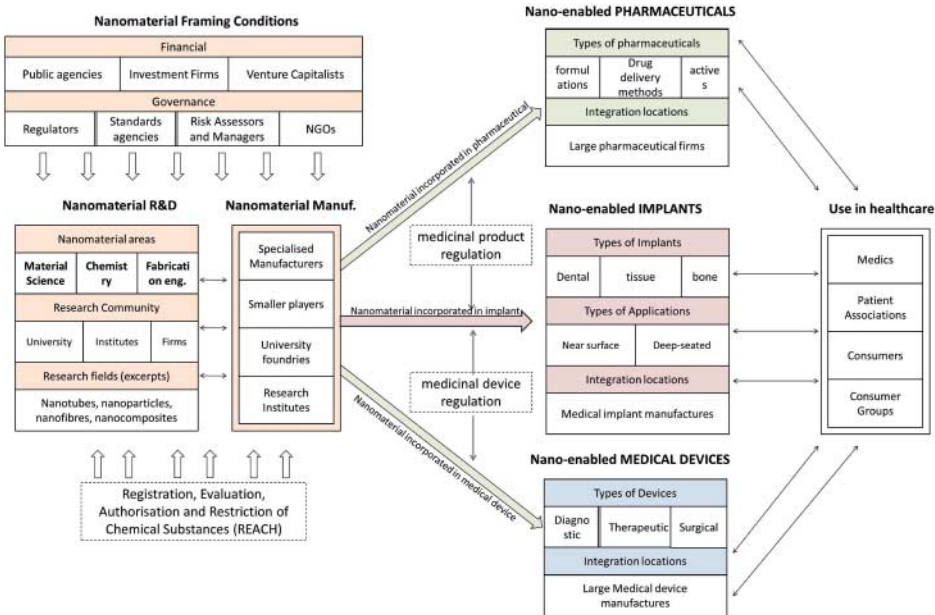


Figure 1. Nanomaterial supply chains feed into three broad medical innovation chains: pharmaceutical, implants, and medical devices.

for the potential users (patients, doctors, health care authorities), medical innovation related firms developing devices, drugs and implants, and also researchers (who are eager to explore nanotechnology for the life science and biomedical applications).

In the past eight years, a number of anticipatory coordinating forums have emerged which attempt to align actors to create such value chains amidst the high uncertainty of nanotechnologies and the diversity of its forms and applications. Looking at Europe, one platform is the European Technology Platform for Nanomedicine, which is a public research and private R&D network which determines strategic agendas (formalised expectations of the community) and creates roadmaps (Parandian, Rip, and te Kulve 2012 – see this issue, detail this platform further). Articulating futures and stabilising expectations has been the aim and has led to some success; however, interaction with the potential users of the nanomedicines (located at the right hand side of the value chain) has been less visible. A focus on the users has been the aim of CLINAM, an annual conference where the medical community (doctors and medical researchers) congregate to explore the current state of the art of nanomedicine related research and to speculate about potential and desirable futures. NanoBioRAISE was a European project aimed at articulating potential governance and ethical challenges for nanomedicine in order to provide intelligence for both governance actors and innovation actors alike.

Looking at the whole value chain, MEDITRANS (see Parandian, Rip, and te Kulve 2012) focuses on translating R&D on nanotechnology into medical value chains. Comprised of a diverse set of firms (including large pharmaceutical firms) they assess expectations and project innovation pathways that are the most promising (and these act as a guide to align value chains). Other similar activities, such as strategy articulation workshops, have been incorporated in R&D consortia for Nanomedicine. The Nanomed Round Table project was organised to provide European stakeholders with a set of recommendations to support decision making regarding nanomedical innovations.

For example, the 6<sup>th</sup> European Framework network of excellence for nano and the life sciences (FRONTIERS) included Constructive Technology Assessment projects to explore potential configurations of actors in terms of value chains, governance and actors roles and activities (Robinson 2010).

These indicate that, to be able to align actors to create value chains in nanomedicine, R&D actors have created forums for articulating potential futures, and use these as scenarios for evaluating optimum routes, technological and innovation challenges, societal issues and governance challenges. This is important intelligence for those developing regulatory activities.

In the remainder of this section, we will shift away from nanomedicine research actors and explore the different types of regulation and the issues that are distributed across the value chain depicted in Figure 1.

#### ***(a) Nanotechnologies incorporated in medicinal products in Europe***

In Europe, medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules. The general medical legislation is supported by a series of guidelines. According to Article 6 of the Directive 2001/83/EC,<sup>11</sup> no medicinal product can be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member. Regulation 2309/93 sets down procedures for the authorisation and supervision of medicinal products and established a European Agency for the Evaluation of Medicinal Products.<sup>12</sup> The regulation was updated in 2004 by Regulation 726/2004, at which time the name of the agency was changed to the European Medicines Agency (EMA).<sup>13</sup> The EMA consists of six scientific committees: including the Committee for Medicinal Products for Human Use (CHMP).

