Is the European medical products authorization regulation equipped to cope with the challenges of nanomedicines?

BÄRBBEL DORBECK-JUNG and NUPUR CHOWDHIRY

This article analyses the emerging European regulatory activities in relation to nanopharmaceuticals. The central question is whether the regulatory responses are appropriate to cope with the regulatory problems nanomedicinal development is posing. The article explores whether the medical product regulations are robust enough, whether there are certain regulatory gaps, and whether the competent bodies have the expertise to evaluate nanomedicinal products when approval is applied for. Based on a social-constructive approach the article identifies significant regulatory actors, their ideas on regulatory problems and preliminary governance responses to them. It finds that the current dynamic regulatory structure seems robust enough to adapt to some of the technological challenges that are being posed by nanomedicines. It concludes that regulators have not yet responded adequately to regulatory gaps related to definitions, classification and specific safety, quality and efficacy standards nanopharmaceutical development seems to require. As a consequence of these deficiencies legal certainty, a principle that has a high priority in European medical regulation policy, cannot be provided sufficiently.

INTRODUCTION

Nanomedicines have been on the market for more than 17 years. In the past, nanodrugs have been treated as ordinary products in the marketing process. Since some years awareness about particular regulatory questions and problems are
emerging. At present, many of the relevant stakeholders including the competent authorities, pharmaceutical companies, pharmacists and other scientists, as well as bodies like the International Standards Organisation (ISO), the European Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), and the European Group on Ethics in Science and New Technologies (EPE) are addressing various kinds of regulatory issues. Some of them have questioned the appropriateness of the existing regulations to provide for the safety, quality and efficacy of nanodrugs because of new product properties, new modes of action and unknown toxicity (Gaspar and Duncan 2009; Dorbeck-Jung 2009; Linkov et al. 2008; Sanhai et al. 2008; Gaspar 2007; Chan 2006; Wilson 2006; Kagan et al. 2005; Mehta 2004). Following are some of the recurrent questions that have emerged within these regulatory debates: Are the medical product regulations robust enough to cope with the challenges of nanomedicines or do we need a new regulatory regime? Are there certain regulatory gaps? Have regulatory bodies respond adequately to address the regulatory problems? Do the competent bodies have the expertise to evaluate nanomedical products when approval is applied for?

This article aims to explore answers to these questions. It analyses the emerging European governance structure that is shaping the approval of nanomedical products for human use. The main research question is whether the European medicinal products authorisation regulation is equipped to cope with the regulatory challenges of nanomedicines. The inquiry attempts to provide insights into how existing regulation is applied, whether regulatory problems (including regulatory gaps) are encountered in regulatory practice and how governance responses are emerging. The analysis explores whether the current governance responses are
appropriate in the face of the regulatory challenges and problems that were identified before. Since the European medicinal product regulations regime seems to exert an influence on the other regulatory regimes of the medical technology applications (Kent et al. 2006; Altenstetter and Permanand 2006; Altenstetter 2003)² the regulatory responses to nanopharmaceuticals may indicate the general direction in which the nanomedical products regulation will develop. Considering the increasing trend towards exploring international collaborative responses to drug regulation (EMA 2010; Valverde 2007; Vogel 2001) this article can provide lessons for how to regulate promising, but potentially risky new technologies.

The exploration of the robustness of the European medical products authorization regulation is based on an analysis of the regulatory problems nanomedicines are posing and the governance responses that they have evoked so far. The article is organised into four sections. First, we give an overview of nanomedical development, potential benefits and regulatory challenges. Second, we outline the theoretical framework for the analysis of regulatory problems and governance responses. Third, we describe the relevant EU regulatory framework. In the fourth section regulatory problems and emerging governance responses will be identified and analysed. The analysis leads to tentative conclusions on whether the current European pharmaceutical regime is equipped to address the development of nanomedicines.

The description of regulatory structures, challenges, problems and responses is based on literature, legal documents, policy documents and interviews with regulatory actors. All regulatory actors we interviewed are key representatives of a company, regulatory bodies or scientific advisory bodies. In this context ‘key’ means that the respondent has been involved in the marketing of nanomedicines or
in the consultation on nanomedicinal regulation. We interviewed 3 representatives of pharmaceutical companies that have marketed nanomedicines. Interviews were also held with two representatives of the European Medicines Agency (EMA), representatives of three national medicines evaluation bodies, one representative of the SCENIHR, one representative of the EPE, one representative of the ETP platform on nanomedicine and one representative of the of N&ET Working Group3. Below, we will refer to them as representatives of companies, the EMA, national medicines evaluation bodies, the EGE, the SCENIHR and the N&ET.

NANOMEDICAL DEVELOPMENT, POTENTIAL BENEFITS AND REGULATORY CHALLENGES

NANOMEDICAL DEVELOPMENT

Nanopharmaceuticals are part of the therapeutics area of nanomedicine which is divided into “nanopharmaceuticals” and “nano-enabled devices”.4 Other areas include surgery, diagnostic (including imaging), implant technology, bionics, bioactive surfaces, tissue engineering, textiles and actuators. Nanopharmaceuticals refer to innovation in drug delivery and medicines based on the use of nanoparticles of the active ingredient. Nanoparticles can also be used as a carrier material or porous material from which the active ingredient is released in a controlled manner. Cancer, Parkinson and Alzheimer are diseases in which products are being developed.5 Nanomedicines have been on the market for more than 17 years. A survey stated in 2006 that there were 23 nanoscale drug-delivery systems which had already been launched in the market (Wagner et al. 2006: 1214-15). To date, 10 nanodrugs have come through the centralized authorization procedure overseen by
the EMA. Since there are no statistics available on approvals of nanopharmaceuticals that have come through the mutual recognition procedure the total number of European authorizations is unclear. In the case of the United States, reports have suggested that the number of nanomedicines authorizations by the American Food and Drugs Authority (FDA) stand between 12 to 18 and that there are several new products in the pipeline that will be launched in the near future. The FDA also identified drug delivery and in vivo imaging as the most active areas. In the field of drug delivery dozens of products are in development. Estimates indicate that by 2015 about half the drug delivery systems will be based on nanotechnology (Zijverden et al. 2008:43). In the next decade breakthroughs are also expected in the development of nanodrugs (e.g. activation of a nanomedicine using an external medical device) and the targeting of drugs to facilitate cell differentiation. Upcoming products are said to display distinct characteristics like complexity of clinical use, multifunctionality, as well as integration of different areas of nanomedicine and technology subsets from drugs to medical devices and human material (‘combined products’).

