Healthy doubts

Perceived uncertainties during the development of nanomedicine

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1. Introduction

Uncertainty is a widely recognized phenomenon in innovation. According to literature it may have positive as well as negative influence on the innovation process of a technology (Koppenjan & Klijn, 2004; Jauch & Kraft, 1986; Jacobsson & Bergek, 2004). Uncertainty is a main factor influencing decision making regarding innovations and this holds in particular for emerging technologies (Nelson & Winter, 1977; Meijer, 2008; Van Merkerk and Van Lente, 2005).

Nanotechnology can be classified as an emerging technology (Wiek et al., 2009; Kuzma & Priest 2010) It is an enabling technology, providing tools, materials, and devices for further technological development in different sectors (Niosi & Reid, 2007). Also it is characterized by high uncertainty regarding the benefits and risks for human health and the environment (Bowman & Hodge, 2007; Marchant & Sylvester, 2006).
New nanotechnological knowledge is expected to produce groundbreaking insights and solutions in various sectors, like the automotive industry, electronics, energy and the medical sector. Whether such commercial expectations will come true is uncertain, of course. Simultaneously, there exists only a small amount of data on the effects of exposure to nanomaterials on the environment and human health (by manufacturing, use and disposal) and much is still unclear about the risks, accident scenarios and long term effects (Breggin & Carothers, 2006; Wijnhoven et al, 2010).

Moreover, some studies on the possible risks of nanotechnology indicate some cause for concern. They suggest that nano-particles infiltrate deeper in the lungs, are capable of interacting with subcellular structures such as DNA, and are able to move across cellular and tissue barriers (Vishwakarma et al. 2010). Further, Hubbs et al. (2011) state that some nanoparticles are more toxic in comparison to larger particles. A variety of adverse biological and physiological responses triggered by inhalation of nanoparticles are inflammation, fibrosis, genotoxicity and carcinogenicity (Hubbs et al. 2011). In the context of uncertainty regarding the risks, this makes it worthwhile to make a difference between technologies which contain either free or (initially) immobilized nanoparticles and technologies which are being applied either outside the body or inside the body. This categorization applies to nanomedicine, and since this also is a sector with high expectations (for instance in relation to targeted therapy, medical diagnostics and molecular imaging), we have chosen to concentrate on nanomedicine in this research. An important distinction here is made between nanopharmaceuticals and nanomedical devices (in vivo and in vitro). This can be explained by the fact that it concerns two sorts of products, on which two different kinds of regulations are applicable. Further, the sub categorization of nanomedical devices is makes it possible to investigate the difference in risk perception between products being applied inside the body (pharmaceuticals & in vivo medical devices) and outside the body (in vitro medical devices). Apart from uncertainty regarding the technology itself (functionality and risks), other uncertainties which can influence the innovation process can be found in the field of regulation, the society and the economy (Walker et al., 2003; Meijer et al., 2007).

Uncertainties can be studied in different ways. The uncertainties are in this research not interpreted as 'objective uncertainty' which means a description of the state of the environment, but as 'perceived uncertainty', which reflects it as a perceptual phenomenon (Milliken, 1987). The reason to use individuals' perceptions of the environment is that decision making regarding innovations is affected by

what is perceived and not by what has stayed unnoticed (Miles et al., 1974). Basically, effects of perceived uncertainties on innovation can go two directions:

- either being hesitant or rather being proactive in relation to decision making;
- being less or more willing to invest in it;
- either seeking for new partners or rather go for internal innovation governance;
- being open to the society or rather withhold information in order to avoid public backlash. (Koppenjan & Klijn, 2004; Meijer et al., 2007; Stanko and Calantone, 2011; Virdi, 2008).

The aim of this research is, firstly, to obtain a clear view on the perceived uncertainties from different stakeholders (i.e. companies who initiate a technological innovation themselves, the government, authorities who evaluate the medical products for market approval, the Dutch Healthcare Insurance Board etc.) on the risks and benefits of nanomedical products, and secondly to describe how these uncertainties are related to the innovation process of several technologies. This relatedness is not only investigated by looking at the innovation process in general, but also more specifically with regard to the different phases of the innovation process (search, select and implement). The influence of the uncertainties is determined by the activities which are being executed in each phase in order to decrease the uncertainties. Additionally, a comparison is made between SMEs and large firms. By exploring how the uncertainties are handled by the different stakeholders involved in the innovation process, by the three product categories and by SMEs and large firms, at last an advice will be given on how the uncertainties could be handled for improvement of the innovation process. The results of this research may be useful for several parties being involved in the innovation process of an emerging technology, for instance companies, the government and intermediary bodies.

This leads to the following research question:

How do various perceived uncertainties (from different stakeholders) influence the innovation processes of nanopharmaceuticals and nanomedical devices (in vivo and in vitro)?

2. Theory

'Innovativeness' is an important characteristic of the pharmaceutical industry as well as the medical devices industry (Demirel and Mazzucato, 2010). For the pharmaceutical industry, this can be explained by the fact that the R&D-intensity in this industry is high, which is a common parameter for the innovativeness of companies. Also, innovation in this sector is an important way to compete with other firms (ETP, 2009; Ornaghi, 2007). This is also the case for the medical devices industry, considering the fact that the improvements on a new product generally are made within 18-24 months (Vallejo-Torres et al, 2008).

Decisions about innovations are not only being made by companies themselves that are involved in the innovation process of a specific emerging technology. They are also being made by other actors, institutions and social subsystems (also called: 'the social system' in the Innovation System approach) (Geels, 2005; Meijer, 2008; Pinch and Bijker, 1984; Nelson and Nelson, 2002). The interaction of innovation processes and the presence of multiple actors within this 'social system', operating at different levels, makes the development of emerging technologies, like nanomedicine, uncertain and unpredictable (Smits et al., 2008).

2.1 Uncertainty

2.1.1 Context and nature of the uncertainty

In order to investigate the role of uncertainties, the following dimensions will be discussed*: context of the uncertainty and nature of uncertainty* (Walker et al., 2003).
'Context' is defined as the circumstances under which the problem is being examined. Different contexts of uncertainty exist, i.e. in the field of technology, regulation, society and economy. This comes back in previous research on the definition of uncertainty (Walker et al., 2003). But even more importantly, innovation processes are also highly dependent on the dynamics of these areas (Markard et al., 2009).
Another aspect is the cause of the uncertainty. Causes can be divided into two categories: epistemic uncertainty (based on the imperfection of our knowledge) and variability uncertainty (based on the influence of human behaviour, societal dynamics, technological surprises and natural processes) (Walker et al., 2003; Milliken, 1987). The causes give an indication about what should be done to handle the uncertainty.

The knowledge on what should be done to handle the uncertainty is also dependent on the question *whether* and *how* one can describe the (probabilities of) outcomes of an uncertainty. The categorization suggested by Walker et al. (2003) appears useful here: determinism, statistical uncertainty, scenario uncertainty, recognized ignorance, and total ignorance (Fig. 1). For instance, when one has an idea of the outcomes or even can make an indication of the probabilities of certain outcomes, it is more obvious one can make a plan how to handle the uncertainty better than when the outcomes and probabilities are unknown.

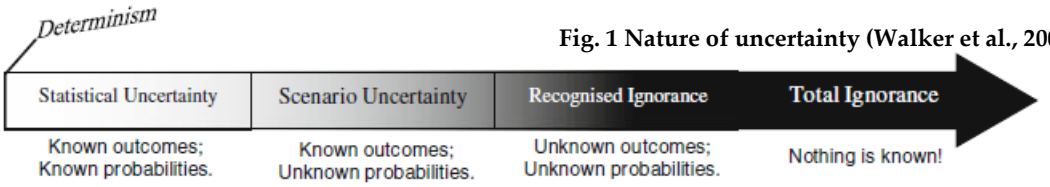


Fig. 1 Nature of uncertainty (Walker et al., 2003)

2.1.2 Perceived uncertainty vs. objective uncertainty

A common discussed subject in literature with regard to 'uncertainty', is the existence of 'objective' and 'perceived' uncertainty. The former implies a description of the state of the environment which can be measured objectively. The latter means that uncertainty is a phenomenon being perceived by someone, which cannot be measured objectively (Miliken, 1987; Meijer & Hekkert, 2007). This means, an environment is not certain or uncertain in itself, but it depends on the way it is perceived by an individual. These different ways of measuring uncertainty are applicable to different kinds of studies. Objective measures are appropriate to investigate external constraints imposed on a firm, and perceptual measures to understand managerial behavior and decision-making (Boyd & Fulk, 1996).

2.1.3 Categories of uncertainties used in this research

Technological innovations are dependent on the dynamics of social, economic, technological and political factors (Markard, 2009; Schot, 1992; van de Ven, 1993). Uncertainty may be perceived on all these aspects, which makes it a challenge for the decision-maker to manage this complex set of factors. The factors on which uncertainty may be perceived with respect to innovation decisions will be defined as follows:

Social uncertainty:
Individuals may perceive uncertainty regarding the demand of the consumer (Duncan 1972, Meijer, 2007). A distinction can be made between the *needs/preferences of the future consumer* (benefits of the innovation) the *acceptance of the consumer in relation to the possible risks* of the innovation. Further, with regard to the application of nanomedical products, some innovations will create more control of the patient on the administration of the medicine (point of care). This leads to a *shift in the relation between the doctor and the patient* of which uncertainty may be perceived regarding the preference and acceptance of the future consumer.

Economic uncertainty:
Penrose (1952) illustrates the relation between economic performance of firms, and their survival. When firms make profits, this means they are being adopted by the environment. When they do not, they will disappear. The profitability of the technological innovation is dependent on several factors, like the *availability of resources (human and financial)* and the *competitiveness* of the product. These both are aspects on which uncertainty may be perceived, either about how to acquire sufficient resources or how to cope with competitors (Duncan, 1972, Meijer, 2007). Important aspects regarding the competitiveness are: 'first mover advantages', economies of scale and the number of competitors (Wernerfelt and Karnani 1987). Further, with regard to resource uncertainty, important factors are the state of the economy (capital resources), and the educational system and the labour market (human resources) (Tidd et al., 2005).
For medical applications, it is also important to take into consideration whether the (treatment with the) nanomedical product will be *reimbursed* by the insurance company.

Regulatory uncertainty:
Uncertainties may be perceived regarding the *present legislation* and *future legislation* (future introduction of court-rulings and regulations). Uncertainty on current regulations may be caused by the policy that is being implemented, lack of regulations, or unclear regulations. Uncertainties about future regulations are aimed at 'not knowing' which changes will be made in current regulations or which new legislation will arise in the future (Meijer, 2007). This aspect is expected to be of importance for developments with regard to nanomedical products, because of the lack of knowledge and uncertainties about risks for human health and the environment. The unpredictability of future legislation is also caused by the crucial dilemma of the government: *how to protect human health and the environment, and simultaneously stimulate the economy* by promoting innovative capacity and the creation of jobs in this field.

Technological uncertainty:
This concerns the *available knowledge on the performance of the technology*. In case of a technological innovation, information on the characteristics is limited, which makes it difficult to evaluate the technological innovation and make decisions. The technological uncertainty increases when the technology is more complex (Meijer, 2007).
The technical uncertainty is in the case of nanomedical products also concerned with lack of knowledge on the *possible benefits and risks of the technology for human health en the environment*.

2.2 The innovation process

Various phases can be distinguished in the innovation process which need to be completed to accomplish a successful innovation (fig. 2). A broad categorization which can be used to describe an innovation process in practice and which is elaborated by Tidd et al. (2005) includes: scanning of the environment for threats and opportunities for change (search), deciding on which of these signals from the environment to respond to (select), translating the potential into something new and subsequently launching it (implement), and learning from the way in which the process has passed and possibly improve this process (learn). Tidd et al. (2005) describe the search, select and implement phase in more detail, by identifying several routines per phase which make it possible to successfully go through the innovation funnel (table 1).

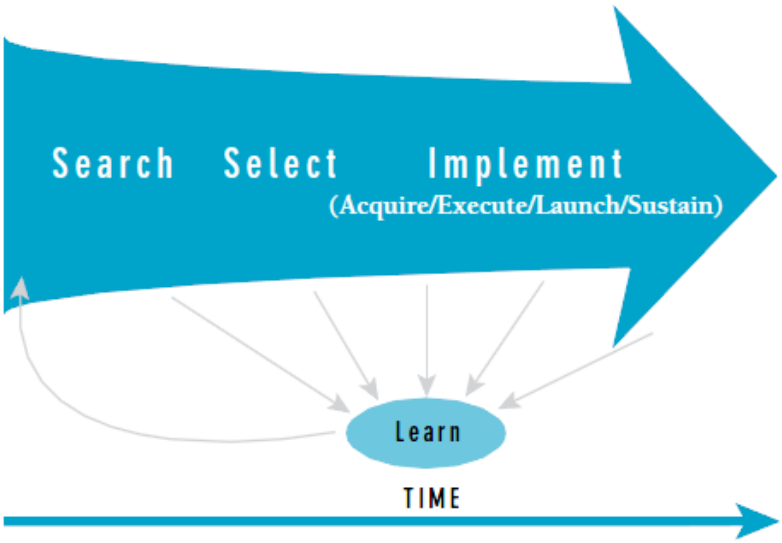


Fig. 2. Innovation funnel (Tidd et al., 2005)

	Routines / basic abilities	**Activities**
Search	Understanding market dynamics	Communicate and interact, for instance by making use of lead users, customer panels or surveys
	Involving stakeholders	Include customers or users in the innovation process and work together with them
	Trendspotting	Pick up signals of trends where you can act upon (in regard to society as well as regulations)
	Communication and connection	Involve the communication of the user perspective through the whole organization (by making use of so-called 'gatekeepers')
	Monitoring technological trends	Observe websites
		Visit conferences
		Keep closely connected with research labs
	Learning from others	Demonstration projects
		Reverse engineering
Select	Strategic analysis	SWOT-analysis
	Strategic choice	Portfolio management (making a bubble chart)
	Strategic monitoring	Make initial criteria and take possible project based- and environmental changes into consideration
Implement	Resource acquisition	Brainstorming
		Expert panels
		Research and development
		Outsourcing, joint venture, collaboration
	Execution of the project	Decision making by stage gate approach
		An early involvement or an interplay of stakeholders
		Managing team building
		Creating a shared and clear project vision
		Managing an appropriate project structure (by taking into account what is in need for the development project as well as the underlying operating structure)
	Launch	Develop a marketing strategy
		Develop a marketing plan
		Create a clear change management strategy
		Establish a form of communication in the organization which is open, active and two-way in operation
	Sustain	Customer services
		Incremental innovations

Table 1: Routines and activities which generally can be labelled to each phase

2.3 Specification of the research subject: product categories and firm size

This research is aimed at assessing the influence of different uncertainties on the innovation process of nanomedical products. In particular, this is assessed more elaborately for pharmaceuticals, in vivo nanomedical devices and in vitro nanomedical devices. Further, also the influence of the uncertainties is being researched, on the one hand for SMEs and on the other hand for large firms who go through the innovation process. Literature has shown that the way this trajectory is carried through, depends both on the size of firms (large firms or SMEs) and the nature of the technology (product category) (Lee and Chen, 2009; Pietzsch and Shluzas. 2009). The categorization will be explained more elaborately below.