The CHMP released a reflection paper on nanotechnologies in medicine in 2006. In this paper, the CHMP concluded that nanomedicinal products are adequately regulated under existing legislation. However, the CHMP accepts that the development and commercialisation of increasingly sophisticated nano-products that span regulatory boundaries between medicinal products and medical devices are likely to challenge the current criteria used by EMA in relation to classification and evaluation. As such products are developed, appropriate expertise and guidelines are likely to be needed to ensure quality, safety, efficacy and risk-management (CHMP 2006).

#### ***(b) Nanotechnology in medical devices***

Medical devices are regulated by Directive 93/42/EEC (The Medical Devices Directive),<sup>14</sup> Directive 90/385/EEC (The Active Implantable Medical Devices Directive)<sup>15</sup> and Directive 98/79/EC (The In Vitro Diagnostic Medical Devices Directive).<sup>16</sup> Manufacturers of medical devices are under a legal duty to carry out risk assessments, demonstrate the effectiveness of the device, implement a procedure for post-market surveillance and comply with the essential requirements of Annex 1 of the Medical Devices Directive (MDD) pertaining to design, use and safety (Article 3). Compliance with essential requirements of Annex 1 is presumed if the device is in conformity with relevant national standards adopted pursuant to harmonised standards published in the Official Journal of the European Union (MDD, Article 5).

A product is said to fall within the scope of the Active Implantable Medical Devices Directive (AIMDD) if it complies with the definition of an AIMD: it must be a 'medical device' and at the same time, both 'active' and 'implantable'. Examples of active implantable medical devices include implantable cardiac pacemakers, implantable nerve stimulators and implantable active

drug administration devices. As in the case of the MDD, Annex 1 of the AIMD sets out the general requirements for compliance as well as certain requirements regarding design and construction. When an AIMD is intended to administer a substance defined as a medicinal product, that substance shall be subject to the system of marketing authorisation provided for a medical product (AIMDD, Article 1(3)). Where an active implantable medical device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product, that device must be evaluated and authorised in accordance with the provisions of the AIMDD (Article 1(4)).

The In Vitro Diagnostic Medical Devices Directive (IVDD) covers the placement and subsequent service requirements associated with *in vitro* diagnostic medical devices. Devices used *in vitro* for the examination of a specimen derived from the human body, including reagents, instruments and specimen receptacles, fall within the scope of the Directive. All *in vitro* diagnostic devices, including those that incorporate nanomaterials or are manufactured using nanotechnology-based processes, must meet the applicable 'essential requirements' on safety, performance and labelling as outlined in Annex I of the IVDD. The fulfilment of the essential requirements has to be demonstrated by the manufacturer for all devices. This includes both new devices and those that have been previously available on the market. Thus a critical aspect of medical devices regulation is conformity to various harmonised standards.

#### ***(c) Registration, evaluation, authorisation and restriction of chemical substances (REACH)***

European chemicals regulation has been consolidated and integrated with the creation of REACH.<sup>17</sup> Provisions relating to the classification and labelling of substances are dealt with in a separate Regulation on Classification, Labelling and Packaging (CLP)<sup>18</sup> of substances. The REACH Regulation contains broad exemptions for pharmaceuticals and medical products but there remain important regulatory obligations pertaining to disclosure of information and acceptable use (Breggin et al. 2009). Since the main exemption for pharmaceuticals only covers substances that are explicitly 'used in' medicinal products, other substances used in the manufacturing process are likely to be subject to the full scope of REACH. Even if the substances are not subject to most of the REACH requirements when intended for medicinal products, pharmaceutical companies are likely to be affected by the restrictions applying to their suppliers. Despite there being no explicit provision for nanomaterials, they are considered to be covered by the 'substance' definition in Article 3 of REACH (Breggin et al. 2009). In June 2008, the EC concluded that the current EU legislative framework was, in principle, adequate to regulate nanoscale substances effectively (EC Communication 366 2008). However, the Commission also acknowledged the need for fundamental scientific research to be undertaken in order to determine if the existing standards and risk assessment methodology underpinning the REACH regime are appropriate for nanoscale substances.

#### ***(d) The challenge of borderline products***

The boundaries between medicinal products, devices and therapies are also likely to become increasingly blurred with advances in medical technology and nanoscience. The convergence between these is commonly referred to as 'borderline products'. To date, the most frequent borderline products have occurred between medical devices and medicinal products. In order to determine whether a product is a device or a medicine, the definitions of both need to be

considered, along with the claims for the product, the mode of action on the human body and the intended purpose of the product (D'Silva and Van Calster 2009).

Another consideration is the jurisdictional line between the IVDD and the MDD. Advances in medical technology generally, and nanoscience more specifically, are likely to blur this line and make it harder to determine under which regime a product *prima facie* falls (D'Silva and Bowman forthcoming).