POTENTIAL BENEFITS

Nanopharmaceuticals are currently regarded as the most promising field of nanomedicine. According to influential commentators (Zijverden et al. 2008: 41) the great strength of nanomedicines lies in the controlled release system. The effectiveness of the drug can be increased by the modification of the surface of nanoparticles. Nanodrugs are expected to make a positive contribution to the prevention, diagnosis and treatment of diseases such as cancer, infections, autoimmune diseases and inflammations. They may also be suitable to treat diseases
which at present can only be treated with drugs that have many adverse effects. It is expected that nanomedicines have less adverse effects because the drug can be more accurately targeted at its destination and because a reduced amount of the drug will have to be administered.

REGULATORY CHALLENGES
Nanotechnologies question the appropriateness of the existing regulatory frameworks and the space they leave to tailor rule implementation to new technological and product development. These technologies put pressures on the capacity of regulators to keep pace with developments of (nanomedical) science, new applications and risk assessment. They pose challenges to the expertise of regulators and their ability to balance technological benefits against risks. Nanotechnologies require prudential regulators that are able to facilitate responsible development and to gain trust of stakeholders (including the public).\(^\text{10}\) Regulatory challenges are induced by a large range of technological, scientific, normative, conceptual and institutional uncertainties. There is insufficient knowledge about the paths of technological developments and the characteristics and behaviour of nanomaterials, including data on exposure and hazards (NIOSH 2009; RCEP 2008; Zijverden et al. 2008; SCENIHR 2007). Knowledge gaps about product formulations and nanoparticles concentration raises questions about the applicability of European regulations on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH, see Hansen 2009: 22; Chaundhry et al. 2006). In this context a conceptual question is whether nanoparticles are considered as ‘new substances’ to which the requirements of REACH apply. Uncertain and ambiguous risk problems of nanotechnologies (IRGC 2006) raise questions on whether regulators can
wait until there is more knowledge or whether they must respond promptly. According to the precautionary principle the European Commission adopted in 2000 (EC 2000) scientific uncertainty about technological risks is no reason for inaction if there might be immense adverse effects. Particular regulatory challenges are posed by conflicting norms and values that play a role in the perception and interpretation of ‘immense adverse effects’, as well as in the decisions on risk-benefit balances, on how to gain public trust and acceptance of regulation (Everson and Vos 2009; Vos 2004). Institutional uncertainties refer to knowledge gaps on the costs and the effectiveness of increasingly dynamic and fragmented multi-level and multi-actor regulation (Rothstein 2009: 70; Hood et al. 2001).

Analyses of the scientific committees of the EU, its member states, the United States and the OECD have concluded that there are still many knowledge gaps about the risks of nanomaterials to humans and the environment. Knowledge gaps in relation to the toxicological aspects of nanomaterials (particularly free, non-degradable and insoluble nanoparticles) and their implications for health and environment pose crucial challenges to safety regulation. To date, toxicological studies have indicated that free nanoparticles might penetrate through blood and brain barriers, or remain lodged in capillaries (Poland et al. 2008). These particles could also have an impact on the immune system and be consumed by macrophages.

Another challenge is related to uncertainties about the biocompatibility of medical products/materials in which nanoparticles have been used (Zijverden et al. 2008: 47). The toxicological risks of nanoparticles depend on material properties, exposure route and dose (Geertsma et al. 2007). When nanoparticles are fixed in or on a device health risks are indicated only if they are released due to, for example, a chemical reaction. According to influential accounts the risks of the use of
nanomedicines could, among other things, lie in a different distribution of the particles in the body compared to medicines not in a nano form (Zijverden et al. 2008: 46). Further toxicological risks of nanomedicines are as yet unknown (Jong and Borm 2008).

ANALYTICAL FRAMEWORK: BASIC CONCEPTS OF SOCIAL CONSTRUCTIVISM

Our analysis of regulatory problems and emerging regulatory responses refers to basic concepts of social constructivism. This approach views regulation as a ‘project under construction’ which evolves on the basis of collectively meaningful structures and processes. It offers a broad framework for the analysis of emerging regulation. Social-constructivist inquiry includes all actors at all regulatory levels and all activities that exert influence in regulatory practice to achieve certain policy goals. It includes legal rules (‘hard law’) and rules that do not have legally binding force, but which nevertheless have effects in legal practice (‘soft law’, see Senden 2004). It draws the attention not only to the regulatory activities of standard-setting, implementation, oversight and enforcement (Scott 2002), but also to preliminary activities of organised reflection on potential regulatory responses.

The version of social constructivism we are relying on refers to Giddens’ account of social structure functioning as both as a medium for, and an outcome of the practices it repeatedly organises (Giddens 1984: 25; Berger 1991). By interacting in daily practice actors are collaboratively creating, reproducing and modifying rules, values and principles. Social structure is therefore seen as dynamic and
as both constraining and enabling in turns while co-evolving. Another basic as-
sumption of the socio-legal version of social constructivism is that rules are evolv-
ing in reflexive processes of learning based on intersubjective knowledge, ideas,
beliefs, and a ‘logic of appropriateness’ whereby actors try to figure out the ap-
propriate rule for a given situation (Trubek et al. 2006: 72). Rules are regarded as
being shaped by interactions among actors in the context of power relations where
influence and change build on certain pressures. Regulatory actors are recognised
as significant when they exert influence on regulatory activities. This means that
significant regulatory actors can involve legally mandated actors, but also other
actors that are influential in regulatory practice. This broad view is captured in the
language of governance which is used to explain a range of processes and prac-
tices that have a normative dimension but do not operate primarily through formal
hierarchic mechanisms of traditional command-and-control legal institutions (De
Búrca and Scott 2006:2).