- Pharmaceuticals and medical devices:

Different regulations are applicable to medical devices than to medicinal products. In fact, in respect of the existing legislation, they are considered to be two worlds apart. Despite the fact that both product categories have to fulfil many requirements before they will be approved for market access, the way these requirements are structured and controlled differs considerably. For pharmaceuticals, the approval of drugs is carried out by the regulatory authorities based on a dossier containing results to fulfil the requirements. Tasks of the health authorities, are: the approval of clinical trials applications and granting market access; monitoring of the safety of the marketed product; and the withdrawal of a marketing license in case of non-compliance (Rang, 2006). The medical devices also have to fulfil several requirements before they can be marketed, though the requirements to obtain approval are generally not that time consuming. Furthermore, the assessment of the fulfilment of the requirements is not being done by the health authorities, but by so-called Notified Bodies who are assigned by the government. Such a Notified Body is an independent organization which assesses whether a medical device meets the requirements. The degree in which the Notified Body is occupied to do this assessment depends on the risk class of the medical device (I, IIa, IIb or III). For instance, each particular product has to be assessed by a Notified Body in the case of class III products, while the less risky categories (I, IIa and IIb) generally are being tested on product type and is there is less involvement of the Notified Bodies. Less involvement of a Notified Body, generally leads to a less time consuming innovation process. The company itself has in this case more responsibility regarding the control of the requirements (Kaplan et al., 2004).

Further, another important difference between pharmaceuticals and medical devices is the life cycle of the products. While pharmaceutical companies can profit from their medicine for multiple years because of the intellectual property protection of twenty years by patents (Dickson, 2004). Further, the type of product brings along that incremental innovations are in less degree possible for pharmaceuticals, while this is better possible for medical devices. It is also the case that incremental innovations in the medical device industry are generally made within 18-24 months (Vallejo-Torres et al, 2008).

- In vitro and in vivo medical devices & pharmaceuticals

As has been mentioned in the introduction, nanoparticles are expected to be of highest risk for human health when they are free and are capable to diffuse inside the body (Vishwakarma et al. 2010, Hubbs et al. 2011). In vivo medical devices & nanopharmaceuticals always go inside the body, which makes it expected to be a product category characterized by high risk perception. Since in vitro nanomedical devices are not being applied inside the body, the risk perception is expected to be lower for this kind of medical devices than it is in the case of in vivo nanomedical devices & nanopharmaceuticals.

- SMEs and large firms:

There are different reasons to make a distinction between SMEs and large firms. First of all, usually in the pharmaceutical industry, the SMEs play an important role in the initial phases of the innovation process. A main reason why SMEs are more capable of becoming radically innovative, is that there is less bureaucracy, which makes them more flexible and respond quickly to the market (Schumpeter, 1934; Lee & Chen, 2009). Just when enough evidence has been provided, large firms will get involved in the innovation process. They will take over the technological concept of the SME or they will collaborate with the SME during the further stages of the innovation process. This means, regarding the whole product innovation process, the SMEs are more actively involved in the initial phases, while the large firms have a more important role in the latter phases. This possibly results in different perceived uncertainties which they have to deal with.

Another reason to make a distinction in firm size, is the fact that large firms have more products to get profits from, which makes their survival less dependent on the technological innovation in comparison to SMEs.

Finally, an important characteristic of large firms is that they are able to provide more resources to the product innovation and to manage uncertainties. These resources are expected to be in benefit of the development and launch of a new product (Lee & Chen, 2009)

3. Methods

3.1 Research design

This research was performed in three phases: a literature study, interviews and data analysis. These phases are elaborated in the 'Data collection' section.
The type of the research can be defined as an exploratory multiple case study (Yin, 2009), since it was the aim to explore the influence of different kinds of perceived uncertainties on the innovation process of an emerging technology, by investigating the innovation process of several products in the field of nanomedicine. Table 2 shows which products (and corresponding companies) were included. It was tried to acquire in-depth information on the perceived uncertainties by exploring which uncertainties are perceived and how these uncertainties are handled. Based on the results, an advice is given how the uncertainties could be handled differently for improvement of the innovation process.

	SME	Large firm
Nanopharmaceutical	- Drug delivery or controllable drug release (**Anonymous**)	- Targeted drug delivery&imaging (**Philips)** - Targeted drug delivery (**GSK**)
In vivo nanomedical device	- Micro needle arrays (**MyLife Technologies)** - bone inducing materials (**Xpand Biotechnology**)	
In vitro nanomedical device	Lab-on-a-chip technology (**Medimate, Micronit and Lionix**)	Nano-based sensors (**Philips**)

Table 2. Nanomedical technologies

3.2 Data collection

3.2.1 Literature study

The literature study was in the first place done as an introduction on nanotechnology in order to determine a possible focus area for this investigation. The research is limited to the Netherlands due to time restrictions and since it belongs to the most successful nations regarding nanotechnology; a position which it intends to maintain (Chen et al., 2008). After identifying high expectations regarding nanotechnology in the medical field and high investments from the Dutch government in order to keep up with the other leading countries on this area, but simultaneously the presence of many uncertainties regarding this new technology, it was decided to perform an in-depth research on the relatedness of the different uncertainties from several levels in society on the innovation process of nanomedical products. This in-depth research is based on theoretical background and scientific literature, which means the literature study also will be used for answering the research question.

3.2.2 Interviews

For a multiple case study, interviews can be seen as one of the most important sources for data collection (Yin, 2009) and this is also the case for this research. By the interviews it was tried to acquire the targeted and in depth information on the perceived uncertainties and the activities linked to this. The interviews were held with the companies who are involved in the development of a technology; and with several other actors since the development of an emerging technology is also dependent on their decisions. By having the interview questions based on scientific literature and theoretical background, and making the interview questions as clear and unambiguous as possible, the reliability of the research is increased. Further, the interviews are semi-structured and they were done mainly by asking open questions and when necessary by asking closed questions (in order to obtain specific information) (Baarda en De Goede, 2006).

Interviews companies:

At the start of the interview of the companies, a brief explanation of the study was given focussed on the three phases of the innovation funnel and the four categories of uncertainty. Hereafter the interviewee had the opportunity to explain what is being done in each phase of the innovation process in his/her company. In case the descriptions are too broad or too vague, for instance 'We explore the market', additional questions were asked how (by which routines or activities) this is being done by the firm. While making a reconstruction of this innovation process, it was investigated which uncertainties were of influence and which activities were done in order to reduce this uncertainty.

Interviews other stakeholders:

The construction of the interviews for the other stakeholders differs in some degree in comparison to the interviews for the companies. The other stakeholders included are: the government (Ministry of Health, Welfare and Sport and Ministry of Economic Affairs, Agriculture and Innovation), the Dutch Health Care Insurance Board (CVZ), a Notified Body, the Medicines Evaluation Board, the Association of Medical Specialists and a Patient Association. For these stakeholders, the same categorization of uncertainties was used as for the companies. However, since they do not go through the whole innovation process themselves, with its specific routines/activities of the product innovation process, they were not interviewed about the routines, but more general how they act upon their perceived uncertainties.

3.2.3 Data analysis

The interviews were recorded using a voice-recorder, by which it was possible to transcribe them. Subsequently, the transcripts were elaborated by making use of the method of 'coding'. The codes were partly based on existing literature (deductive coding) and partly on the data (inductive coding) (Patton, 2002).

The codes were attached to phrases or sentences in the interviews and in this way, the data are being subdivided and categorized. The reason why coding is useful for the analysis of the qualitative data, is that different terminology of the respondents is being harmonized and this will facilitate comparing the data.

The codes include the following three aspects, based on the theoretical elaborations in Ch. 2:

- The category of uncertainty (economic, technological, social, regulatory, see 2.1.3)
- The phase(s) in which the uncertainty was perceived (search, select, implement, see 2.2, in particular Table 1)
- The activity (categorized) being executed to handle the uncertainty (codes derived after interviews, see list in 4.3).

These codes will give for each stakeholder an overview of the sorts of activities which are being executed in order to reduce specific categories of uncertainty in one or more phases or in general (fig. 3). Based on these overviews, ultimate an impression is given of the influence of the different uncertainties on the innovation process, by a description of activities being executed in rather high or low degree as a consequence of the perceived uncertainty. For each phase, it is being analyzed what is the number of activities being executed as a consequence of each uncertainty, and what are the main sorts of activities done.
In some cases, firms or other stakeholders may perceive an uncertainty related to the development of nanomedical products in general rather than an uncertainty restricted to one specific phase in the innovation process. This is taken into account separately by the term: 'non-phase related uncertainties'.

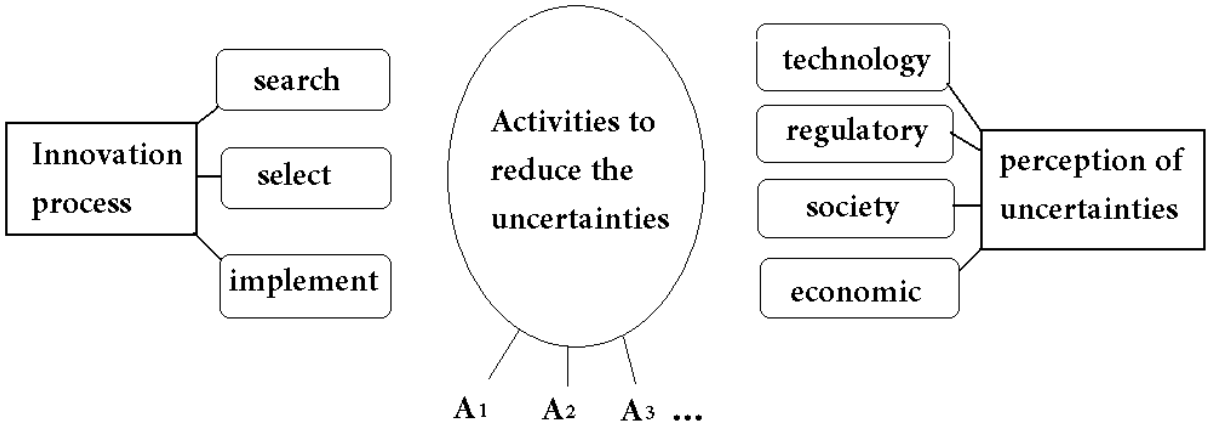


Figure 3. Coding of the interviews

Ultimately, as point of discussion, the results of this specific emerging technology are put broadly into perspective of innovation processes in general and uncertainties (regarding nanotechnology) as emerges from scientific literature, to identify possible significant similarities or differences.

4. Analysis of the Results

The results of this research are based on 19 interviews, done at a variety of companies, institutes, associations and Ministries involved in the development of medicines. To start, all of them will be introduced, by which their role in this research will be explained.
Regarding the analysis, initially the categorization of activities being done by the stakeholders will be presented. Then, the influence of uncertainties in the nanomedical world as a whole (i.e. the companies and other stakeholders) will be presented, to give an overall view of the situation. Subsequently, this is analysed more extensively, by making a comparison between the three product categories to analyse possible differences or similarities. Additionally, the influence of uncertainties is being compared between innovations done by SMEs and by large firms.

4.1 Introduction of the companies and other stakeholders

- Philips (MagnoTech):

The interview was held with a research fellow at Philips Research and part-time professor at Eindhoven University of Technology (department of Applied Physics) and he is the man behind the technological innovation, and a Technology Director at Philips Healthcare Incubator.

The Magnotech technology is a biosensor technology, which uses magnetic nanoparticles to measure picomolar concentrations of target substances in blood or saliva in a few minutes. The biosensor cartridge fills itself with blood or saliva, by which the magnetic nanoparticles execute the assay process with the help of magnetic fields.

- Philips (targeted drug delivery):

The interviewee is a research fellow at Philips Research and part-time professor at Eindhoven University of Technology (Faculty of Biomedical Engineering), the man behind the technological innovation, and he is scientifically responsible for several research projects on new agents for molecular imaging and therapy.

The technological innovation concerns a temperature-mediated local drug release under MRI guidance. This technique combines MRI, ultrasound and small chemotherapy drug containing particles. A specific ultrasound beam heats the target area to 42 °C, by which the nanoparticles (liposomes) release the drug. The MRI is used to identify the tumour and guide the ultrasound heating.

- Medimate:

The interview was done with the general manager of Medimate. He is responsible for the financial business and market aspects, but also guides the technical activities.

The company is a spin-off from the University of Twente and it develops medical devices based on lab-on-a-chip technology, applied in the Point-of-Care segment. The device is used for medical diagnostics, with the first

practical application for manic depressed patients. The product measures lithium in blood by a fluidic chip and stores the measurement.

- Xpand Biotechnology:

The interviewee is the initiator of the technological innovation, sr. scientist at Xpand biotechnology and sr. Scientist at the University of Twente, Department of tissue regeneration.

It is a life sciences company that is aimed at developing innovative technologies based on adult stem cells and appropriate scaffolds for the regeneration, reconstruction or augmentation of defected tissues and organs. The technological innovation which is included in this research concerns a new generation of orthopaedic materials: Instructive Bone Grafts. A completely new class of inorganic bone inducing materials is being developed, namely by combining nano-shaped apatite with an appropriate polymeric matrix. This allows the preparation of mechanically strong bone inducing materials.

- SME (targeted drug delivery)

- Lionix:

The interview was held with the Executive Vice-President, Marketing & Sales of the company. In the past he has carried out research and development work for products like chemical or magnetic sensors. Also he has work experience as project manager and department head for microsystems development for (big) industrial companies.

The technological innovation Lionix is aimed at, is the combining of integrated optics and micro/nanofluidics in one technology platform. The technology is integrated with complementary technologies of partners/customers. This means, their customers are other companies, who can use the technology in the bigger picture, for instance for medical diagnostics.

- Micronit:

The interviewee is the Chief Technical Officer.

Micronit Micofluidics develops lab-on-a-chip based products and it is a key supplier of microfluidic devices to life sciences and chemistry markets. Partners can be found both science and industry.
The nanotechnological aspect in the technology is clearly applicable in the form a coatings which are being applied on the surface of the microfluidic chips. Namely, the glass surface is hydrophilic, but in certain applications you would need the surface to be modified with a coating that prevents adsorption of small molecules. This can be useful in drug development, where compounds can be screened using microfluidic chips. In order to prevent compounds to stick to the walls, a coating should be applied to the channel walls.