Depending on the classification, regulatory requirements for pre-market and/or post-market processes kick in accordingly, with variation in the regulatory pathway existing for medical devices, medical products or therapies (ibid.). One can see this often in nano-enabled implants (see Figure 1 where implant value chains show two routes for regulation). The essential requirements and conformity assessment procedures of the MDD, which were developed and adopted on the premise that the directive shall not be applicable to *in vitro* diagnostics, is a case in point here. Several harmonised standards have been designed for a certain type of device, as in the case of standards for *in vitro* devices; these would hence not give rise to the legal presumption of conformity if applied to devices that are not clearly *in vitro* devices. It can also be argued that the blurring of these traditional boundaries has the potential to challenge the competencies of notified bodies charged with the responsibility to assess and authorise these borderline products.

#### **(e) Standards in nanomedicine**

The complex web of EU Directives applicable to nanomedicines do not prescribe specific features to ensure safety, but rather incorporate a series of 'essential requirements'<sup>19</sup> that are designed to eliminate or reduce risks as far as possible. Compliance with these requirements is necessary in order to obtain CE marking. Products that are subsequently manufactured in conformity with harmonised standards are presumed to conform to essential requirements of the various directives, and meet the relevant safety and risk assessment requirements: this is often referred to as presumption of compliance or conformity (Delaney and Van de Zande 2000, 10–11).

However, most of the standards were designed and introduced prior to the emergence of nanotechnologies and, are therefore, not designed specifically to address any additional risks and/or challenges that may be posed by the use of nanomaterials and nanoparticles in products. Recognition of this potential shortcoming, in concert with the growing appreciation of the importance and potential market size of nanotechnology-based products, resulted in the establishment by CEN of CEN/TC 352 – Nanotechnologies (CEN 2005).<sup>20</sup>

While the technical committee still has much work to do in this area, its work to date has without doubt assisted in the harmonisation of nano-standards. However, various conformity assessments and standards are still being developed and their effectiveness and adequacy is yet to be ascertained (CEN 2005).

#### **(f) To define or not to define – that is the question**

As nanomedicine evolves and becomes more complex, finding suitable and accepted definitions will become increasingly important. The development of definitions and standards in fields like nanomedicine has and is likely to continue to face two main problems – the lack of scientific and technical knowledge required, and the different approaches and specifications being developed by different bodies.

According to Bergeson and Auer (2011), 'the definitional void is frustrating nanomaterial stakeholders as the lack of definitional clarity invites commercial, legal, and compliance uncertainties.

Similarly, the lack of a regulatory definition has created uncertainty and possibly complexities for regulators as well'.

It remains to be seen if such nano specific aspects or definitions will be introduced in the nanomedical sphere in the near future. Risk assessment, safety and quality requirements are to be fulfilled by conformity to established quality systems and product standards, which – based on the current scientific state of the art – may or may not be suitable to address various concerns relating to nanomedicine.

As progress in medicine and nanoscience accelerates in the manufacture and characterisation of nanoscale materials and nano-enabled products, it will become increasingly important for researchers, manufacturers, regulators and other stakeholders to have agreed upon nanotechnology standards. Such standards will have to address the evaluation of the quality, safety, efficacy and risk-management of nanomedicinal products.

### **III. Discussion: of waiting games and regulation**

Nanomedicine is a complex area of technological application with various actors playing a role, be it pharmaceutical companies, manufacturers or patients. The intersection of various actors and dependencies in nanomedicine is complex and uncertain and hence likely to lead to waiting games as actors wait for others to take an initiative. Uncertainties in terms of risk, acceptance by patients (public) and the scope of future developments in nanomedicine means that, more often than not, companies and manufacturers of nanomedical products will be very cautious, if not preferring to wait and watch. Interdependent actors can hope that other actors will act to reduce uncertainties and thus wait before they themselves invest (see Parandian, Rip, and te Kulve 2012 in this special issue). Waiting games in areas like nanomedicine then become almost unavoidable. As in the case of the nano-food and packaging sector (Robinson 2009b), for the successful development and embedding of nanomedicine, business and non-business actors and civil society groups, constitute a significant set of actors (see Te Kulve 2010; Robinson 2011). Health, safety and environmental regulations in turn have an impact in various degrees on these actors. These actors will tend to be cautious about cooperation while uncertainties and risks are likely to create further waiting games between firms and regulatory authorities (Shelley-Egan 2011).

Coordinating entities and forums such as the ETP-Nanomedicine (researchers and firms though few pharmaceutical players involved), MEDITRANS (focused on industrial manufacturers (including pharmaceutical firms) and links with researchers) and CLINAM (focused on medical community and practitioners) have provided locations in Europe to articulate future developments of nanomedicine and articulate the demands for regulation.

Projects such as NanoMed Roundtable, the constructive technology assessment activities of the Frontiers network and NanoBioRAISE have provided ways of articulating ethical and societal issues (and the socio-technical linkages) with respect to potential future nanotechnologies.

Arenas for multi-stakeholder interaction and articulation of views and potential elements of a governance landscape are viewed as an important tool in the design of the governance landscape and in restoring public faith in innovation and in regulatory oversight of science and technology (see, Mandel 2009, 9–10). Initiatives such as the Responsible NanoCode, FP7 NanoCode and the European Code of Conduct for Nanoscience and Nanotechnology act as means to improve (or create more robust) soft law mechanisms. These provide support tools and intelligence for the move towards responsible development by researchers and manufacturers of nanotechnologies.