According to the social constructivist approach basic concepts of our analysis
are: the regulatory structure (rules and significant regulatory actors) related to the
authorization of nanopharmaceuticals; the ideas and beliefs of regulatory actors in
relation to regulatory problems induced by nanomedicinal applications and their
interactions to ‘reproduce’ and to ‘produce’ new regulation (‘governance re-
ponses’). In this inquiry governance responses focus mainly on preliminary pol-
icy-making activities related to regulatory standard-setting and implementation
(amongst which research and discussion). By ‘significant regulatory actors’ we
refer to institutional players and stakeholder groups that exert influence on the
regulatory activities in relation to the authorization of nanomedicines. The signifi-
cance of these actors lies not only in their actual influence on the regulatory proc-
ess but also in their position and therefore their ability to influence debates and discussions on this issue in the future. Given the explorative character of this investigation we attempt to find indications for the (potential) significance of certain regulatory actors. Indicators are found in how these actors are participating in regulation (highly active, moderately active, marginally active and dormant or present non-active), whether their regulatory activities are recognized and whether regulatory advice is followed. Herein it is also important to note that some regulatory actors will play a direct role in terms of shaping regulation while the influence of others is indirect. This is the case, for example, with scientific bodies ('indirect regulatory actors') whose scientific inputs will provide the basis for regulatory decisions. However the nature, scope and coverage of any new regulation/guidance will have to be negotiated between the regulatory agencies and other stakeholders like manufacturers and patient groups that will play a more direct role in negotiating regulatory policy decisions in the case of nanomedicines in Europe.

EUROPEAN REGULATORY STRUCTURE ON THE APPROVAL OF NANOMEDICINES: RULES AND SIGNIFICANT ACTORS

DEVELOPMENT OF THE REGULATORY STRUCTURE

The general EU pharmaceuticals regime under which nanomedicines may fall is a well-established, dynamic and complex system of multi-level regulation (Dorbeck-Jung and Oude Vrielink 2007; Feick; 2005; Broscheid and Feick 2005; Feick 2002; Abraham and Lewis 2000; Vogel 2001; Hart and Reich 1990). It is com-
posed of European and national legislation which is accompanied by a large body of soft law.\textsuperscript{15} Compared to the drugs regulation the European medical devices regulation provides more room for private authorization bodies and private standards. Its implementation has been widely delegated to industry and national governments (Hanson 2005; Altenstetter 2003; Altenstetter and Permanand 2006).

Drug disasters of the late 1950s like the thalidomide crisis gave rise to European regulations which have been launched in the 1960’s to ensure a high level of public health protection in terms of safety, efficacy and quality. In 1993, fundamental institutional changes were initiated through two new authorization procedures (‘centralised procedure’ and ‘mutual recognition procedure’) that replaced the existing procedures.\textsuperscript{16} In the opinion of the Commission this was necessary to create a centralised authorization that is compulsory for high-technology medicinal products, particularly those resulting from biotechnological processes, in order to maintain the high level of scientific evaluation of these products in the EU. In 1993, a European agency for the evaluation of medicinal products was established. Eleven years later new legislation was laid down and existing legislation was amended.\textsuperscript{17} With regard to nanomedicines a relevant change is that Regulation 726/2004 which enlarged the scope of the centralised procedure to new active substances for four medical indications.\textsuperscript{18} Another important revision was the inclusion of manufactured cell therapy products with a pharmacological mode of action into the scope of the Medicinal Products Directive.\textsuperscript{19} According to Directive 2004/27/EC the applicant is required to provide an evaluation of the potential environmental risks posed by the medicinal product and to limit them by specific arrangements.\textsuperscript{20} Potential environmental impact, however, it is not a criterion for the rejection of an approval application.\textsuperscript{21} Responding to developments of bio-
medicine (such as gene therapy, somatic cell therapy, and tissue engineering)

Regulation 1394/2007/EC on advanced therapies medicinal products (ATMPs) was launched in 2007. This Regulation established the Committee on Advanced Therapies (usually referred to the acronym CAT) which is consulted in the authorization process. Other specific regulatory carveouts include Medicinal Products for Paediatric Use and for Orphan Medicinal Products.

RULES GOVERNING NANOMEDICINES

To date, in the EU no specific rules have been established with regard to nanomedicines. Thus the current regime as it stands is applicable to the market authorization of nanodrugs as well. The approval follows either the centralised or the mutual recognition procedures laid down in the medicinal product regulation. Nanopharmaceuticals that are qualified as advanced therapy medicinal products can be approved only by the centralised procedure. To nanomedicinal products that combine medical devices and medicinal products (‘borderline products’) provisions of the EU medical devices Directives may apply. The application of the regulatory regime depends whether the product falls within the definitions of medicinal products, ATMPs or medical devices. The primary mode of action is the criteria for determining the applicable regulatory regime. This means, for example, that nanomedicines with a primary mechanical action and secondary pharmacological action are brought under the medical devices regulation regime. In this regime approval is granted by a notified body appointed by a member state on the basis of conformity assessment and certification. With regard to nanomedicinal applications that combine advanced therapies medicinal products with devices, however, the centralised procedure is mandatory. In this case the
EMA is required to take the notified body’s opinion as to the conformity to the safety requirements for the device part of the product into account. Market authorization depends on a positive outcome of the risk-benefit balance. In this context the applicant must demonstrate sufficiently the product’s safety, quality and efficacy on the basis of a large set of objective scientific data. It is required that the scientific evaluation of applications is based on the highest level of expertise and the highest possible standards. Another set of general conditions refers to the three benchmarking guidelines for good clinical practice in the conduct of clinical trials for medicinal products, good manufacturing practice for both medicinal products and investigational medical products and good clinical practice regarding investigational medicinal products. Apart from these two sets of general conditions that will horizontally apply to all medicinal products, there are two sets of additional conditions that vertically crown the general conditions. The first set of additional conditions is with reference to specific regulatory carveouts for ATMPs, paediatric and orphan medicinal products. The second set of additional conditions relates those medicinal products that use or include specific substances like GMOs (genetically modified organisms), human blood and plasma and human tissues and cells. Thus if the medicinal product is either an ATMP, paediatric or orphan or uses specific substances (viz. human blood and plasma, GMOs or human tissues and cells) then it will have to conform to the applicable set of rules in addition to those discussed under ‘general conditions’.