- Glaxo Smith Kline:

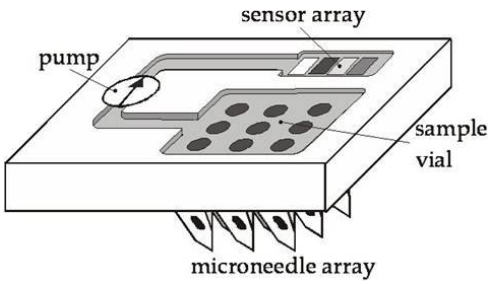
The interview was held with the medical director and vice president External Scientific Collaborations for Europe of GSK. Also he is Professor at the faculty of Pharmaceutical Sciences at Utrecht University.

Glaxo Smith Kline is a broad international organization, existing out of three segments: one part is aimed at the development of vaccins, another at the regular pharmaceuticals, and a third part is aimed at

consumer health products (toothpaste etc). The technological innovation which is included in this research is targeted drug delivery for the treatment of cancer. GSK itself is not a frontrunner in the research and development of these products, though it is involved in research, in collaboration with other companies. This means, it is of high importance for GSK to extend and maintain their network.

- MyLife Technologies:

The interview was done with the Chief Scientific Officer of the small organization which formally is not yet a company. The interviewee is also Assistant Professor at the Faculty of Science and Technology, University of Twente.



The technological innovation concerns the technology to produce microneedle arrays. The needles are of micrometer dimensions, by which the sensitive nerves are not being reached at application. Because of the small volume of the needles, multiple microneedles are placed in an array, which is integrated in a patch. The company has not decided yet whether to concentrate on the application of diagnosis or smart delivery systems, or develop both sorts of application. The microneedle array can be integrated in a lab-on-a-chip technology, by which the diagnosis can be done at the patients' home. The smart delivery systems are aimed at the development of 'intelligent patches' by which newly developed nanomedicine could be administered.

- Ministry of Health, Welfare and Sport:

The interviewee is a senior policy officer at the Ministry.

The Ministry tries to stimulate the society to live healthy and it to offer proper, accessible and affordable care.

- Ministry of Economic Affairs, Agriculture and Innovation:

The interview was held with a project leader Nanotechnology, who mainly works on policy development in the area of innovation, entrepreneurship and research. Second interviewee works on the informing aspects of nanotechnology for the Department for Innovation and Knowledge.

The Ministry promotes the strong international competitive position of the Netherlands, the focus for sustainability and it tries to create an excellent entrepreneurial business climate.

- The Dutch Health Care Insurance Board (CVZ):

The interviewee is a senior advisor health policy and medicines.

The Health Care Insurance Board provides advice and implements the Dutch statutory health insurance. It has a major role in maintaining the quality, accessibility and affordability of health care in the Netherlands.

- A Notified Body (BSI Group):

The interviewee is Head of Regulatory and Clinical Affairs.

BSI Group is a leading global business services organization providing standards-based solutions. It is an independent, private, non-profit distributing company which main activities are:

- development of private, national and international standards;
- assessment and certification of management systems and medical devices;
- testing and certification of products and services;
- provision of governance, risk and compliance solutions;
- training services.

- The Medicines Evaluation Board (MEB):

This interview was held with three employees of the MEB. One employee is a senior assessor Pharmacology-toxicology, the other two interviewees are non-clinical assessors of human medicines.

The Medicines Evaluation Board (MEB) assesses and monitors the efficacy, risks and quality of human and veterinary medicinal products. It also assesses the safety of novel foods for human consumption.

- The Health Care Inspectorate (IGZ):

The interview was held with the Chief Inspector of Pharmaceutical Products and Medical Technology.

The Health Care Inspectorate is aimed at an effective enforcement of the quality of health services, prevention measures and medical products. It advises the responsible ministers and applies various measures (e.g. advice, encouragement etc.) to ensure that health care providers offer only 'responsible' care. The Inspectorate investigates and assesses independent of party politics and unaffected by the current care system.

- The Association of Medical Specialists ('Orde van Medisch Specialisten'):

The function of the interviewee is Chief Professional Quality.

It is a association of specialists, for and by medical specialists. Its main tasks are:

- Initiating, coordinating and stimulating the improvement of the quality of medical-specialised care
- Representing of interests of medical specialists
- Offering legal and financial advice to its members.

- A Patient Association: the Asssociation for Manic Depressed patients and their Nearest (VMDB):

The interview was held with the Chairperson of the patient association.

It is a national association which represents the interests of manic depressed patients and their nearest.

- 'Experts' in the area of regulation or the pharmaceutical world:

S. Hoekstra-van den Bosch, MSc, PharmD: she is defined as 'expert on regulation' because of her broad work experience in the area of regulations. Earlier positions include:

- senior adviser at the Ministry of Health, Welfare and Sports
- coordinator for EU policy of the Directorate of Pharmaceutical Affairs and Medical Technology
- delegate on behalf of the Ministry to the EU Medical Device Expert Group and attached Working Groups
- vice-chair of the European Central Management Committee on Medical Devices
- chair of the EU Working Group on New and Emerging Technologies in Medical Devices
- manager of the Department of Scientific Advice of the Medicines Evaluation Board

Ir. J. G. Hanstede: Through his work experience in the area of medical biotechnology, pharmaceuticals and vaccins he has much knowledge about developments in these industries and what have been important issues through the years. Positions are: founder and secretary general of BioFarmind, business development manager at Amgen Inc. and founder and chairman at the Dutch Vaccines Group.

4.2 Categorization of activities

A categorization of the activities was made after having the interviews done, for the benefit of the method of coding. The categorization is based on a combination of scientific literature (Cooper, 1994; Tidd et al., 2005) and on the data themselves. The categories of activities are as follows:

R&D:	• doing scientific and technological research • using a dissertation.
External communication:	• having contact with research labs, spin-off companies, large pharmaceutical companies, Universities, insurance companies, the government, other involved authorities and/or doctors; • visiting conferences • ask for advice to expert panels and/or clinical parties.
Collaboration:	• work together with other companies (SMEs or large companies), research labs; • include shareholders, insurance companies or a Counsil of Advice in the innovation process
Market analysis:	• monitor competitors, for instance by: websites, conferences and publications; • explore different potential markets/disease areas • do a cost-benefit analysis • involve a marketing department • trendspotting • monitor signals from the society • do a SWOT-analysis
Financial support	• i.e. among others subsidy, venture capital, capital investment • acquisition of approval for (conditional) reimbursement • acquisition of a tax measure ('de fiscale maatregel').
Focus:	• make early, tight and target-oriented choices (by forward thinking)
Internal communication/ teambuilding	• focus on an open climate in communication and documentation inside the firm; • focus on management of a growing organisation; • focus on teambuilding.
Customer-oriented	• pay special attention to: the medical need, preferences of doctors, patients or customers, therapeutic benefit.
Inform the society	• Inform the society about nanotechnology or the technological innovation by making use of internet, a marketing department, publications (in popular and scientific journals), conferences and/or fairs.
Resource acquisition	• acquire technological components; employ interns or PhD students.
Work on regulation	• explore current regulation and requirements for approval of the nanopharmaceutical or nanomedical device • be actively involved in projects where it is investigated whether current regulations in the field of pharmaceuticals and medical devices are still suitable • critically consider the requirements for market approval; • change directives for evaluation of pharmaceuticals for market approval.

Table 3. Categories of activities

4.3 Overall nanomedical world

The results will be presented in a categorization of the companies who try to develop a technological innovation and the other stakeholders who are involved in the innovation process. The latter are either involved in the innovation process in a general way (patient association, ministries), or from the moment of implementation (MEB, notified bodies, the Dutch Health Care Insurance Board, the Association of Medical Specialists, the Health Care Inspectorate), which makes it more appropriate to discuss them in relation to the innovation process in general.

4.3.1 Companies

For companies, in the beginning of the innovation process, most activities are done in relation to technological uncertainty, accompanied by economic uncertainty. Subsequently a shift takes place during the innovation process to economic uncertainty in particular. Doing '*market analysis*' is the most executed activity in order to handle economic uncertainty and *R&D* for the reduction of technological uncertainty. This stays a prominent activity for the reduction of technological uncertainty during the innovation process. Common other activities in relation to both uncertainties are external communication (i.e. among others visit conferences and have contact with other companies, research institutes or research labs) and collaboration.

After having paid most attention to market analysis to handle economic uncertainty in earlier phases, the implement phase is characterized by *informing the society (about the technological innovation to enlarge awareness of the existence of the product), collaboration (for the actual launch of the product: collaborate with (academic) hospitals where the product can be applied or another company), R&D (make the technology as good as possible, and possibly make already improvements, in order to be competitive) and external communication (about how to get the product reimbursed)*. The high attention regarding these activities can be explained by the fact that the firms come near to the launch of the product. This makes them pay more attention towards getting it implemented in the market as fast and successful as possible.

Initially, for the reduction of social uncertainty considerably less activities are executed than for the initial two discussed uncertainties. Common activities in respect of this uncertainty are *external communication (to find potential clients), collaboration and market analysis (to explore opportunities for application)*. Later, more attention is paid to *thinking customer-oriented (i.e. focus on the user-friendliness of the product and on preferences of customers)* and *offer information to the society (to find customers).*

Finally, out of regulatory uncertainty, there is minimal incentive to take action. Only to some extent this happens to trigger firms to communicate externally in order to gain information on the required tests for market approval, but the remaining activities to reduce this uncertainty seem not to be of importance until they have reached the implement phase. Then, some firms emphasize the benefit of 'communicate externally', and 'working on regulation' to talk about/explore how to get market access and investigate whether current regulations are still suitable.

With regard to the nanotechnological aspect of the technological innovation, the interviewees of the firms do not think more research should be done, than currently is being demanded by the authorities. They think risks are sufficiently covered, since the regulations are already very strict and demanding.

The technological uncertainty is therefore not higher than for any other drug/medical device. Out of regulatory and economic uncertainty, one interviewee mentions that the nanotechnological aspect makes him to decide **not** to mention explicitly the term 'nanotechnology' in the reports of the research trials. This, in order to prevent the demand of more safety research by the Notified Body. Regarding the other uncertainties, no particular activities are being executed on the nanotechnological characteristic.

Non-phase related uncertainties

Most activities are done out of economic uncertainty, which mainly include: *being focused, market analysis, and collaboration*. The high attention regarding economical uncertainty can be explained by the fact that the development process of medicines rather needs high investments.

Social uncertainty comes in second place, for which companies mainly think *informing the society* about the technological innovation and the application of nanotechnology, is of importance. Other ways are external communication, and market analysis. These activities are often aimed at getting a clear view of the wishes of the future customer.

Further, since it concerns technological innovations, the creation of the best technology is throughout the whole process of importance, considering the high degree of technological research (*R&D)*.
The main activity for the reduction of regulatory uncertainty is*: external communication*. This external communication is mainly done for two reasons, in order to get a clear view on how to go through successfully the tests for market approval, and in order to express companies' opinion regarding the regulation and/or politics and possibly induce changes in the regulations.

Various statements were made regarding the nanotechnological aspect of the product. An important statement which all firms in overall share, is that current regulation on pharmaceuticals and medical devices just has to be followed, since no specific regulations regarding the application of nanotechnology jet exists. Technological uncertainty is by this point of view mainly covered. Further, Philips and Xpand Biotechnology emphasize the purpose of having experience and knowledge in-house in multiple disciplines for the development of a nanotechnological product.

With respect to social uncertainty, several activities are being performed out of different considerations. Most interviewees of the firms prefer to be transparent about the fact that nanotechnology is being applied and have a rational discussion about it, but only in situations when it is asked (for instance by the press). Some use the term 'nanotechnology' as a tool to sell the product. Lastly, in one interview at a SME (in vivo medical device) it was mentioned that the term 'nanotechnology' consciously should *not* be mentioned when you are sure there are no risks, in order to prevent public fear.

4.3.2 The other stakeholders

Other stakeholders execute most activities in response to technological uncertainty. They try to reduce this uncertainty particularly by allowing and stimulating fundamental research and doing technological research at the evaluation of nanomedical products, external communication (to share information and knowledge about nanotechnology), the use of financial support (to stimulate research and innovative activities by firms), and working on regulation.

The high attention towards technological uncertainty can be clarified by the role of these stakeholders, namely, it largely concerns authorities and organizations who have to evaluate the technological innovation for a large part on technological aspects. Examples of these authorities and organizations are the Medicines Evaluation Board, a notified body, the Dutch Health Care Insurance Board, the Health Care Inspectorate, the Association of Medical Specialists. Also is 'nanotechnology' part of the topsector 'High tech' of the Dutch government, through which the government stimulates research in this area.

In relation to the nanotechnological aspect, there is no clear and shared vision on how to deal with the technological uncertainty. Should nanopharmaceuticals and nanomedical devices be treated as a specific group of products, or should they be treated as any other product? Even within some of the interviews, there is discrepancy in what an interviewee says how it should be handled.

For instance, the senior advisor of the explains that the Dutch Health Care Insurance Board (CVZ) does not take into consideration the nanotechnological aspect of a medicine/medical device. It follows the decision made by the MEB and Notified body; and for reimbursement, the same requirements must be fulfilled as any other medicine/medical device. However, internally they do act upon technological uncertainty about 'nanotechnology', by informing their employees: what is nanotechnology, what are current developments etc? For instance, this is done by inviting a guest speaker.

The Head of regulatory and clinical affairs of BSI Group (Notified Body) also explains that BSI demands the same requirements as is being done for each innovative product, and handles in this way the technological uncertainty. The interviewee mentions:

"*You can not do more, than compare it with the state of art. You can look to the overall safety, short term safety. In the clinical trials this shall always be done, and especially for innovative products the clinical trials will be always done since you can not refer to earlier proof, after all it is an innovative product. Generally, these are short term and medium long term studies which will be considered in the evaluation, in some cases also with clinicians. Though, the long term is not known.*" (interviewee BSI Group)[1]. However, they **do** anticipate to the fact that nanotechnology is involved, by only employing people who have worked with comparable technologies in the past. Also, they have specific rules for medical devices in which free nanoparticles are present. In this case, similar requirements are demanded as is being required for pharmaceuticals, and only employees with above average experience in the field of pharmaceuticals are being allocated to these cases.

[1] "*Ja, je kunt niet veel meer doen dan vergelijken met state of art. Je kunt kijken naar de basisveiligheid, de korte termijn veiligheid, in de klinische studies zul je dit doen en zeker voor innovatieve produkten zullen er altijd klinische studies gedaan zijn want per definitie kun je je niet beroepen op dingen die al eerder gedaan zijn, je hebt immers een innovatief product. Dat zijn over het algemeen korte en middellange termijn studies en dat wordt meegenomen in de beoordeling, in gevallen ook met clinici die aan het front staan van de innovatie. Maar de lange termijn is niet bekend*." (geïnterviewde BSI Group)

In the MEB there are different opinions about the possible risks of nanomedicine. One of the interviewees of the MEB mentions that nanoparticles bring indeed more knowledge, but not that many risks. Furthermore, these risks can be investigated sufficiently by the current techniques and guidelines, and by just thinking critically about the safety. Also, it was emphasized that the size of the particles indeed is of importance, but it does not matter whether it is a nanoparticle or something else:

"That is what I do not like about the term 'nano', many things are included in this term, while it barely has something to do with one another. In fact, you can not make things that general. That is why pharmaceuticals are approached case by case, the question is: what type of particle is it? This makes it more appropriate to talk about the type of the particle, instead of the term 'nano'. Because the term nano does not add something to it, and each particle has such a different characteristic, which makes it necessary to investigate each product individually. In this context, the term 'nano' causes confusion, since you expect it to have similar characteristics..but.." (interviewee CBG)[2]

However, another employee of the Medicines Evaluation Board does think nanoparticles should be investigated more thoroughly. This person points out it could be useful to describe more elaborately the physical-chemical characteristics of nanoparticles.