For more governmental and international level initiatives, since harmonised standards form an integral part of medical regulation, it seems certain that the 'wait' for standards will have a direct

effect on current regulatory initiatives in the case of nanomedicine. Although this is not the case for nanomedicine to date, the EU is already incorporating nano-specific initiatives as evidenced by the inclusion of provisions into EU Cosmetics Regulation in 2009 while a recommendation on the definition of a 'nanomaterial' was adopted by the EC in 2011. Legislators in the EU are likely to continue regulating nanomedical products and devices under the existing regulatory structures wherever possible rather than create a *sui generis* regime for nanomedicines. This wait and watch strategy arguably is a logical step in the short term as the regimes for medical products and devices regulation are relatively elaborate and involve not only pre-market authorisation processes but also post-market surveillance and compliance requirements. The regimes generally have been kept up to date and relevant by careful adaptation of new product development into product safety, quality and efficacy (Dorbeck-Jung and Chowdhury 2011, 293). However, in the long term none of the legislation was written with nanomedicinal applications in mind. It, therefore, seems likely that this legislation will need to be revised in due course in order to take account of specific risks and challenges (EGE 2007; N&ET 2007; SCENIHR 2007).

Though modification of existing regulations and standards to incorporate nanomedicine seems to be one potential approach, such action will not address the more fundamental issue – that existing risk assessment methodologies may be inadequate primarily due to their reliance on mass metrics. Hence if existing regulations are modified to make them more nano-conversant, existing risk methodologies will also have to be adapted to introduce agglomeration, particle size, shape and surface reactivity into the assessment criteria (Handy et al. 2008), as well as steps initiated to bolster expertise.

#### IV. Conclusion

This paper has outlined another type of waiting game based on the entanglements and co-evolution of regulation approaches and nanomedicine innovation. We argued that the logic of the traditional wait and watch strategies of legislation actors, coupled with the high uncertainties for nanotechnologies for the healthcare sector, meant that one would expect a waiting game leading to innovation stagnation to be inevitable.

This has not been the case however, and we argue that it is due to the breakdown of the traditional locations of new product development and regulation and a redistribution across and around value chains.

For nanomedicine, this has involved a distribution of responsibilities as well as a reliance on creating situations where innovators and regulators can be mutually responsive.

In regulation, we see a distribution of regulation in the broad sense (Braithwaite 1982, 1993), with codes of conduct, voluntary reporting, development of standards, principles of oversight etc. stemming from a variety of actors (firms, industry associations, NGOs, user groups, and standards agencies, trade unions).

In innovation, we see a distribution of agenda setting and selection through forums like the ETP-Nanomedicine, CLINAM and MEDITRANS where the articulation of future nanomedicine scenarios by those involved in the health care value chains has provided room for manoeuvre for the innovation actor, and has facilitated the continuation of mutually responsive development of nanotechnologies and regulation. This is not without tensions, inevitably so, however, the goal of creating a situation of (reflexive) co-evolution and responsible development is a productive aim.

For nanomedicine and regulation, 'co-regulation' and 'responsible development' is the solution for the present, even though uncertainty (and associated risks) remains high.

The case shows that regulatory waiting games are avoidable.<sup>21</sup> One way in which to facilitate the process, beyond the scope of this paper but in line with the special issue, is the possibility of stimulating reflexivity in innovation-regulation through the orchestration of forums for further articulation of supply and demand expectations with regards to regulation, coupled with future-oriented analysis. Most foresight has focused on technocentric approaches, looking at the core technology and seeing how it will fare in the current regulatory landscape. As we have argued, regulatory landscapes can change quite rapidly when civil based regulation is included. Thus foresight approaches need to include anticipation on how potential technology options will emerge, how the regulatory landscape will change and more importantly, how they may co-evolve.

Some first attempts at forecasting governance landscapes has been attempted (Robinson 2009a) and it is here where the intelligence provided in this paper could aid in creating more productive situations so as to mitigate or avoid waiting games and support reflexive-co-evolution of nanotechnology and the emerging governance landscape.