Figure I provides an overview of the applicable rules that regulate the marketing approval of various types of nanomedicines (‘pure’ pharmaceuticals and combination products).
Figure I: Overview of applicable rules governing the marketing approval of types of nanomedicines

**MEDICINAL PRODUCTS (MPs)**

I. **GENERAL CONDITIONS (GC)**

Marketing Authorization Conditions:
1. 2001/83/EC (Mutual Recognition Directive - optional)
2. EC/726/2004 (Centralized Procedure Regulation – mandatory and optional)

Principles and Guidelines
1. Good Clinical Practice – clinical trials of MPs (Directive 2001/20/EC)
2. Good Manufacturing Practice for MPs (Directive 2003/94/EC)

II. **ADDITIONAL CONDITIONS (GC+)**

Specific Product Regulations (Implies Additional Conditions)
1. Advanced Therapy MPs (Regulation EC/1394/2007)
2. MPs for Paediatric Use (Regulation EC/1901/2006)
3. Orphan MPs (Regulation EC/141/2000)

Specific Substances Directives (Implies Additional Conditions)
1. GMOs (Specific provisions under Dir. 2001/83/EC)
3. Human Tissue and Cells (Directive 2004/22/EC)


- MPs incorporated as integral part of device/AIMD (Directive 90/385/EEC)

**MEDICAL DEVICES (MDs)**

- Active Implantable MDs (Directive 90/385/EEC)
- MDs (Directive 93/42/EEC)
- In Vitro MDs (Directive 98/79/EC)
SIGNIFICANT REGULATORY ACTORS

To provide explorative indications of the influence regulatory actors are exerting in the regulatory process of nanomedicines we distinguished between highly active, moderately active, marginally active and dormant actors. These actors operate at multiple levels i.e. at the EU member state (national), the European level (regional) and the international level. However, according to our empirical research, the influence regulatory actors are exerting on the regulation of nanomedicines does not depend on the regulatory level but rather on their functional relation with regulation. According to the functionalities we observed in the arena of nanomedical product regulation the regulatory actors are divided into five groups, viz. regulatory bodies, manufacturers of nanomedicines and their associations, users associations, advisory bodies and other regulatory bodies. The first three groups are directly involved in the EU regulation on nanomedicines, while the last two groups’ influence is rather indirect. Figure II identifies certain actors as critical in terms of the scale of their influence on emerging regulation.
Figure II: Significant Actors in the context of Nanomedicine Regulation in the EU

Dormant

Marginally active

Moderately active

Highly active
The group of regulatory bodies includes the European Medicines Agency, the
competent authorities of the member states, the notified bodies, the European
Commission (with DG Health and Consumers at the operative level), the Euro-
pean Parliament and Council, the European Directorate for the Quality of Medi-
cines and Health Care (EDQM). In the past years the EMA has employed only a
few regulatory activities with regard to nanomedicines. Since this Agency cur-
cently is more actively organising and participating in regulatory workshops it is
characterised as a moderately active regulatory actor. According to our interviews
the competent authorities of the member states have taken minimal regulatory ac-
tion to respond to nanomedical development. A few of them have held internal
debates, have established a working group or informally contacted the EMA about
the topic. This is why we regard them as marginally active. Notified bodies on the
other hand have been dormant in these debates. However, given that the majority
of next generation nanomedicines will be combination products, notified bodies
are expected to play an important role not only in downstream regulatory imple-
mentation but also in shaping upstream debate on the scope and nature of regula-
tory guidance required for such combination products that include medical de-
vices. In contrast, DG Health and Consumers is characterised as moderately ac-
tive, because it has periodically organised workshops on nanotechnologies (in-
cluding nanomedicine). It is providing funding to various research activities re-
lated to the regulation of nanomedicine. Since the European Parliament and
Council, the EDQM have not yet been involved in any regulatory activities on
nanomedicine we characterise them as dormant.
The group of manufacturers includes large, medium and small (pharmaceutical) companies and their associations. According to our interviews large companies have been moderately active in contacting the national competent bodies and the EMA on regulatory issues around nanomedicines. However regulatory activities by small and medium enterprises (SME’s) on this issue were limited. Pharmaceutical companies are exerting influence through the European Technology Platform (ETP) on Nanomedicine, which is active with road mapping nanomedicinal development and has taken up regulatory policy issues for discussion internally. Regarding the high participation of companies within the ETP and the Platform’s pro-active stance in coordination activities it can be expected that the ETP will support a more active participation of the private sector on regulatory policy issues in the future. At present, it is still marginally active.

The group of users is formed by the organisations of doctors and patients. Doctors’ and patients’ associations have the potential to exert influence on regulatory activities. To date, however, these organisations have not yet participated in the current debates surrounding the regulation of nanomedicines. Nevertheless, like the notified bodies, this group is also expected to play a greater role in the future.

The group of advisory bodies includes the Working Group on New and Emerging Technologies in Medical Devices (N&ET), the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), and the European Group on Ethics in Science and New Technologies (EGE). Regarding its report on nanotechnology and its current work on particular regulatory guidance the N&ET Working Group is characterised as highly active. We regard the SCENIHR as well as being highly active. This Committee has published opinions on health risks
nanotechnologies and on definitions relating to products of nanoscience and nanotechnologies. It is actively involved in DG Health and Consumers debates on regulatory issues (Delogu 2009). Although the EGE’s 2007 Opinion on the ethical aspects of nanomedicine made several important points which could have a regulatory impact, its influence seems to be marginal. According to the interview with a representative, the EGE as a body does not follow up on the impact and implementation of its own recommendations. It is an expert body constituted for the purpose advising on a range of ethical issues which is not usually in a position to become engaged with a specific issue over the long term.

The group of other regulatory bodies includes the ISO, the Organization for Economic Co-operation and Development (OECD), the ICH, and the World Health Organisation (WHO). Both the OECD and the ISO have been highly active in setting up standardisation processes and dedicating resources to nanotechnology. Since all the other actors involved in nanomedical regulation rely on the regulatory work of these two bodies their leadership seems to be accepted and recognized. According the empirical research the ICH and the WHO have not yet been involved on the issue of nanomedicine.