Lastly, the government has funded several national and European research programmes where 'nanotechnology' is a main research subject.
The Ministry of Economic affairs, agriculture and innovation handles technological uncertainty in several ways: by getting knowledge of the risks and possibilities of nanotechnology through collaboration with several ministries; trust on signals from other institutions (like the RIVM, Rathenau Institute, Ministry of Health, welfare and sport); and allow the execution of research, and communicate about it. Further, a senior policy officer at the Ministry of Health, welfare and sport explains that the Ministry sees benefit in workshops for the industry, science and government to keep each other informed (such a workshop was recently organized with help of the RIVM); allows research and developments in the field of nanotechnology; and emphasizes that the government needs to stay alert. The benefit of workshops with the industry, science and government has also to do with regulatory uncertainty. Through the communication between the different groups, the ministry tries to keep everyone (themselves included) informed in the best way and with this information the ministry can check whether the regulations are still adequate.

In relation to social and regulatory uncertainty, a main activity is *external communication*. By communicating with several stakeholders and patient organizations about nanotechnological

[2] "*Maar dat heb ik ook een beetje tegen op dat hele begrip nano.. er wordt heel veel onder gestopt wat eigenlijk nauwelijks met elkaar te maken heeft. Je kunt het niet zo algemeniseren in feite. Vandaar dat ook bij medicijnen het steeds een case by case benadering is, van: over welke type deeltjes hebben we het.. Dan kun je denk ik net zo goed praten over het type deeltjes, en het hele begrip nano laten vallen.. Want nano voegt niet echt iets toe, en de deeltjes zijn zo verschillend qua karakter en eigenschappen, dat je elke keer weer naar hele andere dingen gaat kijken per produkt. En dat het begrip nano dan een beetje verwarring schept. Nano, denk je van: ze moeten allemaal ongeveer dezelfde eigenschappen hebben want daarom heten ze nano.. maar..*" (geïnterviewde MEB)

developments, a view will be created on the needs and acceptation from society. For regulatory goals, the external communication involves mainly talking about the adequacy of existing and future regulations and guidelines. For instance: The European Commission initiated the launch of the New and Emerging Technologies (NET) workgroup. This workgroup explored the developments in the field of nanomedical devices, and looked critically whether the regulations were still suitable in relation to these developments. The eventual advice of the workgroup was to change the regulation regarding free nanoparticles in medical devices. These kind of medical devices had to be considered as the highest risk class of the medical devices. Another example is the notified body (BSI Group), of which the interviewee explains to be involved in debates to discuss the required safeguards for society, by which 'nanotechnology' is an important subject of discussion.

Further, *informing the society* is also main activity to reduce social uncertainty and *working on regulations* to decrease regulatory uncertainty.
The European Commission and the Ministries have taken responsibility in informing the society about nanotechnology in a nuanced way, for instance by information magazines for a large public, or making use of a website. Further, the Commission Social Dialogue (Commissie Maatschappelijk Dialoog) has done many projects on nanotechnology and its awareness in the society (at the request of the Ministry of Economic affairs, agriculture and innovation).

Regarding the social uncertainty, the Head of regulatory and clinical affairs of BSI Group discusses the following dilemma:

".. little has changed in legislation in the past twenty years, but our vision on what is safe slowly changes and it gets tougher: more clinical trials and data are preferred... However, the difficulty is, we do not know how much tougher it should be to meet these preferences. Because there is no scientific report that says that innovative products are dangerous...or that medical devices in which nanotechnology is applied, create irresponsible risks. We do not know." [3]

Lastly, it should be mentioned that the other stakeholders perform few activities for themselves out of economic uncertainty, but they know economic uncertainty is of more importance for the companies. This is why the number of activities done for *financial support* is relatively high. Also an important change in regulation has taken place, i.e. the introduction of a 'temporary reimbursement' for pharmaceuticals and in the future possibly also for medical devices. This gives the firm time (2 till 4 years) to proof the effectiveness of the product.
Further, to serve society in times of weak economy (by the reduction of health care costs) the following activities are applicable: the Dutch Health Care Insurance Board pays more attention to 'cost-effectiveness' during the evaluation of the pharmaceutical and medical device for reimbursement; and makes cutbacks on the basic coverage (het basispakket) of medical products being reimbursed, at the request of the Ministries.

[3] *"…in de afgelopen twintig jaar is er weinig veranderd in de wetgeving maar onze visie op wanneer het veilig genoeg is, is langzaamaan aan het evolueren en wordt strenger; er moeten meer klinische studies en data zijn… Het lastige is dat we ook niet weten hoeveel dat precies zou moeten zijn om aan die emotie te voldoen. Want er is geen wetenschappelijk rapport dat schrijft dat innovatieve producten gevaarlijk zijn.. of dat nanotechnologie-gebaseerde medical devices onverantwoorde risico's met zich meebrengen. Dat weten we niet."* (Geïnterviewde BSI Group)

4.4 Nanopharmaceuticals, in vitro nanomedical devices and in vivo nanomedical devices

4.4.1 Nanopharmaceuticals

Search
Most activities are done for reduction of technological uncertainty. Firms try to respond to it in particular by focussing on *external communication* (i.e. visit conferences and other institutes; speak with contacts about technological developments; and keep in contact with research labs). Other activities are: R&D (in collaboration) and market analysis (to monitor other technological developments). Further, firms try to decline economic uncertainty also especially by *external communication*, accompanied by market analysis, R&D and being focused. Regulatory and social uncertainty are least reacted upon. Both are only handled by *external communication*. The 'external communication' is mostly done by having contact with research labs, spin-off companies, Universities and by visiting conferences, except in the case of regulatory uncertainty, for which specifically is reached out to the government.

Select
Main activities concern: market analysis and being focused, as a reaction to technological and economic uncertainty. According to the vice president External Scientific Collaborations for Europe of GSK, these activities seem to be more and more crucial for the development of pharmaceuticals:

"Well, times in which we, a pharmaceutical firm, could work out anything, and bring it to the market just with the help of some marketing, are over. That is very clear. I am a Professor Technology Assessment in Utrecht and know we are moving to a demand-driven market. When you start a development of a new pharmaceutical, you should understand what is the medical need and the clinical difference of the new product in comparison to the existing product should be so big, that it is being recognized by the patient, the doctor and the ones who decide whether the product is being reimbursed. This means, the rules of the game have changed through the years, which has led to a market-oriented way of thinking by the companies. From the start of the development we try to indicate what the market needs.. otherwise you are doomed."[4]

The specific activities in the area of market analysis are trendspotting, exploration of potential markets/disease areas, and cost-price analyses.

Regulatory uncertainty is not acted upon till the implement phase.

[4] *"Ja.. kijk, de tijd dat wij als geneesmiddelenfirma zelf konden bedenken wat we wilden en dat vervolgens de markt aanboden en dat via marketing ook wel een plek gaven, die is voorbij. Dat is heel duidelijk zo. Ik ben zelf hoogleraar TA in Utrecht en we schuiven steeds meer toe naar een vraaggestuurde markt waar je eigenlijk al als je begint met de ontwikkeling van je nieuwe geneesmiddelen uit gaat van de medical need en de definitie van wat je wil maken als geneesmiddel zodanig invult dat het verschil met wat er is op dit moment zodanig groot moet zijn, dat het klinisch een duidelijk verschil moet zijn dat door de patient herkend kan worden en door de behandelaar en daarnaast groot genoeg is om vergoed te worden door degenen die uiteindelijk de vergoeding regelt. Dus de regels van het spel zijn hele andere geworden dan er vroeger waren en dat betekend dus ook dat we heel erg markgericht denken en vanaf de reageerbuis al bezig zijn met in te vullen wat de markt nodig heeft.. anders ben je kansloos."*

Implement

A main activity in relation to technological uncertainty is *technological research*. Economic and social uncertainty both are mainly handled by *external communication* (with insurance companies and other stakeholders) and by *collaboration* with other research labs and SMEs.

The main goal of this external communication is to make the final implementation in the market as successful as possible, i.e. by having agreements on how to implement the technology in the hospital(s) and/or getting the pharmaceutical reimbursed by the government. However, this external communication is not yet what it supposed to be, as could be assumed out of an observation from the Chief Professional Quality of the Association of Medical Specialists:

"From the pharmaceutical industry we sometimes hear complains.. they think it takes too long before their product is included in the guidelines.. And when the government decides to reimburse it, only when it is included in the guidelines, we (the pharmaceutical companies) have a problem. Well, then I say: I understand, however, it should have helped when you had informed us about the developments in time. And when you had pointed out that you wanted it to be evaluated on a certain time. What I want to say, is that it is convenient for companies to let us know in time about their product development."[5]

Lastly, to reduce regulatory uncertainty, activities include: external communication (with the government and other institutes which are of importance) and work on regulation by being actively involved in projects to take the current regulations in reconsideration and by exploring the requirements and regulations for market approval.

Non-phase related uncertainties

Economic and social uncertainty are the kinds of uncertainty to which most attention is paid in general. In relation to the former, activities concern: market analysis, being focused and collaboration. In relation to the latter, the following activities are emphasized: external communication (with large pharmaceutical firms and other stakeholders), market analysis and inform the society.

4.4.2 In vivo medical devices

Search

In the beginning of the innovation process, social and regulatory uncertainty are not acted upon. The principal uncertainty applies to the technology itself. The firms deal with this by doing R&D, employ interns, do research in collaboration and try to make contacts in the academic world.

[5] *"En vanuit de farmaceutische industrie wordt bij ons wel eens geklaagd van: het duurt allemaal zolang voordat het in de richtlijnen terecht komt.. En als de overheid besluit om pas te vergoeden als het in de richtlijn staat, dan hebben wij een probleem. Dan zeg ik: dat snap ik, maar dan moet jij op tijd aankondigen dat je ermee bezig bent. En dat je het op een gegeven moment beoordeeld wil hebben. Het is voor bedrijven dus voordelig om ons tijdig te laten weten dat er iets nieuws komt. "*

Select

To the select phase, a shift takes place from technological uncertainty to economic and social uncertainty. Ways to incline these uncertainties, are: market analysis (trendspotting, explore different potential markets and monitor competitors), acquire financial support (by subsidy), and being customer oriented. In relation to regulatory uncertainty still no activities are executed. Lastly, out of economic consideration, also attention is paid to being focused, i.e. make in an early stage tight choices how to proceed in the innovation process.

Implement

In the implement phase, still most activities are done out of economic uncertainty. These are a whole variety of activities, namely making public of the technological innovation, making the product as customer friendly and cheap as possible, searching for co-developers and acquire financial support.
Related to the nanotechnological aspect of the innovation, one of the interviewees thinks it is best to avoid mentioning the term 'nano' out of economic and regulatory considerations. In this way he tries to prevent higher requirements regarding the safety experiments. However, for marketing purposes, it would indeed be good to mention 'nano', because this means it is 'unique' or special, and that is also the goal, to 'make something unique for the market'.

Non-phase related uncertainties

Many activities are concerned with economic uncertainty. Examples are: financial support, focus on the medical need and the preferences of the patient, monitor competitors and do technological research.
Specifically aimed at the fact that nanotechnology is being applied, economic uncertainty is tried to reduce by having/getting knowledge and experience on different scientific fields in-house. More activities which are related to the nanotechnological aspect are recognized regarding social uncertainty. One of the interviewees stressed the importance of not mentioning the term 'nano' in case you know it does not encompass a risk, and further mentions that the solution to possible fear for risks of nanotechnology from the society is just to obey the current regulations and requirements.

4.4.3 In vitro medical devices

Search

There is an equal proportion of activities in relation to economic, technological and social uncertainty. The main activity to reduce economic and social uncertainty is 'market analysis', which involves: monitoring other competitors and technological developments, trendwatching and explore different potential markets/disease areas. Another important activity for all three categories of uncertainty is collaboration, followed by external communication (which mainly means: visiting conferences to make contacts). Specifically regarding technological uncertainty, R&D is by far the most important activity. Lastly, no activities are done because of regulatory uncertainty in this phase, as well as in the next phase.

Select

The proportional distribution of activities as has been discussed above, has shifted to a priority on activities to reduce economic uncertainty. Still, this uncertainty is most importantly tried to be reduced by doing market analysis, but also in less degree by being focused and trying to acquire financial support. Technological and social uncertainty both are significantly less acted upon in this phase, in comparison to the search phase.

Implement

The distribution of activities in relation to the uncertainties is nearly identical in comparison to the previous phase. A difference is that market analysis is not anymore a prominent activity. For economic uncertainty, this has been replaced by a variety of activities, among others: collaboration, financial support, being focused (for instance: explore in time for improvements of the product), being customer oriented (patient friendliness of the product) and inform the society about the innovation in order to find customers.. Further, there are no remarkable differences in comparison to the select, in exception of the fact that only in the last phase attention is paid to regulatory uncertainty, i.e. by talking in time with the appropriate authorities about the development and what should be done in the clinical trials.

Non-phase related uncertainties

Economic uncertainty is acted upon mostly. Remarkably, firms pay significantly more attention to being focused in response to this uncertainty as a general activity, than as a phase-restricted activity and they see this as the most important way to decrease this uncertainty. Further, one interviewee also underlines benefit to launch the product as soon as possible in order to have first-mover advantage. In order to realize this, it is important to have shareholders and think and act future-oriented (by involving the right people in the innovation process in time and negotiate/make agreements in time).

Comparing the results of the product categories

Comparing the results of the three product categories leads to the following remarkable similarities and differences.

Search

Both for in vivo medical devices and pharmaceuticals, mainly activities are done out of technological and economic uncertainty, while for in vitro medical devices an equal proportion of activities is executed out of economic, technological and social uncertainty. Also, the way to deal with the uncertainties differs:

- Economic uncertainty: nanopharmaceuticals pay most attention to *external communication*, an activity to which rather no attention is paid by the medical devices. For in vitro and in vivo medical devices, attention is spread over a *variety of activities*, though a main one is *collaboration*, to which no attention is paid by nanopharmaceuticals.
- Technological uncertainty: for nanopharmaceuticals emphasis again lies on *external communication,* while for both sorts of medical devices emphasis lies on *R&D*.
- Social uncertainty: this uncertainty is only substantially acted upon by vitro medical devices, for which *market analysis and being customer oriented* are the most important activities. The activities are mainly aimed at getting a view of the future market, the wishes of the future customers and getting in contact with future customers The only way how nanopharmaceuticals try to reduce this uncertainty, is again by external communication (in order to find out what are preferences of possible future customers).