## Notes

1. Several authors/commentators have linked the narrative of asbestos to that of nanotechnologies up to claiming that nanomaterials such as nanotubes could have similar properties see, Kane and Hurt 2008; Poland et al. 2008.
2. Regulation No. 1223/2009 OJ L 342/59
3. The European Union Council (EUC) and European Parliament (EP) failed to reach a decision in March 2011. The lack of agreement on 'cloned meat and its offspring' led to the abandonment of the entire Novel Foods recast process, sending the European Commission back to the drawing board. The Commission has, however, indicated that it intends to make a new proposal for the Novel Foods Regulation recast as soon as possible, focusing on those aspects that had already been agreed during the negotiation process.
4. Under these mechanisms, government no longer functions as the regulatory authority; however, the state can still have some level of involvement in the broader governance framework
5. Often combined with studies of legal aspects and dubbed ELSA/ELSI (Ethical, Legal and Societal Aspects/Issues)
6. European Commission 2008. A code of conduct for responsible nanosciences and nanotechnologies research. A Commission Recommendation of 07/02/2008. See <ftp://ftp.cordis.europa.eu/pub/ftp7/docs/nanocode-recommendation.pdf>
7. See [http://www.nanoriskframework.com/files/2011/11/6496\\_Nano-Risk-Framework.pdf](http://www.nanoriskframework.com/files/2011/11/6496_Nano-Risk-Framework.pdf)
8. For a detailed assessment of gaps in nanotechnology regulation, see, Frater et al. 2006, 57–75.
9. A value chain is 'the series of activities required to produce and deliver a product or service' (Porter 2001).
10. Collective expectations may not be present, and there may not be agreement on potential futures, but the articulation process is essential to be able to make a diagnosis of the spread of expectations and how they are (mis)aligned. Only then is it possible to decide whether to maintain a fragmented and diverse ecology of visions of the future, or attempt alignment activities.
11. OJ [2001] L311/67.
12. OJ [1993] L 214/1.
13. OJ [2004] L 136/1.
14. OJ [1993] L169/1.
15. OJ [1990] L189/17. Directive 2007/47/EC amended Council Directive 90/385/EEC but did not make any amendments to the In Vitro Diagnostic Directive.
16. OJ [1998] L331/1
17. Regulation (EC) 1907/2006.
18. Regulation (EC) 1272/2008
19. Generally expressed in Annex I of the directives.
20. Several other national and international standardisation efforts are being made, for example, ISO TC229.
21. Whether waiting games may be productive is an arguable point. For example, those actors concerned about the toxicity and hazards of nanomaterials may argue for a moratorium whilst an increased understanding of the safety issues is obtained. Waiting would be desirable in their framing.



## Notes on contributors

*Joel D'Silva* is an Affiliated Researcher at the Department of Legal & Economic Governance Studies (LEGS), University of Twente, Netherlands. Prior to this, he was Research Fellow at the Faculty of Law, KU Leuven, Belgium on a project dealing with legal regulation of nanotechnologies. His research focuses primarily on regulatory and policy issues relating to new technologies like nanotechnologies and synthetic biology.

*Douglas K. R. Robinson* is Managing Director of teQnode, a consultancy firm which specialises in the mapping, understanding and prospective analysis of a variety of new and emerging science and technologies. Prior to this, he has conducted an 18-month post-doctoral research project on the theory of technological design regimes and lock-in at Ecole des Mines, Paris (F). He has a PhD in Sociology of Innovation and Constructive Technology Assessment from the University of Twente, the Netherlands.

*Clare Shelley-Egan* is a Post-Doctoral Researcher at the Law & Regulation Group, Department of Public Administration, University of Twente, the Netherlands. Her current research focuses on the identification of regulatory responsibilities in regulatory networks and the contribution of vigilance regulation to responsible nanotechnological development.

## References

- Agogu , M., P. Le Masson, and D.K.R. Robinson. 2012. Orphan innovation, or when path-creation goes stale: A design framework to characterize path-dependence in real time. *Technology Analysis and Strategic Management* 24, no. 6: 603–616.
- ANEC. 2011. Statement – Nanomaterials: A very small step on the long and bumpy road to consumer safety. <http://www.anec.eu/attachments/ANEC-PR-2011-PRL-021.pdf> (accessed 15 December 2011).
- Bakker, S., and B. Budde. 2012. Technological hype and disappointment: lessons from the hydrogen and fuel cell case. *Technology Analysis and Strategic Management* 24, no. 6: 549–563.
- Bergeson, L., and C. Auer. 2011. Nano disclosures: Too small to matter or too big to ignore? *Natural Resources & Environment* 25, no. 3: 26. [http://www.actagroup.com/other\\_pdfs/00070483.PDF](http://www.actagroup.com/other_pdfs/00070483.PDF) (accessed 5 January 2012).
- Bowman, D., and G. Hodge. 2008. A big regulatory tool box for a small technology, *Nanoethics* 2, no. 2: 193–207.
- Bowman, D.M., and G.A. Hodge. 2008. ‘Governing’ nanotechnology without government? *Science and Public Policy* 35, no. 7: 475–87.
- Bowman, D., J. D’Silva, and G. Van Calster. 2010. Defining nanomaterials for the purpose of regulation within the European Union. *European Journal of Risk Regulation* 1, no. 2: 115–22.
- Bowman, D. 2010. Shaping behaviour through regulation: Subtle and not so subtle approaches. In *Nanotechnology: Environmental, health and safety*, ed. Matthew Hull and Diana Bowman, 73–95. Oxford: Elsevier Science.
- Braithwaite, J. 1982. Enforced self-regulation: A new strategy for corporate crime control. *Michigan Law Review* 80, no. 7: 1466–507.
- Braithwaite, J. 1993. Responsive regulation for Australia. In *Business regulation and Australia’s future*, ed. P.N. Grabosky, and J. Braithwaite, 81–96. Canberra: Australian Institute of Criminology.
- Brownsword, R. 2010. The age of regulatory governance and nanotechnologies. In *International handbook on regulating nanotechnologies*, ed. G.A. Hodge, D.M. Bowman, and A.D. Maynard, 60–80. Cheltenham: Edward Elgar.
- Cefic. 2011. Practical nanomaterials definition needed to push forward next great innovation breakthroughs. <http://www.cefic.org/newsroom/2011/Practical-nanomaterials-definition-needed-to-push-forward-next-great-innovation-breakthroughs/> (accessed 14 November 2011).
- CHMP. 2006. Reflection paper on nanotechnology-based medicinal products for human use. [http://www.emea.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/01/WC500069728.pdf](http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069728.pdf) (accessed 10 April 2011).
- Chemical Watch. 2011. Nanomaterials: Now we have a definition, what next? <http://chemicalwatch.com/index.cfm?go=9030> (accessed 10 January 2012).
- Chowdhury, N. 2010. Regulation of nanomedicines in the EU: Distilling lessons from the paediatric and the advanced therapy medicinal products approaches. *Nanomedicine* 5, no. 1: 135–42.
- Committee to Review the National Nanotechnology Initiative, National Research Council. 2006. *A matter of size: Triennial view review of the national nanotechnology initiative*. Washington DC: The National Academies Press.
- Davies, C. 2006. Managing the effects of nanotechnology. [http://www.nanotechproject.org/process/assets/files/2708/30\\_pen2\\_mngeffects.pdf](http://www.nanotechproject.org/process/assets/files/2708/30_pen2_mngeffects.pdf) (accessed 10 May 2011).