REGULATORY PROBLEMS AND GOVERNANCE RESPONSES

REGULATORY PROBLEMS

Regulatory problems identified by the interviewees include the lack of a definition of nanomedicines, unnecessary regulatory hype, as well as the inappropriateness of safety, quality and efficacy standards and methods to analyse the potential envi-
ronment impact. In the case of products that combine medical devices and drugs other problems are the applicability of the regulatory regime and the lack of tailored standards in the medical devices assessment. According to our interviews most of the significant regulatory actors have encountered only a few regulatory problems. The respondents affiliated to companies have not experienced specific nano-related problems in the market authorization process of nanomedicines. To date, evaluation bodies have treated nanopharaceuticals as ordinary products. For some years, awareness about particular questions and problems related to nanodrugs is emerging. However, most of the interviewed evaluation bodies are not sure whether there are many nano-product related regulatory problems and what kind of problems this can be. Two representatives of such a body indicate that they suspect that the hypothesis of regulatory problems that nanomedicine authorization is facing within the current regime may contribute to a regulatory hype in terms of creating a specific regulatory framework which, to their mind, is not necessary.

Above we indicated that toxicity problems may induce particular regulatory problems with nanomedicines. Another problem may be to mobilise the appropriate expertise for the quality, safety, efficacy evaluation of nanomedicinal products. According to most interviewees, the European rules on the authorization of medicinal products for human use, the methodology of the current regime of drugs evaluation with its case-to-case risk-benefit balance approach is robust enough to address nanomedicines. All respondents affiliated to authorization bodies judge the current system of risk-benefit balance analysis to be sufficient. The in vitro and in vivo clinical testing processes are seen as robust in validating that the product is safe. The representatives of the authorization bodies cannot see a reason
why specific evaluation criteria should be developed for nanomedicines. All the nanomedicines that have been approved by now have not encountered particular risk, quality and efficacy problems related to 'nano properties'. One of these representatives reports that two applications related to nanomedicines have been withdrawn by the companies because there were concerns about the efficacy of the product. In this context other respondents stress that the European evaluation system does not take a ‘zero risk approach’. As long as the product meets its intended purpose and the risk-benefit balance is positive the product will be licensed. Certain risks are accepted (also on the basis of a risk minimisation plan the applicant has to handover) if there are certain benefits to be gained and if the balance is positive. Representatives of competent bodies and companies experience that the measurement of the benefit depends on the kind of disease and on whether the product seems to fulfil unmet health needs. As one of them put it:

“In cancer we accept a larger risk than in the case of headaches. In the case of headache we already have so many products. Therefore the new product will have to pass higher standards of safety.”

This is also the experience of the companies that were interviewed. One of these respondents mentions cancer drugs that contain nanoparticles. These products were approved before all effects (including toxicity) were entirely investigated. In this context, however, a representative of an authorization body stresses that benefits that are mentioned in the application are not taken for granted. They are carefully assessed on the basis of mortality studies and data on the quality of life.

With regard to the characterisation of nanomedicines all respondents and commentators conclude that adequate standards are lacking. An actual problem is the characterisation of liposomal particles which needs differentiation. With regard to
the definition of nanomedicines the competent bodies refer to the work of the International Standardisation Organisation (ISO) under the TC (Technical Committee) 229.

Considering the environmental impact analysis respondents of large and medium-sized companies indicate that are not yet prepared to identify the environmental impact. A leading expert has identified this analysis as regulatory problem of major importance, because it depends on reported physical characteristics and available information from the biologic effects of specific nanomaterials which are widely unknown (Gaspar 2007: 143). This expert has questioned the adequateness of the general drug assessment standards to evaluate the safety, quality and efficacy of coming nanopharmaceuticals. He stated,

“the fact that the new nanopharmaceuticals can be more complex in their structure, with major differences in biofate and increased complexity of clinical use, integrating different technology subsets from therapeutics to imaging and integrated non-invasive diagnostics will probably force the creation of an new regulatory environment.”

In Gaspar’s view, new standards and new administration routes need to be considered to assess drugs inside nanosystems. An important issue of standardisation is the characterisation of nanopharmaceuticals including availability of validated assays to detect and quality nanoparticles in tissues, medicinal products and processing equipment. Among the most important quality aspects, there is the need to incorporate novel techniques for the characterization of different materials and technological options, looking at different structures, from colloidal systems to carbon nanotubes.

Interestingly, the experiences and views of the interviewed evaluation bodies are different. One of them mentioned that large pharmaceutical companies have
undertaken environmental risk assessment. These companies seem to be well equipped to carry out the evaluation. In this context the competent bodies stress that environmental risks are not a reason to reject an authorization application. Applicants have only to demonstrate that they will take measures to limit potential environmental impact.

According to all commentators nanomedicines that combine pharmacological, immunological or metabolic action on the human body with mechanical action (‘borderline products’) pose a ‘classification’ problem. Given the complex multi-functionality nanopharmaceuticals are exhibiting, the regulatory principle that the regulation regime of the primary mode of action applies is regarded as being too simplistic. Respondents from companies report that there is much uncertainty about the applicable regulatory regime in the case of combined products. Companies tend to contact the competent bodies when borderline products raise questions of regime applicability. They are seeking certainty, because, as an ETP Nanomedicine representative argued, “trying to get around the more stringent requirements can be detrimental to the sector’s reputation.”

In the context of combined products all commentators agree that standards validated specifically for nanoparticles are lacking in the current guidelines for the assessment of medical devices. The voluntary standards of the medical devices assessment system are less harmonised and less stringent compared to the drugs system. As a consequence of its non binding character the scientific advice notified bodies are required to request from the drugs evaluation bodies can be ignored without sanctions. According to a representative of an evaluation body this has happened on several occasions in the past.
GOVERNANCE RESPONSES