As a point of discussion, it should be taken into consideration that two out of three nanopharmaceutical products developed by large firms. Earlier research already stated that SMEs are more capable of becoming radically innovative and large firms later get involved in their innovation process (Schumpeter, 1934; Lee & Chen, 2009) . This means, large firms are more externally oriented regarding technological developments, and much pay attention to keep being informed (through external communication), while small firms are more oriented on their own R&D.

Further, the fact that social uncertainty only considerably is taken into account by companies developing in vitro medical devices and not by the other categories is in contrast with what should be expected. Namely, Vishwakarma et al. (2010) and Hubbs et al. (2011) described the expected high health risk of nanoparticles which diffuse inside the body. For this reason, it would be expected that the companies who develop a nanopharmaceutical or in vivo medical device would pay more attention to the future customers and their preferences, instead of the in vitro nanomedical device companies.

Select

For both sorts of medical devices, most activities are done out of economic uncertainty, while nanopharmaceuticals execute rather an equal number of activities due to economic, technological and social uncertainty.

- Economic: All three product categories try to handle the economic uncertainty most importantly by 'market analysis'. However, a significant difference is the fact that in vivo medical devices pay relatively much attention to *financial support*, in comparison to the other two product categories.
- Technological uncertainty: It is of minimal influence on in vivo medical devices, but also for the other product categories its influence is rather low or moderate. By comparing the activities done between the different sorts of products, the only significant difference is regarding *being focused*. This activity is more relevant for nanopharmaceuticals than for the other two product categories.
- A clarification regarding the equal spread of economic, technological and social uncertainties for nanopharmaceutical companies (in contrast to the priority of economic uncertainty for the medical devices) can be given through the citation from the interviewee of GSK (see page 29). In this citation the necessity for pharmaceutical companies was emphasized to oversee the whole picture of what will be needed in the future in an early stage and act upon it.

Implement

For all product categories, most activities are done out of economic uncertainty; and technological and social uncertainty come in second place. However, concerning regulatory uncertainty, a substantial difference exists between nanopharmaceuticals and medical devices. At the development of the medical devices, only few activities are done in relation to regulatory uncertainty, while this is considerably higher in the case of nanopharmaceuticals.

- The activities to reduce economic uncertainty differ on two main points:
  - At the development of nanopharmaceuticals, most attention is paid *to external communication*.
  - At the development of the medical devices, a whole *variety of activities* are being executed. Remarkable with this, is that almost the only one activity which is <u>not</u> being executed is: external communication.
- Regarding technological and social uncertainty, no striking differences or remarkable similarities have occurred.
- Regulatory uncertainty: firms developing a nanopharmaceutical take considerably more action than the medical device firms to reduce this uncertainty. The two main activities being focused on are: *working on regulations* and *external communication*. A way in which it is handled by an in vivo nanomedical device firm, is by avoiding to mention the term 'nano'. In this way the firm tries to prevent higher requirements regarding the safety experiments.

As a point of discussion, it should be taken into consideration that the difference regarding regulatory uncertainty most likely is being caused by the fact that two out of three firms in the sample of nanopharmaceutical firms is a large company. Only in these firms the benefit of paying attention to regulatory uncertainty is emphasized. This assumption is being supported by the fact that one out of the two medical device firms which also execute an activity as response to regulatory uncertainty also is a large firm.

<u>Non-phase related uncertainties</u>

For all three product categories, the main uncertainty which is responded to by certain activities, is economic uncertainty. The other categories of uncertainty is acted upon rather low, with the exception of social uncertainty. The latter is for the nanopharmaceuticals in general fairly present.

- Economic uncertainty: The activities executed by the three product categories largely correspond to each other. Most important difference lies between in vivo medical devices and the other two product categories: former does not see *collaboration* and *being focused* as important activities to do in general, while the other two sorts of products **do** see the benefit of this.
- Technological uncertainty: In general, this kind of uncertainty is little acted upon by all three sorts of products, besides the execution of R&D. Further, there are no remarkable activities or differences between the product categories.
- Social uncertainty: This is taken more into consideration by nanopharmaceuticals, than by the medical devices. Despite the fact that in all product categories, *informing the society* is mentioned as a way to reduce this uncertainty, nanopharmaceuticals also pay much attention to *external communication* and *market analysis*. The medical devices do not execute these activities at all.
- Regulatory uncertainty: There happen to be no substantial differences between the product categories. It only can be mentioned that for all of them, external communication is mentioned as a way to reduce this uncertainty in general.

4.5 SMEs vs. large firms

4.5.1 SMEs

Search

Most attention is paid to economic and technological uncertainty. In second place comes social uncertainty. Regulatory uncertainty is least acted upon in a specific phase, but more in general during the whole innovation process. For the three former categories of uncertainty, important activities in this phase are external communication and collaboration. Above of that is R&D most executed activity to reduce technological uncertainty, market analysis for the reduction of economic uncertainty, and the latter activity is also a main way as a response of social uncertainty.

Select

Attention has shifted substantially to the reduction of economic uncertainty in the select phase, especially by doing market analysis. Other activities in relation to this uncertainty concern the acquisition of financial support and being focused. Secondly comes technological and social uncertainty. Also here for, market analysis is executed most often to get more certainty (for instance, to evaluate the technological choices in comparison to other developments) and R&D stays important for the reduction of technological uncertainty.

Implement

Still, most activities are done out of economic uncertainty. However, the sorts of activities differ compared to what is done in earlier phases. The focus in the last phase lies on R&D, collaboration with/selling of the product to a large company, being customer oriented and inform the society about the product. For technological uncertainty, generally the same variety of activities are done. Difference is an emphasis on internal communication/teambuilding in relation to technological uncertainty. To reduce social uncertainty, i.e. uncertainty about obtaining potential customers, benefit is seen in informing the society about the product.

Non-phase related uncertainties

Most activities are done in relation to economic uncertainty, including: being focused, R&D, communicate externally, collaborate, acquire financial support, and being market/customer oriented. In relation to social uncertainty, it concerns among others external communication and collaboration (by including future customers in the Advice Board). By these activities an indication is made on the social needs. And further, for regulatory uncertainty, the main activity is: external communication. In this way, the companies try to intervene with discussions about the adequacy of the regulations. Also, external communication is done in order to explore what steps should be taken in order to acquire market access and get the product reimbursed.

4.5.2 Large firms

Search

Many activities are done out of technological uncertainty, followed by economic uncertainty. Social and regulatory uncertainty is minimally acted upon. External communication is by far the most important activity to reduce technological uncertainty; other activities are R&D, collaboration and market analysis.
The interviewee of GSK underlines the importance of collaborations with SMEs and sees this as a source of innovation, but he thinks the government supports this too less. The government makes cutbacks and mainly helps the large firms, while it are the SMEs who need it. In comparison to other countries, who are actively focused on this cooperation between firms, the Netherlands lag behind, while we were their example in the past.

Also related to economic uncertainty, external communication is an important activity, accompanied by market analysis and being focused. Finally, market analysis is also the main way to reduce social uncertainty in this phase.
Despite the fact that technological uncertainty is most acted upon, an important statement being made by both large companies, is that they underline the importance of knowing what are your strengths on technological area, but also explore the developments in the market. In other words: strategic positioning.

"The innovation process has started from both the technology and the market. That is called strategic positioning. So, as a company you have certain competences where you are good at, meanwhile you monitor developments in the market, and that combination was the drive to start. We saw developments in the area of micro-electronics, the chips, small structures... we noticed there was a scope and new technologies like DNA chips. This made us consider whether we (Philips) could also play a role in this market." (Technology Director, Philips)[6]

Another interviewee of Philips adds to this, that this a rather different approach than small spin-off companies have. They are largely aimed at the technological development in the beginning of the innovation process:

"We start in an explorative way. So this is not a dissertation, based on a study of many years…like the way it goes in the academic world. Then, a research group investigates something for multiple years and suddenly this leads to an invention which possibly can be commercialized in the future." (Research Fellow, Philips) [7]

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[6] "*Het innovatieproces is begonnen vanuit de technologie en markt allebei. Dat is de strategische positionering. Dus je hebt bepaalde competenties waar je als bedrijf goed in bent, je ziet ontwikkelingen in de markt en ja, die combinaties zijn de drive denk ik geweest om dit te beginnen. Op het vlak van micro-electronica, de chips, kleine structuren.. En je ziet ontwikkelingen in de markt, groeimarkt en nieuwe technologieën zoals men noemde de DNA chips. En dan kijk je: kunnen wij als Philips daar ook een rol in spelen*." (Technology Director, Philips)

[7] "*We beginnen op een exploratieve manier. Dus dat is niet een gedegen proefschrift met een onderzoekslijn waaraan jaren gewerkt is., zoals dat gaat in de academische wereld.. ja.. een onderzoeksgroep werkt ergens jaren aan en opeens is er een vinding die commercialiseerbaar zou kunnen zijn en daar gaat men dan op verder bouwen*." (Research Fellow, Philips)

Select
Highest attention is paid to economic uncertainty, by doing market analysis, being focused and search for collaborations out of technological considerations, as well as for acquiring market channels. Further, out of technological and social uncertainty, one of the firms emphasizes the advantage of being focused. In an early stage, decisions should be made about the further development of the product, by taking into consideration all kinds of aspects (technological, economical, social). In this way, chances are increased to realize the best product in technological sense, and in the sense of what the market wants.

Implement
The number of activities done for reduction of the four categories of uncertainty is rather equal spread. Though, still economic uncertainty is acted upon most, by external communication, collaboration, and being focused, in other words: rather the same activities as in earlier phases. Regarding technological uncertainty, emphasis lies on R&D and for social uncertainty this is being customer oriented and informing society. Lastly, remarkable is the fact that only in the implement phase activities are done to reduce regulatory uncertainty. Firms try to deal with this uncertainty by paying attention to the execution of comprehensive research, external communication and working on regulations (i.e. exploring the requirements for market approval, but also being actively involved in projects where it is investigated whether current regulations in the field of pharmaceuticals and medical devices are still suitable).

Non-phase related uncertainties
Activities which are expected to be of importance more generally during the innovation process are market analysis, collaboration and being focused for the reduction of economic uncertainty; and to decline social uncertainty: informing the society and also market analysis.

Comparing the results of the different sized firms

Comparing the results of the different sized firms leads to the following remarkable similarities and differences.

Search

The degree in which activities are done in relation to the different uncertainties are ranked for both firm sizes the same. Most till least is: technological – economic – social – regulatory. Exploring them in a more nuanced way, shows that there are some significant differences in the way the uncertainties are tried to be reduced:

- Economic uncertainty: For SMEs, *collaboration* is one of the main activities, while the large companies pay less attention to this activity. On the other hand is *external communication* and *being focused* for the large companies of considerably more importance than for the SMEs.
- Technological uncertainty: Main difference in this context is the fact that the most executed activity by each firm size is of substantial less importance for the other firm size. SMEs are trying to reduce this uncertainty mainly by doing *R&D*, while large firms principally try to do this by *external communication*. This external communication eventually must lead to collaboration with other organizations.

- Social uncertainty: With regard to social uncertainty, both firm sizes see the purpose of *market analysis* and *being customer oriented*. Though, some extra activities SMEs perform and large firms do not, are: *external communication* and *collaboration*.
- Regulatory uncertainty: this uncertainty is of no influence for SMEs. For large firms it is of little influence. They try to reduce it by external communication, i.e. giving their opinion about the policy through contact moments with the government and through presentations. Further, they try to reduce the uncertainty (regarding possible regulations in the future) by being customer oriented, i.e. choose an innovation that offers obvious health benefits:

"*You look what is the difference you can make with the product.. and when this difference is just small, you will not invest in further development... because you have to defend towards the government that you accept some risk in terms of long term risks. Also you have to defend it towards the consumer, by discussing the following dilemma: should we let people die because we are afraid of these nanoparticles, without evidence for the risks. So you have to sum up all those external reference points and consider whether this is in balance with the therapeutic benefit of the innovative product. Only then you have a reason to invest in it.*" (Vice president external scientific collaborations for Europe of GSK) [8]

Select

Also in this phase, the number of activities done for the different uncertainties are ranked for both firm sizes the same. Nevertheless, relatively speaking, SMEs take more action for reduction of the uncertainties than large firms do. The sort of activities executed, on the other hand, do not differ that much between the two firm sizes. The only remarkable difference is the relatively high attention being paid to *market analysis* by the SMEs in comparison to large firms, as a consequence of economic, technological and social uncertainty.

Implement

The degree in which economic and technological uncertainty are acted upon is for both firm sizes equal, while the degree in which social and regulatory uncertainty are acted upon is for large firms significantly higher in comparison to SMEs.

- Economic uncertainty: Both firm sizes execute pretty much the same variety of activities. One prominent difference is the fact that large firms pay most attention to *external communication* to reduce this uncertainty, an activity which is not being executed at all by the SMEs. The main goal of this external communication is to make the final implementation in the market as successful as possible, i.e. by having agreements on how to implement the technology in the hospital(s) and/or getting the pharmaceutical/medical device reimbursed by the government.