- D'Silva, J. 2011. What's in a name? – Defining a 'nanomaterial' for regulatory purposes in Europe. *European Journal of Risk Regulation* 2, no. 1: 85–91.
- D'Silva, J., and D. Bowman. 2010. To label or not to label? – It's more than a nano-sized question? *European Journal of Risk Regulation* 1, no. 4: 420–7.
- D'Silva, J., and D. Bowman. 2011. The regulation of nanomedicine, in *Nanomedicine in health and disease*, ed. R. Hunter, and V. Preedy, 20–42. Boca Raton, FL, USA: Science Publishers.
- D'Silva, J., and G. Van Calster. 2010. For me to know and you to find out? Participatory mechanisms, the Aarhus Convention and new technologies. *Studies in Ethics, Law and Technology* 4, no. 2: 1–34.
- D'Silva, J., and G. Van Calster. 2009. Taking temperature – A review of European Union regulation in nanomedicine. *European Journal of Health Law* 16, no. 3: 249–69.
- Dana, D. 2010. Can the law track scientific risk and technological innovation? The problem of regulatory definitions and nanotechnology. Northwestern Public Law Research Paper No. 10–83. In *The nanotechnology challenge*, ed. David Dana, 1: Cambridge University Press, UK. <http://ssrn.com/abstract=1710928> (accessed 12 April 2011).
- Delaney, H., and R. van de Zande. 2000. NIST special publication 951 – a guide to EU standards and conformity assessment: 10–11. [http://gsi.nist.gov/global/docs/EU\\_Stds&CA\\_2000.pdf](http://gsi.nist.gov/global/docs/EU_Stds&CA_2000.pdf) (accessed 19 April 2011).
- Department of Environment Food and Rural Affairs. 2006. *UK voluntary reporting scheme for engineered nanoscale materials*. London: Defra.
- Dorbeck-Jung, B., and N. Chowdhury. 2011. Is the European medical products authorisation regulation equipped to cope with the challenges of nanomedicines? *Law and Policy* 33, no. 2: 276–303.
- EEB. 2011. *Press release – Nano definition too narrow*. <http://www.eeb.org/EEB/index.cfm/news-events/news/nano-definition-too-narrow-says-eeb/> (accessed 10 December 2011).
- Environmental Defense and DuPont. 2007. *Nano risk framework, EDF*. New York. [http://apps.edf.org/documents/6496\\_nano%20risk%20framework.pdf](http://apps.edf.org/documents/6496_nano%20risk%20framework.pdf) (accessed 1 March 2012).
- Environmental Protection Agency. 2008. Notice: Nanoscale materials stewardship program. *Federal Register* 73, no. 18: 4861–6.
- Eprecht, T. 2010. Producing safety or managing risks? How regulatory paradigms affect insurability, in *International handbook on regulating nanotechnologies*, ed. G.A. Hodge, D.M. Bowman, and A.D. Maynard, 163–174, here 169. Cheltenham: Edward Elgar.
- ETC. 2006. *Nanotech Rx. Medical applications of nanoscale technologies*. <http://www.etcgroup.org/upload/publication/593/01/etc06nanotechrx.pdf> (accessed 5 April 2011).
- ETC. 2010. *The big downturn? Nanogeopolitics*. <http://www.etcgroup.org/fr/node/5245> (accessed 5 April 2011).
- European Commission. 2008. Commission Recommendation of 07/02/2008 on a Code of Conduct for Responsible Nanosciences and Nanotechnologies Research. Available at <ftp://ftp.cordis.europa.eu/pub/ftp7/docs/nanocode-recommendation.pdf> (accessed 1 March 2011).
- European Commission. 2011. *Recommendation on the definition of nanomaterial*. [http://ec.europa.eu/environment/chemicals/nanotech/pdf/commission\\_recommendation.pdf](http://ec.europa.eu/environment/chemicals/nanotech/pdf/commission_recommendation.pdf) (accessed 28 June 2012).
- European Group on Ethics in Science and New Technologies (EGE). 2007. *Opinion on the ethical aspects of nanomedicine. Opinion 21*. [http://ec.europa.eu/bepa/european-group-ethics/publications/opinions/index\\_en.htm](http://ec.europa.eu/bepa/european-group-ethics/publications/opinions/index_en.htm) (accessed 28 June 2012).
- Faulkner, A. et al. 2004. *Regulation and governance of tissue engineered technologies in the United Kingdom and Europe: Social science research, Summary of results*. <http://www.uwe.ac.uk/hlss/research/pdf/TERG-FinalReportSummary04.pdf> (accessed 8 May 2011).
- Frater, L. et al. 2006. *An overview of the framework of current regulation affecting the development and marketing of nanomaterials: A report for the DTI*. <http://www.bis.gov.uk/files/file36167.pdf> (accessed 8 May 2011).
- Gunningham, N., and R. Rees. 1997. Industry self-regulation: An institutional perspective. *Law and Policy* 19, no. 4: 363–414.
- Handy, D.R. et al. 2008. The ecotoxicology of nanoparticles and nanomaterials: Current status, knowledge gaps, challenges and future needs. *Ecotoxicology* 17: 315–25.
- Hodge, G. et al. 2010. Introduction: The regulatory challenges for nanotechnologies. In *International handbook on regulating nanotechnologies*, ed. G.A. Hodge, D.M. Bowman, and A.D. Maynard, 3–24. Cheltenham: Edward Elgar.
- Hunt, G. 2004. Nanomaterials: Nomenclature, novelty and necessity. *Journal of Materials* 56, no. 10: 13.
- Kane, A., and R. Hurt. 2008. Nanotoxicology: The asbestos analogy revisited. *Nature Nanotechnology* 3:378–379.
- Kearnes, M., and A. Rip. 2009. The emerging governance landscape of nanotechnology. In *Jenseits von Regulierung: Zum politischen Umgang mit der Nanotechnologie*, ed. S. Gammel, A. Lösch, and A. Nordmann, 97–121. Berlin: Akademische, Verlagsgesellschaft.