A literature review and our interviews show that EU governance responses include mainly the collection of data on characteristics and effects of nanomedicines, the institutionalisation of particular forums, and the organisation of ad hoc reflection and the funding of particular initiatives. It seems that regulatory action is still in the stage of reflection and preparation. A preliminary governance initiative was the 2006 EMA Scientific Committee’s Reflection Paper on nanotechnology-based medicinal products for human use. This Paper concludes that novel applications of nanotechnologies (amongst which combined products) challenge the regulatory classification rules, regulatory expertise and the existing guidance of drugs evaluation. To deal with these issues the EMA has created the Innovation Task Force to ensure coordination of scientific and regulatory competence and to provide a forum for early dialogue with applicants. The EMA’s Small and Medium Size Enterprises Office provides regulatory support. An ad hoc Expert Group of its Scientific Committee has been established which met in April 2009. In September 2010, an international workshop on problems of borderline products will be held with the EMA. In contrast, evaluation bodies of the member states have been relatively slow in responding to these developments. While some are confident that current methodologies and disciplines are adequate in dealing with nanomedicines, others have been informally in touch with the EMA to coordinate their approach. Since 2007 DG Health and Consumers has organised annual workshops on nanotechnology. In the interviews several informal forums for exchanges of views on regulatory responses between the EMA and the FDA, and between national level authorities were mentioned.
Both evaluation bodies and companies emphasise that they need to learn from each other to answer regulatory questions. Representatives of companies report that they seek to contact evaluation authorities in an early stage of product development and to build a kind of a partnership. Interviews with evaluation bodies indicate that briefing meetings that are offered free of charge to all companies and all academic centers, which have developed innovative nanomedicinal products, are very important for the bodies to ascertain the direction in which product development is heading. In its proposed Road Map to 2015 the EMA emphasizes the growing importance of the structural involvement patients and healthcare professionals in its activities, as well as the increasing transparency.

With regard to the lack of definitions and standardisation the respondents affiliated to the EMA mentioned that they are participating in different initiatives of the ISO as an observer or an invited expert. The EMA will look at the ISO’s modification and improvement of the definition in the future. It is also closely following the sponsorship programs for manufactured Nanomaterials that have been undertaken by OECD’s Working Party on Manufactured Nanomaterials. The interviews indicated that there are no specific regulatory activities of the International Conference on Pharmaceuticals, the World Health Organization and the European Directorate for the Quality of Medicines and Health Care.

To respond adequately to the problems of borderline products a respondent affiliated to a national evaluation body points to lobbying activities to put the harmonisation of the medical devices regulation in the direction of stricter safety, quality and efficacy requirements on the EU agenda. Harmonisation would dissuade manufacturers from going forum shopping in terms of identifying notified bodies with the most lax operating standards. Another response to this problem
has been to apply the drugs regulation in authorisation practice. In this context a representative of an evaluation body reports that some products with an initial apparent physical main mechanism of action, like some contrast media, have been considered as medicinal products. The evaluations of other borderline products containing nanostructures with a systemic distribution through imaging media have led to the same consideration. According to the respondent, the underlying reasoning is that if there is a potential risk with respect to borderline products you apply the most stringent regulatory regime.

ANALYSIS

The regulatory problems the interviewees addressed specify some of the regulatory challenges of nanomedicinal development we identified above in the literature. They indicate that there seem to be only a few regulatory gaps induced by the lack of a definition of nanomedicines, inappropriate classification rules for combined products and lacking tailored safety, quality and efficacy standards. Although there has been a scientific consensus on the definition of nanomaterials to be that between 1-100 nanometers, this still has to be translated into a legal definition. Such a legal definition would have to be different from and in this case more specific than the scientific definition which is currently being used. The legal definition would have to refer to a specific quantum that would trigger a specific kind of regulatory obligations for all the stakeholders. Only once a threshold is defined will it be possible to identify certain medical applications as nanomedicines for purposes of regulation. Furthermore it is not clear whether the safety, quality and efficacy standards on which the risk-benefit balance evaluation rely are tai-
lored to nanomedicines. High level expertise on nanomedicines and their potential effects seems to be lacking in authorisation procedures.

To date, the EU pharmaceuticals regulation regime has been adapted to new technological development. The preliminary picture of the governance responses to the challenges of nanomedicines indicates that regulatory action is still in the stage of reflection. As has been charted out in figure II, bodies like the OECD, ISO and SCENIHR are highly active to provide for regulatory standards and measurements in relation to nanotechnologies. These are initial governance steps to reduce technical and scientific uncertainties. Interestingly, the EU medical devices advisory group, the N&ET, has been especially active in deliberating on this issue and developing specific regulatory guidance for medical devices manufactured using nanotechnology. In comparison the EMA has only been moderately active in putting together an institutional set up to deliberate on operational issues relating to authorization of nanopharmaceuticals last year. DG Health and Consumers has been active in providing a larger European forum for experts, industry representatives and policymakers across sectors to come and deliberate on a range of safety issues vis-à-vis nanotechnology. However, since these forums cover all sectors in which nanotechnology is being used, it is not expected that specific regulatory issues relating to nanomedicines will be discussed in any great detail.

The dormant nature of the user associations is perhaps not unexpected given that the technology is still under development and there is lack of information in the public domain on the uses and effects of this technology in the medical sector. However the dormancy of the ICH and the WHO is more difficult to explain. The ICH has been the accepted forum for deliberations on medical regulation between the US, Japan and the EU and this was also acknowledged by the interviewees.
The non-involvement of the ICH and the WHO seem to suggest that although international collaboration has been found to be necessary in the case of pooling resources for scientific investigations and standardization activities in the ISO and the OECD that may not be the case of developing regulatory guidance in the case of specific sectors. This also perhaps explains the absence of any concrete coordination mechanisms (in addition to the existing institutional arrangements and the information exchanged during public conferences on nanomedicines) between the EMA and the FDA on the specific issue of regulation of nanomedicines. There seems to be an understanding that regulatory debates would have to take place internally and some kind of consensus would need to be built before attempting regulatory coordination at the international scale.

In comparison, the EMA has only been moderately active in putting together an institutional set up to deliberate on operational issues relating to authorization of nanopharmaceuticals. Very recently, the Agency has taken the initiative to organize an international workshop on key features of nanomedicines and the emerging scientific knowledge in the field. DG Health and Consumers has been active in providing a larger European forum for experts, industry representatives and policymakers across sectors to come and deliberate on a range of safety issues vis-à-vis nanotechnology. However, since these forums cover all sectors in which nanotechnology is being used, it is not expected that specific regulatory issues relating to nanomedicines will be discussed in any great detail. The dormant nature of the user associations (patients and doctors) is perhaps not unexpected given that the technology is still under development and there is lack of information in the public domain on the uses and effects of this technology in the medical sector. However, the dormancy of the EDQM, the ICH and the WHO is more difficult to
understand. It is likely that these bodies are waiting for the outcomes of the general standardisation activities of the ISO and the OECD. This may also be an explanation for the absence of any structural coordination between the EMA and the FDA on nanopharmaceuticals governance.