[8] *"Dus dat betekend ook dat je kijkt van: Nou, dit zou wel net iets beter kunnen zijn ofzo.. mooi niet.. dan ga je er niet in als het net ietsje beter is.. want je moet kunnen verdedigen bij de overheid dat je een risico accepteert in termen van lange termijn toestanden maar je moet ook bij die consument aan kunnen praten: laten we mensen dood gaan dan, omdat we bang zijn voor 'nanodeeltjes' die iemand weer heeft verzonnen. Dus dat is het stapelen van dat soort aanknopingspunten van buiten tot een hoogte waarbij je zegt: als dat in evenwicht is met de therapeutische benefit wat we vinden, dan heb je een punt*." (Vice president external scientific collaborations for Europe of GSK)

One of the interviewees recognizes this low degree of attention being paid to external communication by SMEs. He (Ir. J. G. Hanstede, expert) sees the absence of the right people in-house, who should build up contacts etc., as missing link which SMEs should pay attention to:

" But it is often the case, when a Professor starts a company, he has to realize that very few people possess all required qualities. I mean, a Professor is extremely good in doing research, but often not that good in starting a company. So you need someone else who is good in this. Further, you also need people who are familiar with the market. So you need to lead your company, but you also need your contacts/network/coaches to help you during the development. They should help you to make the right choices and make the right contacts. That is called: business development. And it is important to contact, ask for help and/or hire those people in time."[9]

- Technological uncertainty: The different sorts of activities being executed are obviously higher at the SMEs than it is the case for large firms. Activities concern: R&D, collaboration, being focused, internal communication, informing the society, resource acquisition and work on regulation. In contrast to this, large firms emphasize mainly the benefit of R&D. In relation to this focus on R&D, it is essential to mention that the main difference between large firms and SMEs is, that large firms emphasize the purpose of post marketing surveillance (PMS). This comment was made by both large companies included in this research and by none of the SMEs. The interviewee of GSK emphasizes in this the significance of the right prescription of medicines/therapies and good use and guidance of medicines:

"What you would like to have, is a treatment of your pharmaceutical by a person who really knows how it should be treated. So he should know whom he should subscribe it to. Pharmaceuticals just have to be used and guided in a certain way, but that guidance often is what is missing. Consequently, the value of your pharmaceutical decreases because of incorrect use of it. But that is out of our hands. While appropriate use and guidance is very important to manifest innovations... and it becomes more and more important because there are real life evaluations who are going to determine on longer term whether a registration or approval for reimbursement will be maintained or not." [10]

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[9] *Maar vaak is het zo, als een hoogleraar een bedrijf begint, dan moet ie goed beseffen, het is heel weinig mensen gegeven om alle kwaliteiten in 1 persoon te hebben he. Dus een hoogleraar is verschrikkelijk goed in onderzoek, maar vaak niet zo goed in het opzetten van een bedrijf. Dus je moet er iemand naast hebben die dat wel goed kan. En dan moet je ook nog mensen hebben die in die markt thuis zijn. Dus je hebt een bedrijf aan te sturen, maar je hebt ook je contacten/netwerk/coaches nodig die je helpen binnen dat segment waar je iets wil ontwikkelen, de juiste weg te kiezen en de juiste contacten te zoeken. En dat heet business development. En zulk soort mensen moet je dus op tijd in dienst nemen, contact mee zoeken of hulp bij vragen."* (Johan Hanstede)

[10] *"Nou dat betekend dat wat je graag zou willen, is dat er een behandeling is van je geneesmiddel door mensen die er verstand van hebben, dus weet: aan wie schrijf ik het voor. Geneesmiddelen moeten gewoon op een bepaalde manier gebruikt en begeleid worden, die begeleiding is er vaak niet.. en dat betekend dus ook dat de waarde van je geneesmiddel bij onjuist gebruik omlaag gaat. En daar hebben wij dus geen grip op. Dus om innovaties tot hun recht te laten komen is juist het goede gebruik en de begeleiding daarvan een enorm belangrijke zaak.. en dat wordt steeds belangrijker omdat er real life evaluaties plaatsvinden die ook over langere termijn gaan bepalen of een registratie of vergoeding gehandhaafd blijft of niet."* (Vice president external scientific collaborations for Europe of GSK)

- Social uncertainty: Not much difference exists between the two firm sizes, on what activities are being executed to reduce social uncertainty. However, it must be mentioned that large firms pay fairly more attention to external communication, collaboration and being customer oriented. All three activities are especially aimed at talking with hospitals and doctors, collaborate with them and think about the best practice for doctors and patients.
  This can be explained by the fact that it is a common phenomenon that large firms eventually bring the medical product to the market. This means it is their job, as well as their strength, to do this as successful as possible. This is clearly put forward by one of the interviewees of a SME, developing an in vitro medical device:

  " Well, you need to foresee the limitations of our company. Firstly, that is also good for the shareholders, because with a little luck the financial part will be okay. But when you look to the technological part, it would be best when it will be taken over by a large organization. That is my profound belief. And why? Because we are scalable and we have global markets. When large companies get an eye of those global markets, it certainly will be embraced by one of those companies. And as I said before, I see two or three big pitfalls for small companies, that is: money, the organization itself and the limitations of the company in sense of the future. Our limitation for the future is the lack of the right channels. We need a large organizations who makes all contacts to sell the product. We must not try to do this ourselves, because all channels and contacts are there. They just have to see the benefit of our product." (General manager, Medimate)[11]

- Regulatory uncertainty: An eye-catching phenomenon is the fact that little action is taken in each of the phases by the SMEs. By contrast, large firms **do** feel the necessity to execute activities. The main way to do this is external communication, accompanied by working on regulation. These activities mean chiefly having contact with the appropriate authorities about the product/technological development and how clinical trials should be structured for most optimal defences of the product. Even if it is well-known how to structure the clinical trials, it still is useful to inform the authorities about your plans in order to find out their reaction. Further, they are working on regulation by exploring the specific requirements for approval, but also by being involved in a project where it is investigated whether current regulations in the field of pharmaceuticals and medical devices are still suitable.

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[11] "*De beperkingen van ons bedrijfje moet je gewoon in oogschouw nemen. Ten eerste is dat ook goed voor de aandeelhouders want als het een beetje meezit gaat dat wel goed financieel. Maar als je kijkt naar de technologie is het het beste als het omarmd wordt in een grote organisatie. En ik ben er eerlijk gezegd heilig van overtuigd. En waarom denk ik dat? Omdat we scaleable zijn. Dus het is makkelijk op te schalen. Het is lastig om te maken maar als het eenmaal werkt is het redelijk makkelijk op te schalen en we hebben global markets. Als alleen NL en litium de markt was, dan hadden we geen grote organisatie nodig, maar dat is niet zo. En als grote bedrijven die global market zien, dan moet dit wel omarmd worden door een groot bedrijf. Anders laat je de kansen van de technologie lopen.*

En zoals ik in het begin al zei, ik zie 2 of 3 grote valkuilen voor kleine organisaties, dat is geld, de organisatie zelf en de beperkingen van je organisatie in de zin van de toekomst. Ik zie de beperkingen van onze organisatie naar de toekomst om wereldwijd dé speler te worden. Daar heb ik een voor partij nodig die aan alle deurtjes kloppen: de nefroloog, bij de psychiaters etc. En dat moet ik niet zelf gaan ontdekken. Die kanalen en mensen zijn er allemaal al, ze moeten alleen onze producten ook ff meenemen." (General Manager, Medimate)

Non-phase related uncertainties

- Economic uncertainty: For both firm sizes, economic uncertainty is in general most acted upon in comparison to the other uncertainties. There is no substantial difference in the way the two firm sizes think about the activities that should be executed to reduce this uncertainty, except for the fact that the benefit of *market analysis* is more recognized by the large firms than by the SMEs.
- Social uncertainty: Large firms think that an important activity that should be executed throughout the whole innovation process in order to reduce social uncertainty, is: *inform the society*. This has two reasons: one is to advertise the product, second has to do with the nanotechnological part of the product, which makes the firms to be transparent about 'nanotechnology' and provide objective information, in order to prevent public fear. This attention for possible public fear has been observed in a less degree at the SMEs in this research.
- Regulatory uncertainty: Remarkable is the fact that no activities have been executed to reduce this uncertainty in any of the three phases for SMEs, but it indeed seems to be in general of some importance. This emerges through the relatively high value the SMEs give to *external communication*, in comparison to the other possible activities.

5. Discussion

A reflection will be done on the results of this research, by comparing them to scientific literature about:

- innovation processes,
- the role of uncertainty in innovation processes,
- uncertainty regarding nanotechnology,
- responsible innovation.

Innovation processes

A general description of the innovation process is given by Tidd et al. (2005). They divided the process in a search, select and implement phase, each characterized by different activities. Initially, the environment should be scanned for threats and opportunities for change. Then, selections should be made on which signals to respond and subsequently it is the challenge to make something new and bring it to the market. Through this description, added by multiple routines and activities (see table 1), the authors give advice to organizations how to 'manage innovation'. While giving this advice, they are well aware of the fact that innovation decisions about how to handle the multiple challenges are characterized by high levels of uncertainty (caused by several factors, i.e. technical, social, political etc.). At the early stages, there is less knowledge in the uncertainties and selections are based on "best guesses". Later, the decisions are based more on knowledge, acquired through activities like technological and market research.

Comparing the results with literature leads to the following statements:

Search:
The companies execute most activities due to technological uncertainty, which is tried to reduce by R&D, external communication and collaboration. More specifically this means: doing scientific or technological research, visiting conferences, having contact with research labs, collaborate during research. Further, economic uncertainty is much acted upon by performing a market analysis (e.g. monitoring technological developments, exploring potential markets/disease areas and trendspotting). All activities are aimed at the initial development of a new technology.

The results are partly in line with the search phase, as being described by Tidd et al. as follows: "*..it involves the search for potential for change in the environment, by looking for technological opportunities, or monitoring requirements from the markets*." (see also table 1) Matching results are: the monitoring of technological developments (by visiting of conferences, contact with research labs) and trendspotting. However, 'R&D' and 'collaboration', which resulted as common activities during the search phase in this research, are according to Tidds' description related to the implement phase (for resource acquisition). In the light of these results, it may be derived that the making of the medical product is earlier in the innovation process of importance than it is the case in general.

Select:
Activities related to economic uncertainty dominate for the companies. Main activities are: doing market analysis, accompanied by being focused and generating financial support.
The high attention paid to above-mentioned activities in response of economic uncertainty, corresponds partly to what the select phase is about according to literature, i.e. making a balance between options, in order to make a choice which one(s) eventually to explore (Tidd et al, 2005). Doing market analysis does not match with this description. It is an obvious way to acquire knowledge about other competitors, technologies and potential future markets and this information can be used for making a balance, but the gathering of this information should mainly happen in the search phase according to Tidd et al. However, 'being focused' refers to making decisions how to proceed in the innovation process, which is consistent with the literature.

Implement:
Lastly, 'the translation of signals into something new' not only happens in this phase. During the whole innovation process of the nanomedical products, R&D is of importance for the reduction of technological uncertainty. In this way, it is tried to make something new, so this is not in line with Tidds description. This is accompanied by more activities which are related to the implement phase in literature (see table 1), but happen to be of importance from the search phase for nanomedical products. Examples of activities are: collaboration, brainstorming and managing teambuilding and the project structure.

Other results indeed are in line with the literature, namely the effort to launch the product during the implement phase. Many activities in this phase are aimed at reaching future customers, trying to realize the launch of the product, and exploring how to get actual market access and getting the product reimbursed.

SMEs and large firms

Earlier research on innovation processes also has investigated the difference between SMEs and large firms developing medical products (this also has been described in the theory section). For instance: both firm sizes are more actively involved in different phases of the innovation process. Generally, SMEs come up with a radical innovative idea and try to develop it as far as possible. Later large firms get involved, and they make it possible to bring the product to the market. These different capabilities reflect the different structure and availability of resources of the companies. Strengths of SMEs are that they are more flexible, by which they can react easier to changes in the market and be innovative (Schumpeter, 1934). Strengths of large firms are that they have much skills and resources in-house, obtained through earlier successful innovative products. This makes it possible to make the required investments for the product innovation and it makes their survival less dependent on the new technological innovation (Lee & Chen, 2009).

Comparing the results regarding SMEs and large companies with literature leads to the following statements:

In the search phase, main activities of SMEs are collaboration and R&D, while large firms mainly pay attention to: being focused and external communication. A logical explanation would be that collaboration is for SMEs important in the high degree of R&D they do and large firms do not do

themselves. Large firms make clear decisions which technological development to focus on and try to find innovative SMEs to collaborate with, or buy the innovative technology from, by external communication.

In the select phase, SMEs seem to pay more attention to market analysis than large firms do. This means, developments of other competitive technologies and a clear business case for the future seems more important for SMEs than for large firms. This possibly has to do with the consequences of failure that differs for SMEs and large firms. These are larger for SMEs, for who the innovation is the only possibility for survival, while large firms can rely on the profits of other products being sold. Also, large firms generally have more resources in-house, to make the technological innovation a success (Lee & Chen, 2009). This means, they are more able to trust on their own strengths, due to higher availability of resources, than small firms. This is clearly expressed by the Technology Director of Philips Healthcare Incubator:

"… So the trigger was the match between sensors based on magnetic particles and the magnetic competences within Philips. Initially, that was the reason to start, though during development we gone another way. We stopped investing in magnetic sensors, out of industrialization considerations, and we chose an alternative. However, this alternative again corresponded to another competence within Philips, namely optical detection. So we were able to rely on another competence within Philips… And that is possible because of the size and infrastructure of this company. That makes it possible to make such switches. Otherwise, it may hurt much more…. When you are a small start-up, you have a limited amount of money to invest, and a limited amount of employees, who have knowledge on one specific area. When the business case is not a success in that area, it is end of story."[12]

Further, large firms are far more occupied with having contact with hospitals about how to apply the product in the hospital and/or having contact with appropriate authorities on how to get the product reimbursed. This can be explained by the experience of large firms. They probably know better what practically should be done for a successful launch and have the right people for this in-house.

[12] *"…Dus als je ziet wat de trigger was, de match tussen sensoren gebaseerd op magnetische deeltjes en magnetische competenties binnen Philips, dat was de reden om te beginnen en gaandeweg zie je dat je dus eigenlijk een heel ander pad gaat bewandelen. Want de magnetische sensoren waar we de competentie hadden, hebben we geparkeerd vanuit industrialisatie overwegingen en zijn we met een alternatief gekomen. Dus ondanks dat het de reden was om dat te kiezen, zit het er uiteindelijk niet meer in.*

Maar het sloot wel weer aan bij een andere competentie die weer heel breed aanwezig is binnen Philips, namelijk de competentie van optische uitlezing. Philips heeft aan de wieg gestaan van CD en DVD en dat is heel gevoelige optische detectie. Dus vervolgens konden we terugvallen op een andere competentie die groots aanwezig was…. Dat is wel iets wat dankzij de grootte en de infrastructuur hier kan. Daardoor kun je dat soort switches maken. Anders kan het veel meer pijn doen…..Als je een kleine start-up bent en je hebt eenmalig genoeg geld en een set kennis van mensen die alles weten van magnetische sensoren, op dat pad, en je concludeert: de business case werkt niet. Dan is het einde verhaal." Technology Director of Philips

Another result is that large firms execute more activities in the field regulation. This can be explained by the fact that large firms have a whole 'Regulatory Affairs department' in house, and SMEs generally have not. Above of that comes the fact that large firms eventually will bring the product to the market and for which contact is needed with the authorities about the clinical trials. However, one of the experts (Ir. J. G. Hanstede) suggests it may be useful when this should also be done by SMEs in an earlier stage:

"… that is called business development. You need to have the right contacts… you need to include advice of large companies, or hire someone for advice. It is easy to burn money, though you have to make the right choices. You may have done fantastic research and say to have proven everything. But it must be the right proof which is eventually in need by the large firms for registration."[13]

The role of uncertainty in innovation processes

Literature has shown that uncertainty may be of positive as well as negative influence on the innovation process, by the decisions made to act upon it (Koppenjan & Klijn, 2004, Jacobsson & Bergek, 2004, Jauch & Kraft, 1986). Actors may be hesitant to make decisions, are rather be pro-active; they may be in less or more degree willing to invest in the technological innovation; they may seek for new partners or rely in their own strengths; they may be open to society about the innovation or rather keep it quite to avoid public backlash etc.
Being hesitant in decision making or being less willing to make investments, may result in a situation where important activities for a successful innovation will be missing. In contrast, being more willing to invest in it or being more proactive demonstrates that uncertainty also can be a drive to innovate and can lead to a situation in which consciously activities are performed which benefit the innovation process.