- Levi-Faur, D., and H. Comaneshter. 2007. The risks of regulation and the regulation of risks: The governance of nanotechnology, in *New Global Regulatory Frontiers in Regulation: The Age of Nanotechnology*, ed. G.A. Hodge, D. Bowman, and K. Ludlow, 150. Cheltenham: Edward Elgar.
- Lin, P. 2007. Nanotechnology bound: Evaluating the case for more regulation. *Nanoethics* 1, no. 2: 105–22.
- Linkov, I., F.K. Satterstrom, and L.M. Corey. 2008. Nanotoxicology and nanomedicine: making hard decisions. *Nanomedicine: Nanotechnology, Biology & Medicine* 4, no. 2: 167–71.
- Ludlow, K, D.M. Bowman, and D. Kirk. 2009. Hitting the mark or falling short with nanotechnology regulation? *Trends in Biotechnology* 27, no. 11: 615–20.
- Majone, G. 1994. The rise of the regulatory state in Europe. *West European Politics* 17, no. 3: 77–101.
- Mandel, G. 2009. Regulating emerging technologies. <http://regulation.upf.edu/dublin-10-papers/4B2.pdf> (accessed 12 June 2011).
- Marchant, G. et al. 2010. A new soft law approach to nanotechnology oversight: A voluntary product certification scheme. *UCLA Journal of Environmental Law and Policy* 28, no. 1: 123.
- Marchant, G. et al. 2009. What does the history of technology regulation teach us about nano oversight? *Journal of Law, Medicine and Ethics* 37, no. 4: 724–31.
- Marchant, G. et al. 2009. International harmonization of regulation of nanomedicine. *Studies in Ethics, Law, and Technology* 3, no. 3: 1–14.
- Maynard, A. et al. 2010. Conclusion: Triggers, gaps, risks and trust. In *International handbook on regulating nanotechnologies*, ed. G.A. Hodge, D.M. Bowman, and A.D. Maynard, 573–86. Cheltenham: Edward Elgar.
- Miles, J. 2007. Metrology and standards for nanotechnology. In *New global frontiers in regulation: The age of nanotechnology*, ed. G.A. Hodge, D. Bowman, and K. Ludlow, 333–52. Cheltenham: Edward Elgar.
- Moran, A. 1995. Tools of environmental policy: Market instruments versus command-and-control, in *Market, the state and the environment: Towards integration*, ed. R. Eckersley, 73–85. Australia: Macmillan Education.
- Moses, L.B. 2007. Recurring dilemmas: The law's race to keep up with technological change, *University of Illinois Law, Technology & Policy* 2, no. 7: 239–85.
- N&ET Working Group. 2007. *Report on nanotechnology to the medical devices expert group findings and recommendations*. [http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc\\_id=4865&userservice\\_id=1&request.id=0](http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc_id=4865&userservice_id=1&request.id=0) (accessed 18 March 2011).
- National Industrial Chemical Notification and Assessment Scheme. 2007. *Summary of call for information and the use of nanomaterials*. Canberra: Australian Government.
- National Industrial Chemical Notification and Assessment Scheme. 2008. Industrial nanomaterials: Voluntary call for information 2008. *Australian Government Gazette* C 10, no. 7: 25–38.
- Poland, C. et al. 2008. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nature Nanotechnology* 3, no. 7: 423–8.
- Porter, Michael E. 2001. Strategy and the Internet. *Harvard Business Review* 79, no. 3: 63–78.
- Parandian, A., A. Rip, and H. te Kulve. 2012. Dual dynamics of promises, and waiting games around emerging nanotechnologies. *Technology Analysis and Strategic Management* 24, no. 6: 565–582.
- Rashba, E. et al. 2004. Standards in nanotechnology, *Nanotechnology, Law & Business* 1, no. 2: 185–92.
- Responsible Nanotechnologies Code. Consultation Draft – 17 September 2007. <http://www.responsiblenanocode.org/> (accessed 18 May 2011).
- Rittel, H.W.J., and M.J. Webber. 1973. Dilemmas in a general theory of planning. *Policy Sciences* 4: 155–69.
- Rip, A., and A.J. Groen. 2001. Many visible hands. In *Technology and the market: Demand, users and innovation*, ed. R. Coombs, K. Green, A. Richards, and V. Walsh, 12–37. Cheltenham: Edward Elgar.
- Robinson D.K.R. 2009a. Co-evolutionary Scenarios: An application to prospecting futures of the responsible development of nanotechnology. *Technological Forecasting and Social Change* 76, no. 9: 1222–39.
- Robinson D.K.R. 2009b. Regulating nanotechnology in food. *NANO Magazine*, no. 13, p. 16. <http://www.nanomagazine.co.uk> (accessed 1 March 2012).
- Robinson, Douglas K.R. 2011. Value chains as a linking-pin framework for exploring governance and innovation in nano-involved sectors: Illustrated for nanotechnologies and the food packaging sector. *European Journal of Law and Technology* 2, no. 3.
- Robinson, D.K.R., P. Le Masson, and B. Weil. 2012. Waiting games: Innovation impasses in situations of high uncertainty. *Technology Analysis and Strategic Management* 24, no. 6: 543–547.
- Royal Society, Insight Investment, Nanotechnology Industries Association, Nanotechnology Knowledge Transfer Network. 2007. *Responsible nanotechnologies code: consultation draft – 17 September 2007 (Version 5)*, 1–13. London: Responsible NanoCode Working Group.