The lack of concrete steps in addressing the regulatory issues surrounding nanomedicines has attracted criticism from analysts (Bhogal 2009). The EMA’s putting into place ad hoc structures is considered not to be enough to cope with the regulatory problems. Currently, the EMA has recognized that there is an urgent need that the European competent bodies act in concert with each other to generate awareness and dialogue and to ensure a comprehensive and coherent response. It is however unclear, whether the EU Regulatory System Network the EMA is developing does include structural collaboration with the European Directorate for the Quality of Medicines and Health Care and other regional and international bodies.

CONCLUSION

This article explores whether the European medicinal products authorisation regulation for human use is equipped to cope with the regulatory challenges of nanomedicines in terms of regime robustness and adequate governance responses to regulatory gaps and problems on the basis of high level expertise.

First of all, the analysis indicates that the pharmaceuticals regulation regime has proved to be robust in terms of well-established rules that have been kept up-to-date and relevant by continuous and careful adaptation to new product development and new insights into product safety, quality and efficacy. The principle of
risk-benefit balance that guides the authorization of drugs seems to be capable to accommodate a certain amount of uncertainty. The successful marketing of nanodrugs in the past indicates that EU pharmaceuticals approval regulation has been capable to cope with nanomedicines. The emerging awareness of unknown health and environmental risk as well as the increasing multi-functionality and complexity of coming nanomedical products, however, question the appropriateness of existing safety, quality and efficacy standards. Since new nanomedical products go across the borders of the regimes of the EU medical technology regulatory systems the question arises whether a separate regulatory regime will be required in the future. One condition for singling out a specific regime (like the ATMP regulation) is to isolate an integral thread running across all nanomedical products. To date, such a thread has not yet emerged. Even if it can be isolated in the future the threat of further fragmentation of the pharmaceutical framework might dampen the support for establishing a new specific regime. Regarding the robustness of the drugs regulatory regime another question is whether nanomedicinal products should be approved only through the centralized procedure. This procedure was mandated for high technology products in order to ensure consistent, harmonized authorization and timely access to safe and innovative medicines by pooling the best scientific expertise. Considering the innovative character of nanomedicines and scientifically challenging evaluation we conclude that there is a case for nanomedicines to be authorised through the centralized process. Nanopharmaceuticals should be included as a specific category within the mandatory list of products that have to follow central authorization process (Chowdhury 2010:137). This would allow circumvention of the expertise deficit in the commu-
nity on these issues and also ensure effective harmonization of evaluation techniques necessary to facilitate market access to these products.

Secondly, the analysis shows that *appropriate governance responses to the identified regulatory gaps and problems* have not yet emerged. Regulatory gaps mainly refer to implementation problems which require regulatory guidance tailored to the approval of nanomedicines. With regard to standard-setting the lack of a legal definition of nanomedicines and regulatory thresholds seem to be the most urgent problems. As a consequence of these deficiencies legal certainty, a principle that has a high priority in European medical regulation policy, currently cannot be provided sufficiently. Whether the important regulatory gaps will be filled depends on the Scientific Opinion of the SCENIHR on the scientific basis for the definition of the term ‘nanomaterial’ that has been requested before the end of May 2010. Regulatory responses seem to be in a preliminary stage. Very recently, the European Medicines Agency has taken a proactive stance. The international conference the Agency is convening in September 2010 seems to be an important step to reduce uncertainties on nanomedicinal product properties. Furthermore, in its Road Map to 2015 the EMA has taken the initiative to develop a regulatory science in coordination with the competent bodies of the member states. It remains to be seen whether this development can contribute to the formation of high level expertise on nanomedicines that seems lacking in the evaluation procedures. The present EMA governance activities do not include concrete regulatory steps with regard to combined products and specific safety, quality and efficacy standards. The tendency to apply the ‘stricter’ drugs regime to cope with the classification problems of combined products may not be the appropriate solu-
tion. Medical devices industries and their products, as Altenstetter points out in this Issue, are too diverse for uniform requirements to be workable.

Since appropriate regulatory responses have not yet been developed further research is needed. This article could only identify significant regulatory actors, their ideas on regulatory problems and preliminary governance responses. These are the very first steps to answer the question whether the European medicinal products authorisation regulation for human use is equipped to cope with the regulatory challenges of nanomedicines. Further steps are to identify how much influence significant actors exert on the emerging governance structure and to explain their regulatory behaviour. Moreover, insights are needed on the goals and principles that guide the emerging regulatory activities on nanomedicines. These insights can be provided by further research that builds on an operationalization of the social constructivist concept of the ‘logic of appropriateness’. With regard to in-depth identification of the actors’ influence and the explanation of their regulatory behaviour the social constructivist approach falls short. These parts of the further research agenda can draw on an institutional theory that provides a framework for the analysis of power relations in regulatory networks.

References


Waarden, Frans van. 1996. Regulation, competition and innovation. The Hague: Dutch Advisory Committee on Technology Policy.


Notes

Nanomedicines are medicines made from new or existing substances which are applied on a nanometre scale (Zijverden et al. 2008: 41). In this paper the terminology of nanomedicines, nanomedicinal products, nanopharmaceutical and nanodrugs are used synonymously. Nanomedicines are applications of nanotechnologies in view of treating or preventing diseases. Nanotechnologies mean the design, characterisation, production and application of structures, devices and systems by controlling shape and size at the nanometre scale where properties differ significantly from those at larger scale (see EMA 2006). These definitions are based on reports of the Royal Society and Royal Academy of Engineering (2004) and the European Science Foundation (2005), as well as on a paper of the European Technology Platform on Nanomedicine (2006).
The regulatory regimes that constitute the medical product regulation system refer to medicinal products, medical devices and human material.

European Working Group on New and Emerging Technologies in Medical Devices (established by the European Commission).

The description of the nanopharmaceuticals development is mainly based on reports of the Dutch Institute for Public Health and the Environment (RIVM) and the Roadmap of the European Technology Platform on Nanomedicine (Jong de et al. 2005; Zijverden et al. 2008; European Technology Platform on Nanomedicine 2009). These documents provide the most exhaustive overview of the current and the near term development of nanomedical products.