This study shows the different actors have a proactive attitude towards the technological uncertainty, which is expressed by the willingness to invest in R&D for the development of nanomedical products (companies) and invest in nanotechnological research by national/international research programmes (companies and the government). Small firms rely mainly on their own research, which can be explained by their innovative character (Schumpeter, 1934), while large firms combine this by seeking for new partners. In relation to regulations, the lack of knowledge on the application of 'nanotechnology' leads to a situation in which the government is hesitant to make new regulations. However, it acts rather proactive to reduce this uncertainty, by investing in research, keep being informed about technological developments and by talking about the adequacy of existing and future regulations and guidelines, on national and international level. For the companies, this proactive attitude mainly applies to large firms, by being involved in these discussions/gatherings regarding existing and future regulations and guidelines.

[13] *"… dat is business development. Je moet zorgen dat je die contacten allemaal hebt.. en dat mensen allerlei adviezen van grote bedrijven meenemen, of iemand inhuurt die je kan adviseren. Een berg met geld verbranden is natuurlijk geen kunst maar je moet wel de juiste richting opgaan met je bedrijf. Je kan misschien fantastische onderzoeken gedaan hebben, en dan zeg je: ik heb alles bewezen. En dan zegt 'n groot bedrijf: ja dat heb je zo en zo gedaan maar daar kan ik niks mee. Want voor mijn registratie bij de gezondheidsautoriteiten die daarover gaan, in Brussel en Engeland etc, daar heb ik dat en dat voor nodig en dat heb je niet gedaan, dan kun je het opnieuw doen*." (Johan Hanstede)

Economic uncertainty also leads to a proactive attitude of the firms, by performing several activities to reduce it, and mainly market analysis. Because of times of weak economy and cutbacks from the government, economic uncertainty has increased for the firms. This also has leaded to stricter requirements for getting approval for reimbursement by the Dutch Health Care Insurance Board. Consequently, firms have to make early, tight and target-oriented decisions.

Lastly, social uncertainty regarding the application of nanotechnology leads to a proactive attitude of the government by taking action to inform the society about it. The view of the companies on the issue whether society should be informed about the nanotechnological aspect of the product varies. Some firms use the term 'nanotechnology' as a tool to sell the product; most firms prefer the way of being transparent about the fact that nanotechnology is being applied and having a rational discussion about it, but only in situations when it is asked (for instance by the press); and another firm thinks the term 'nanotechnology' consciously should not be mentioned when you are sure there are no risks, in order to prevent possible public fear.

Uncertainties regarding nanotechnology

There is much literature which is concerned with the uncertainty regarding the possibilities and health risks of nanotechnology. This is being discussed in a many ways: what are the expected risks and break-troughs, how should risks be managed and governed, in what degree are risks accepted (in relation to the benefits) by the society and the government, how to find the right balance between the stimulation of innovation and protect human health etc. In relation to nanomedicine, it can be stated that the expectations regarding the possibilities are high. A large part of the research is aimed at the treatment of cancer. Though there are also some causes for concern. For instance, high risks for human health are expected, through a diffusion (inside the body) of free nano-particles which are either inert or which produce toxic products during the degradation process.

Comparing the results with literature:

The high attention being paid to activities in relation to social uncertainty by firms producing nanopharmaceuticals is in line with literature. Namely, this uncertainty is largely caused by the fact that it concerns nanotechnology and the firms try to decline the social uncertainty by informing the society about nanotechnology in an objective way to prevent public fear/backlash. Risk perception regarding nanotechnology will be higher in case the nanoparticles will be applied inside the body, than when the product will stay outside the body (in vitro medical devices). However, this means that also in vivo medical devices should be influenced more by the risk perception from society, which does not come out of this research. The in vivo medical device firms act very little upon the risk perception of society regarding the application of nanotechnology, which means practice is not totally in line with theory.

Despite the fact that some firms have uncertainty about the acceptation of nanotechnology by the society, they are not uncertain themselves about these possible risks of nanotechnology. The firms think these risks are sufficiently covered, since the regulations are already very strict and demanding. For this reason, there are not more risks attached to the development of nanomedical products than for any other drug/medical device. The other stakeholders are less convinced about the safety of nanotechnology.

There is no clear and shared vision on the issue whether nanomedical products should be treated as a specific group of products, or as any other product. This uncertainty is caused by the lack of technological knowledge, which only can be solved by keep doing/allowing technological research. The lack of knowledge/evidence is related to an important phenomenon, i.e. responsible innovation, which will be discussed as below:

Responsible innovation

Innovation and economic growth are two worldwide aspirations, though through time, awareness has increased of unintended, and even life threatening consequences which may come along. This has caused a growing need to innovate responsibly (Owen et al, 2009). Regulation is an important way to stimulate responsible innovation and generally there has been much trust in this way of safety guarding. However, there are reasons to doubt whether these regulations are sufficient, since the development of regulations mostly happens after the innovative products are already some time on the market. A main reason for this time delay is the need for evidence, on which the regulation can be based. This is also the case for nanotechnology. There are no specific regulations regarding nanotechnology, until new evidence proves this should be done. New evidence is tried to acquire through national and international research programs, which mainly is a slow process and mostly innovative products already have reached the market. This causes lock-in of the technology and impacts on health or the environment may occur in this time.

This indicates the need to innovate responsibly. Owen et al. (2009) emphasize the benefit of 'better foresight' and 'complementary risk governance mechanisms' in order to establish this. The former means that emerging information on innovations is identified upstream during the innovation process; the latter implies that mechanisms to comply regulation are also enacted upstream in the innovation process. The identification of this information can be coupled to risk analysis to identify in an early stage different impact uncertainties of the innovation.

The literature shows that for the guarding of safety of the environment and human health, regulations are not sufficient. Innovators and regulators should act more together in the innovation process, to realize highest safety for human health and the environment.

By the results of this research it can be indicated that this is not happening in a sufficient way. Namely, most companies declare to trust highly on the regulations for covering the (possible) risks of nanotechnology. Also, only a few are involved in projects where it is investigated whether current regulations in the field of pharmaceuticals and medical devices are still suitable. This mainly are large firms. On the contrary, the regulators are less convinced of the safety of nanotechnology and take more action to get more certainty. They are more aimed at the gathering of information/evidence about the possible risks of nanotechnology for which they allow/invest in technological research. They also are more aimed at discussing the adequacy of current regulations, and possible future regulations.

6. Conclusion

Technologies do not come only with promising potential but also with uncertainties. The central research question that has guided this study is:

How do various perceived uncertainties (from different stakeholders) influence the innovation processes of nanopharmaceuticals and nanomedical devices (in vivo and in vitro)?

This study showed that there are many similarities between the three product categories with regard to the uncertainties which are being perceived by the companies during the innovation process. For all product categories, a main thing to act upon in every phase is economic uncertainty. At the same time, least activities are done in each phase to reduce regulatory uncertainty.

Also technological uncertainty is for all product categories an important reason to perform activities. These activities are mainly aimed at the getting knowledge on the performance of the new technology and how to develop it. There is a difference between the product categories in the way they try to handle this. Namely, the nanopharmaceutical firms emphasize much more the benefit of external communication (mostly in addition of R&D), than medical device firms for whom R&D dominates.

Regarding the way economic uncertainty is handled during the innovation process, a similarity between the three product categories is the execution of market analysis in the search and select phase. By this, it is tried to acquire knowledge about other competitors, technologies and potential future markets. In the implement phase, for all product categories, attention has moved to activities aimed at a fast and successful launch of the product, i.e.: by collaboration with a large company, enlarge the probability of getting the product reimbursed (by external communication), and enlarge awareness of the existence of the product/technology. Though, there is also a difference. Namely, the pharmaceutical firms emphasize the benefit of external communication in the search and implement phase, while the medical device firms pay rather no attention to this activity.

The degree in which activities are being executed for the reduction of social uncertainty, is for all product categories in each phase of the innovation process rather low/moderate in comparison to economic and technological uncertainty. On overall, all firms try to handle this uncertainty in a similar way, for instance by executing market analyses and being customer oriented.

Regulatory uncertainty is least acted upon in each phase by the companies, but this increases marginally throughout the innovation process of all product categories. However, mainly the nanopharmaceutical firms see benefit in acting upon it (by 'working on regulation' and 'external communication').

The other stakeholders are mainly involved in the innovation process in a general way (e.g. patient association, ministries), or at the implement phase (CBG, notified bodies, the Dutch Health Care Insurance Board, the Association of Medical Specialists, the Health Care Inspectorate). They execute most activities for the reduction of technological uncertainty, and a main activity in relation to this is technological research. This can be explained by the fact that a substantial part of this group of stakeholders concerns authorities/organizations which have to evaluate the technological innovation for

a large part on technological aspects for market- and reimbursement approval (MEB, notified body, the Dutch Health Care Insurance Board).

The degree in which activities are being executed for the reduction of social and regulatory uncertainty is rather equal. Both are handled mostly by external communication. Further, being customer-oriented is a main activity to reduce social uncertainty and working on regulations to decrease regulatory uncertainty.

Lastly, the other stakeholders perform few activities for themselves out of economic uncertainty, but they know this is of more importance for the companies. This is why the number of activities done for *financial support* is relatively high. Another reason to perform these activities is to serve the society, by the reduction of health care costs. This leads to activities which both are in favour, as well as in disadvantage of the companies. For instance, 'provisional reimbursement' is of advantageous of the companies, though higher requirements regarding cost-effectiveness and cutbacks on the basic packet (basispakket) of medical products being reimbursed are of disadvantage for the companies.

Does it matter that 'nano' in particular is often related to risks?

Firms think these risks are sufficiently covered, since the regulations are already very strict and demanding. Technological uncertainty is for this reason not higher than for any other drug/medical device. However, having knowledge and experience in-house in multiple disciplines is by some firms expected to be very valuable in the field of nanotechnological research. Further, one of the interviewees felt best **not** mentioning explicitly the term 'nanotechnology' in the reports of the research trials, to prevent the demand of more safety research. With respect to social uncertainty, firms have different views about the issue whether to inform society about 'nanotechnology'. Most firms are being transparent about it in a neutral way; others use it as a selling strategy; and in contrast there are also firms who consciously avoid the term to prevent possible public fear.

Within the group of other stakeholders there is no clear and shared vision on the issue whether nanopharmaceuticals and nanomedical devices be treated as a specific group of products, or should they be treated as any other product, with regard to the technological uncertainty. By looking at the way the possible health risks should be handled, it is not only of importance to get knowledge of the technology itself, but also to take into consideration the perception in society about what is safe and what is unsafe. Through time, it seems to evolve what society accepts, and it looks like it accepts less and less risks. It is a challenge for the government to meet these needs of society, and meanwhile keep the industry being motivated to innovate.

Further, as a consequence technological uncertainty, the government has funded several national and European research programmes. The European Commission initiated the launch of the New and Emerging Technologies (NET) workgroup, which explored the developments in the field of nanomedical devices, and looked critically whether the regulations were still suitable in relation to these developments. The Ministry of Economic affairs, agriculture and innovation tries to handle technological uncertainty by: getting knowledge of the risks and possibilities trough collaboration with several ministries; trust on signals from other institutions; include a risk analysis and technology assessment in the Nanonext project; and allow the execution of research, and communicate about it. Additionally, the

Ministry of Health, welfare and sport sees benefit in organizing workshops to come together with the industry, science and government and keep each other informed in this way (also done out of regulatory uncertainty); allow research and developments in the field of nanotechnology; and the government just needs to be alert.

At last, to prevent public fear, an important activity is: informing the society about nanotechnology in a nuanced way, for instance by information magazines for a large public, or making use of a website (as the government does). Further, the Commission Social Dialogue (Commissie Maatschappelijk Dialoog) has done many projects on nanotechnology and its awareness in the society.

Does firms size matter for the role of uncertainty in the innovation process?

Economic uncertainty is for both firm sizes the main thing to act upon in all three phases of the innovation process and technological uncertainty in the search phase. The way the latter is handled differs between the firm sizes. Namely, large firms pay most attention to external communication, but for SMEs R&D is of highest priority.

Economic uncertainty is handled partly similar, and partly differently. Both firm sizes expect market analysis to be important, especially in the search and select phase. However, large firms also lay emphasize on external communication in the search phase, since they are exploring which technological innovation (being developed by another firm) to invest in. This is in contrast with SMEs, who are mainly focused on their own technology.

Further, market analysis is of more importance in the select phase for SMEs than for large firms. This possibly has to do with the consequences of failure that differs between SMEs and large firms. These consequences are larger for SMEs, for who the innovation is the only possibility for survival, while large firms can rely on the profits of other products being sold. Also, large firms generally have more resources in-house, to make the technological innovation a success (Lee & Chen, 2009). This means, they are more able to trust on their own strengths, due to higher availability of resources, than small firms.

Social uncertainty is by both firm sizes in all phases moderately acted upon. In the search and select phases they see mainly the benefit of market analysis. In the implement phase, large firms are more occupied with external communication, collaboration and being customer oriented, which more specifically means: talking with hospitals and doctors, collaborate with them and think about the best practice for doctors and patients.

At last, there is a difference between the firm sizes regarding the way they deal with regulatory uncertainty, especially in the implement phase. Large firms feel in some degree the urge to execute activities, by focusing on requirements for market approval and being actively involved in projects where the adequacy of current regulations is investigated/discussed. SMEs are less active regarding the regulatory aspects. This can be explained by the fact that large firms eventually will bring the product to the market and for this reason have contact with the authorities about the clinical trials and requirements for getting reimbursed, and also because they have more resources (for instance a regulatory affairs department) in house to do this.

Recommendations for improvement of the innovation process

The successfulness of the innovation process is dependent on decisions from all actors involved in this process, which makes it important that there exists a good interaction between the different stakeholders. This is an important way to eventually fulfil shared interests as well as different interests.

Below are some points of interest which currently seem to be not optimal and/or which could increase the successfulness of the innovation process in Dutch nanomedicine in the future:

Government:

- Before making (changes in) regulation, take clearly into account what risks are accepted by the society and what risks are not. An overall shared view is that the current pharmaceutical regulation offers high protection regarding the risks (for health) but simultaneously also everyone agrees that the investments to fulfil the requirements are tremendously high. Before making stricter rules/regulations regarding nanomedicine, because of its possible (health) risks, it should be well considered what the society practically accepts qua risks. In this way, no unnecessary requirements for market approval will be set. Namely, a negative consequence of stricter rules is that generally more research is required, higher investments are needed and health costs rise. And last but not least, it reduces the incentive to innovate.
- Keep invest in research for nanotechnology
- SMEs are an important source of innovation which makes it worthwhile help them more, for instance by financial support/subsidies. This financial support makes for them more difference than it does for large firms.

SMEs:

- Explore in an early stage what research/activities are needed to get market access and to get the product reimbursed.

In vivo nanomedical devices:

- Pay more attention to informing the society about nanotechnology in an objective way to prevent public fear/backlash. Risk perception of nanoparticles which come inside the body is expected to be higher than when the nanomedical device stays outside the body.