- Royal Society and Royal Academy of Engineering. 2004. *Nanoscience and Nanotechnologies: Opportunities and uncertainties*. London: Royal Society and Royal Academy of Engineering. [http://www.raeng.org.uk/news/publications/list/reports/Nanoscience\\_nanotechnologies.pdf](http://www.raeng.org.uk/news/publications/list/reports/Nanoscience_nanotechnologies.pdf) (accessed 14 March 2011).
- SCENIHR. 2007. The appropriateness of the risk assessment methodology in accordance with the technical guidance documents for new and existing substances for assessing the risks of nanomaterials.
- Shelley-Egan, C. 2011. *Ethics in practice: responding to an evolving problematic situation of nanotechnology in society*. PhD Dissertation. University of Twente, Enschede, the Netherlands.
- Sinclair, D. 1997. Self-regulation versus command and control? Beyond false dichotomies. *Law and Policy* 19, no. 4: 529–59.
- Te Kulve, H. 2010. Emerging technologies and waiting games. *Science, Technology and Innovation Studies* 6, no. 1: 8–31.
- Van Calster G., D. Bowman, and J. D'Silva. 2011. Protecting consumers or failing them? *European Journal of Consumer Law* 1, no. 1: 85–113.
- Violet, F. 2010. Analysis of technical standards in the field of nanotechnology. *Nanotechnology Law & Business* 7, no.: 299–307.
- Vogel, D. 2006. The private regulation of global corporate conduct. Berkeley: Centre for Responsible Business Working Paper Series, University of California.
- Wagner V. et al. 2006. The Emerging nanomedicine landscape. *Nature Biotechnology* 24, no. 10: 1211–7.
- Webb, K., and A. Morrison. 1996. The legal aspects of voluntary codes. Paper presented at the Exploring Voluntary Codes in the Marketplace Symposium, 12–13 September, Ottawa.
- Williams, D. 2010. The scientific basis for regulating nanotechnologies. In *International handbook on regulating nanotechnologies*, ed. Graeme A. Hodge, Diana M. Bowman, and Andrew D. Maynard, 109–11. Cheltenham: Edward Elgar.