At the moment nanomedical research is being carried out on the use of nanoparticles, amongst which dendrimers, nanotubes, liposomes, nanocrystals, quantum dots, spheres or rods of substances such as gold, silica and albumin.

The 2006 EMA Reflection Paper on nanotechnology based medicinal products for human use (EMA 2006) specified that these authorized medicinal products containing nanoparticles are in the form of liposomes (Caelyx, Myocet), protein conjugates (PegIntron, Somavert), polymeric substances (Copolyxone) or suspensions (Rapamune, Emend) and nanoparticles (abraxane).

Market survey report on Medical Nanotechnology Markets: Trends, Industry Participants, Product Overview and Market Drivers, pegs the number of authorizations at 18 (Trimark Publications 2008). See also, presentation by Furgeson to the FDA (2008), who puts the number as 12.

FDA approved “nano-scale” therapeutics products include Gadolinium chelate for MRI imaging (Gd-DTPA Dimeglumine), iron oxide particles for MRI imaging (Feridex), liposomes (Doxil, DaunoXome), microemulsions (Cyclosporine) and albumin-bound nanoparticles (Abraxane). Silver nanoparticles for anti-bacterial wound dressing; engineered calcium phosphates (NanOst, duplicates microstructure, composition and performance of human bone) and nanoparticledental restorative (3M ESPE Filtek) are some of the nano-scale devices that have been approved by the FDA (see, Sadrieh 2005).

These breakthroughs were mentioned at the ETP Nanomedicine roadmap meetings in 2009.

Social constructivism is regarded as an ontological approach to social inquiry that serves to explore how social phenomena became what they are (Trubek, Cottrell and Nance 2006; Green Cowles 2003; Adler 2002; Finnemore and Toope 2001; Brunnée and Toope 2000; Finnemore 1996). Constructivist approaches have been developed in many disciplines, amongst which sociology, international relations, international law and technology assessment. Constructivism has also been closely interwoven with historical and sociological strands of institutionalism (Checkel 2001). Regarding the aim of this article we rely mainly on the socio-legal approach of Trubek, Cottrell and Nance (2006) which integrates notions of sociological and international relations theories.

This broad view has been promoted in international relations and international/European law accounts to overcome a legalistic view (Finnemore and Toope 2001; Koslowski 1999).

Regulation is commonly defined as intentional attempts to control or order people or states of affairs (albeit mindful of the unintended consequences of those intentions (Black 2002).

A stakeholder is to mean ‘a person or organization that has legitimate interest in a project or entity’ (Freeman 1983). Stakeholders are regarded as regulatory actors only if they (at least potentially) exert influence on regulatory activities.

Examples of soft law are the Committee for Advanced Therapies (CAT) 2009 Scientific guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMA/CAT/486831/2008), the EC 2006 guideline on the definition of a potential serious risk to public health (2006/C 133/05), the 2006 CHMP Guideline on the environment risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00), the EMA guideline on scientific aspects and working definitions for the mandatory scope of the centralized procedure and the 2005 EC guideline on the packaging information of medicinal products for human use.

According to the Annex to Regulation 726/2004, certain biotechnological products, medicinal products for human use for which the therapeutic indication is the treatment of certain diseases, as well as orphan medicinal products are to be authorised by the Community. Optional access to the centralised procedure is provided for medicinal products, although not belonging to the before mentioned categories, are nevertheless therapeutically innovative.

See, EC 98C 229/03 and Annex 1 2001/83/EEC.


The final approval of pharmaceuticals by the European Commission is based on the EMA’s opinion. This opinion is based on the draft of its Committee for Medicinal Products for Human Use (CHMP). Due to the expertise of the members the recommendations of the EMA’s scientific committees are crucial for the EMA’s evaluation and the final decision of the European Commission.


The final approval of pharmaceuticals by the European Commission is based on the EMA’s opinion. This opinion is based on the draft of its Committee for Medicinal Products for Human Use (CHMP). Due to the expertise of the members the recommendations of the EMA’s scientific committees are crucial for the EMA’s evaluation and the final decision of the European Commission.


The final approval of pharmaceuticals by the European Commission is based on the EMA’s opinion. This opinion is based on the draft of its Committee for Medicinal Products for Human Use (CHMP). Due to the expertise of the members the recommendations of the EMA’s scientific committees are crucial for the EMA’s evaluation and the final decision of the European Commission.
The N&ET Working Group has been established in 2005 on the proposal of the European Commission. Participants are the competent authorities for medical devices of the member states. The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) is an experts committee of European Commission. It is part of the larger risk assessment structure of the European commission. The aim is to provide scientific advice to the commission on risk assessment. It is consulted by the Commission at its own initiative; however in some instances consultations are mandatory if it is provided for under EU legislations. See Dologu (2009).

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceutical for Human use. The EDQM and the ICH are involved in pharmaceutical standardisation activities. In the ICH the European Pharmaceutical Association, the EMA, the FDA and the Japanese Competent Authority are participating

In any case not directly. Although the IFCS (Intergovernmental Forum on Chemical Safety) which is hosted by the WHO, did pass a resolution on the safety of nanomaterials in its Sixth Session, at Dakar in 2008. (IFCS/FORUM-VI/07W).

See Park (2009). The article explores the possibility for an enhanced role for in vitro toxicity studies in the risk assessment of nanomaterials.

With the terminology of ‘classification problem’ we refer to legal analysts like Miller (2007).


For example, the Nanomed Round Table with its Working Group on Regulation, see www.nanomedroundtable.org.


This was suggested in our interview with the member of SCENIHR.

It is important to mention that although the MEDDEV guidelines are legally not binding, but it does create a presumption of conformity for manufacturers adopting these guidelines. This creates an incentive for the uptake of the guidelines. These guidelines therefore do have a de facto legal effect.


The EU Regulatory System Network is a partnership between all EU Regulatory Authorities (see EMA Roadmap, note 40).


On March 1, 2010, the European Commission (EC) issued a request, via the accelerated procedure, for a scientific opinion on the scientific basis for the definition of the term “nanomaterial” from the Scientific Committee on Emerging and Newly Identified Health Risks. (see http://files.nanobio-raise.org/Downloads/scenihr.pdf). See also SCENIHR 2008.