Firms:

- Pay sufficiently attention to the cost-effectiveness of the product in order to get approval for reimbursement.
- It is important to have in an early stage a clear view on which medical need you are going to fulfill with the technological innovation and the product must make a evident difference with the current treatment/medicine.
- Responsible innovation: the innovative firms should act more together with the regulators in the innovation process, to realize highest safety for human health and the environment. After all, nanomedicine holds many promising options for the future, but will serve society best when accompanied with healthy doubts.

References

Baarda, D.B., M.P.M., De Goede. 2006. *Basisboek methoden en technieken*, Wolters-Noordhoff Groningen, vierde druk

Bowman, D.M., G.A. Hodge. 2007. A small matter of regulation: An international review of nanotechnology regulation, *The Columbia Science and Technology Law Review, Vol. VIII*

Breggin, L.K., L. Carothers. 2006. Governing Uncertainty: The Nanotechnology Environmental, Health, and Safety Challenge, *Columbia Journal of Environmental Law, Vol. 31:2*

Chen, H., M. C. Roco, X. Li, Y. Lin. 2008. Trends in nanotechnology patents, *Nature Nanotechnology* ***3****, 123 – 125*

Cooper, R.G. 1994. "New Products: The Factors that Drive Success", International Marketing Review, Vol. 11 Iss: 1 pp. 60 – 76

Cooper, R.G. 1990. Stage-Gate Systems: A New Tool for Managing New Products, *Business Horizons*

Demirel, P., M. Mazzucato. 2010. The Evolution of Firm Growth Dynamics in the US Pharmaceutical Industry, *Regional Studies, 44:8, 1053-1066*

Dickson, M. 2004. Key factors in the rising cost of new drug discovery and development, *Nature reviews. Drug discovery [1474-1776] vol:3 iss:5 pg:417*

ETPN. 2009. Roadmaps in nanomedicine towards 2020, *Joint European Commission / ETP Nanomedicine, expert report 2009*

Geels, F.W. 2005. Processes and patterns in transitions and system innovations: Refining the co-evolutionary multi-level perspective, *Technological Forecasting and Social Change Volume 72, Issue 6,, pp. 681-696*

Hubbs, A., R. Mercer, S. Benkovic, J. Harkema, K. Sriram, D. Schwegler-Berry, et al., 2011. Nanotoxicology - a pathologist's perspective, *Toxicologic Pathology* **39**, 301-324

Jacobsson, S., A. Bergek, 2004. Transforming the energy sector: the evolution of technological systems in renewable energy technology, *Industrial and Corporate Change, Vol. 13, No. 5, pp. 815–849*

Jauch, L.R., K.L. Kraft, 1986. Strategic management of uncertainty, *The Academy of Management Review, Vol. 11, no. 4, pp. 777–790*

Koppenjan, J.F.M, E.H. Klijn. 2004. Managing Uncertainties in Networks, *Routledge, London, 2004*

Kuzma, J., S. Priest, 2010. Nanotechnology, Risk, and Oversight: Learning Lessons from Related Emerging Technologies, *Risk Analysis, Vol. 30, No. 11*

Lee R.P., Q. Chen. 2009. The Immediate Impact of New Product Introductions on Stock Price: The Role of Firm Resources and Size, *The Journal of product innovation management, vol:26 pp. 97-107*

Marchant, G.E., D.J. Sylvester. 2006. Transnational Models for Regulation of Nanotechnology, *The Journal of Law, Medicine & Ethics, Vol. 34, issue 4, pp. 714-725*

Markard, J., M. Stadelmann, B. Truffer. 2009. Prospective analysis of technological innovation systems: Identifying technological and organizational development options for biogas in Switzerland, *Research Policy 38 (2009) 655–667*

Meijer, I.S.M., M.P. Hekkert, J.F.M. Koppenjan. 2007. How perceived uncertainties influence transitions; the case of micro-CHP in the Netherlands, *Technological Forecasting & Social Change 74, pp. 519–537*

Meijer, I. S. M. 2008. Uncertainty and entrepreneurial action**, proefschrift**

Merkerk, van R.O. 2007. Proefschrift: Intervening in emerging nanotechnologies: A CTA of Lab-on-a-chip technology

Merkerk, van R.O., H. Lente van. 2005. Tracing emerging irreversibilities in emerging technologies: The case of nanotubes, *Technological Forecasting & Social Change 72 (2005) 1094–1111*

Miles, R.E., C. C. Snow, J. Pfeffer. 1974. Organization–environment: Concepts and issues, *Industrial relations, 13, 244–64.*

Milliken, F.J. 1987. Three Types of Perceived Uncertainty about the Environment: State, Effect, and Response Uncertainty, *The Academy of Management Review, Vol. 12, No. 1, pp.133-143*

Nelson, R.R., K. Nelson. 2002. Technology, institutions and innovation systems, *Res. Policy 31, pp. 265–272*

Nelson, R.R., S.G. Winter. 1977. In search of useful theory of innovation, *Research Policy, 6, 1, pp. 36-76*

Niosi, J., S. E. Reid, 2007. Biotechnology and nanotechnology: science-based enabling technologies as windows of opportunity for LDCs? *World Development, vol:35 iss:3 pg:426*

Ornaghi, C. 2007. Mergers and innovation in big pharma, *International Journal of Industrial Organization 70-79*

Owen, R., D. Baxter, T. Maynard, M. Depledge, 2009. Beyond Regulation: Risk Pricing and Responsible Innovation, *Environ. Sci. Technol., 43,* 6902–6906

Patton, M. Q. 2002. *Qualitative Research and Evaluation Methods.* Thousand Oaks, CA: Sage.

Penrose, E. T. 1952. "Biological analogies in the theory of the firm." *American Economic Review, 42: 804-819.*

Pietzsch, J.B., L.A. Shluzas. 2009. Stage-Gate Process for the Development of Medical Devices, *Journal of Medical Devices, Volume 3, Issue 2*

Pinch, T.J., W.E. Bijker. 1984. The Social Construction of Facts and Artefacts: Or How the Sociology of Science and the Sociology of Technology Might Benefit Each Other, *Social Studies of Science, Vol. 14, No. 3, pp. 399-441*

Rang, H.P., 2006. *Drug discovery and development,* Churchill Livingstone Elsevier

Shaw, B. 1998. Innovation and new product development in the UK medical equipment industry, *International Journal of Technology Management, 15, 3-5, pp. 433 – 445*

Smits, R.E.H.M., R.O. van Merkerk, D.H. Guston, D. Sarewitz. 2008. "Strategic Intelligence (1): The role of TA in systemic innovation policy" *In Smits, R.E.H.M., P. Shapira and S. Kuhlman (ed.) Innovation Policy book.*

Stanko, M.A., R.J. Calantone. 2011. Controversy in innovation outsourcing research: review, synthesis and future directions, *R&D Management, 41, 1*

Tidd, J., J. Bessant, K. Pavitt. 2005. *Managing innovation: Integrating Technological, Market and Organizational Change,* Wiley and sons ltd, third edition

Vallejo-Torres, L., L. M. G. Steuten, M. J. Buxton, A. J. Girling, R. J. Lilford, T. Young, 2008. Integrating health economics modeling in the product development cycle of medical devices: A Bayesian approach, *International Journal of Technology Assessment in Health Care, 24:4, 459–464.* Copyright Cambridge University Press.

Virdi, J. 2008. Bridging the Knowledge Gap Examining Potential Limits in Nanomedicine, *Spontaneous Generations 2:1*

Vishwakarma, V.,S. Samal, N. Manoharan. 2010. Safety and risk associated with nanoparticles- a review, *Mineral and Mat Char Eng* **9**, 455-459

Walker, W.E., P. Harremoes, J. Rotmans, J.P. Van Der Sluijs, M.B.A. Van Asselt, P. Janssen, M.P. Krayer von Krauss. 2003. Defining Uncertainty A Conceptual Basis for Uncertainty Management in Model-Based Decision Support, *Integrated Assessment, 2003, Vol. 4, No. 1, pp. 5–17*

Wiek, A., L. Gasser, M. Siegrist, 2009. Systemic scenarios of nanotechnology: Sustainable governance of emerging technologies, *Futures, vol:41 iss:5 pg:284*

Wijnhoven, S.W.P., S. Dekkers, M. Kooi, W.P. Jongeneel, W.H. de Jong. 2010. Nanomaterials in consumer products: Update of products on the European market in 2010, *RIVM Report 340370003/2010*

Yin, R.K. 2009. *Case Study Research: Design and Methods,* SAGE Publications, fourth edition

Interviews

- Philips: MagnoTech, 10-02-2012, Interviewee: Jeroen Nieuwenhuis and Menno Prins, Type: face to face
- Philips, targeted drug delivery, 19-12-2011, Interviewee: Holger Gruell, Type: face to face
- Medimate, lab on a chip, 23-12-2011, Interviewee: Huub Maas, Type: face to face
- Xpand Biotenology, bone inducing materials , 15-02-2012, Interviewee: Huipin Yuan, Type: face to face
- SME, targeted drug delivery, 14-12-2011, Type: via telephone
- Lionix, lab on a chip, 2-2-2012, Interviewee: Henk Leeuwis, Type: face to face
- Micronit, lab on a chip, 8-12-2011, Interviewee: Marco Blom, Type: face to face
- GSK, targeted drug delivery, 23-2-2012 , Interviewee: Jan Raaijmakers, Type: face to face
- MyLife Technologies, micro needle arrays , 6-01-2012, Interviewee: Regina Luttge, Type: via telephone
- Ministry of Health, Welfare and Sport, 9-01-2012, Interviewee: Joop van den Wijngaard, Type: face to face
- Ministry of Economic Affairs, Agriculture and Innovation, 23-01-2012, Interviewees: Aukje Visser, Karin Jongkind, Type: face to face
- The Dutch Health Care Insurance Board (CVZ), 7-03-2012, Interviewee: Marja Kuijpers, Type: face to face
- BSI Group (a Notified Body), 16-01-2012, Interviewee: Gert Bos, Type: face to face
- The Medicines Evaluation Board, 17-01-2012, Interviewees: Jan Willem van der Laan, Pim de Waard, Irene Bosselaers, Type: face to face
- The Health Care Inspectorate, 17-02-2012, Interviewee: Josee Hansen, Type: face to face
- The Association of Medical Specialists ('Orde van Medisch Specialisten'), 28-02-2012, Interviewee: Teus van Barneveld, Type: face to face
- VMDB (a patient association), 23-01-2012, Interviewee: Koos van der Span, Type: face to face

'Experts' in the field of nanotechnology or regulation:

- Johan Hanstede, 31-01-2012, Type: face to face
- Sabine Hoekstra-van den Bosch 27-01-2012, Type: face to face

Appendix 1. Coded Interviews

Legend (categories of activities)

R&D/technological research
External communication
Collaboration
Market analysis
Financial support
Focus
Internal communication/teambuilding
Customer-oriented
Inform the society
Resource acquisition
Work on regulation

Nano-phamaceuticals												
Philips												
	search	**activity**	**select**	**activity**	**implement**	**activity**	**search &select**	**activity**	**select&implement**	**activity**	**all phases**	**activity**
economic uncertainty	x	websites in de gaten houden	x	wijziging in applicatie	x	er wordt nog niets ondernomen qua vergoeding, wel plannen ommet zorgverzekeraars in gesprek te gaan			x	tijdig spreken met ziekenhuizen	x	inzet van marketing afd
	x	contact met research labs	x	potentiele markten onderzoeken	x	inzetten vd technologie in academische ziekenhuizen doie onderzoek doen			x	samenwerking aangaan met ziekenhuizen	x	beslissing maken of je partnership aangaat bij de ontwikkeling
					x	internationaal het produkt op de markt brengen en alleen in landen waar het vergoed wordt					x	als gevolg van minder investeringen wordt er minder onderzoek gedaan (aantal onderzoeksprojecten minder)
					x	onderzoek doen om tegen de 'best class' te concurreren					x	kosten-baten analyse uitvoeren
technological uncertainty	x	conferentie bezoeken	x	wijziging in applicatie	x	inzetten vd technologie in academische ziekenhuizen die onderzoek doen					x	onderzoek doen
	x	combineren van interne technologieën met extern onderzoek			x	onderzoek doen om tegen de 'best class' te concurreren. Echter activiteiten v concurrenten is niks aan te doen						
	x	websites in de gaten houden			x	PMS					x	het traject doorlopen met dezelfde eisen als voor een gewoon medicijn
	x	contact met research labs									x	kosten-baten analyse uitvoeren
											x	beslissing maken of je partnership aangaat bij de ontwikkeling
social uncertainty	x	logisch nadenken	x	wijziging in applicatie	x	inzetten vd technologie in academische ziekenhuizen die onderzoek doen			x	tijdig spreken met ziekenhuizen	x	PR afd voor communicatie
			x	potentiele markten onderzoeken					x	samenwerking aangaan met ziekenhuizen	x	informeren via bijv websites: inzet van marketing afdeling
											x	kosten-baten analyse uitvoeren
regulatory uncertainty					x	internationaal het produkt op de markt brengen en alleen in landen waar het vergoed wordt			x	er moet nog gekeken worden naar hoe de drug-device approval in zijn werking gaat -> hiervoor zijn personen in dienst die opgeleid zijn in approval en regulatory pathways en advies kunnen geven	x	het traject doorlopen met dezelfde eisen als voor een gewoon medicijn
all uncertainties			x	hulp van expert panels en klinische partijen								

Nanophamaceuticals												
Anonymous												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x	spreken met farm industrie op conferenties	x	marktonderzoek (commercieel perspectief)							x	contact met pharm industrie en clinici
	x	trendspotting dmv wetensch+ industriele literatuur	x	bubble-chart maken							x	financiering/subsidiëring proberen te regelen door te overtuigen
	x	betere technologie maken tov oorspronkelijke geneesmiddel									x	doelgerichter werken en duidelijke keuzes maken
	x (vergoeding)	spreken met key opinion leaders										
technological uncertainty	x	promotie onderzoek	x	aan de slag gaan voor verbetering	x	creëren van open klimaat wat betreft communicatie en documentatie					x	een rationele discussie voeren
	x	spreken met farm industrie op conferenties	x	selectie maken tussen stoffen	x	voordragen als nieuw geneesmiddel, net als ieder ander medicijn						
	x	trendspotting dmv wetensch+ industriele literatuur	x	bubble-chart maken								
	x	samenwerking met research labs	x	geselecteerde stoffen beoordelen: hoe is de markt en wat is het aantal patienten								
	x	betere technologie maken tov oorspronkelijke geneesmiddel										
social uncertainty	x	gesprekken met key-opinion leaders	x	bij selectie van stoffen medical need meenemen							x	contact met pharm industrie en clinici
	x	spreken met farm industrie op conferenties									x	evaluatie vh geneesmiddel
											x	continue kritisch blijven nadenken
											x	een rationele discussie voeren
regulatory uncertainty					x	voordragen als nieuw geneesmiddel, net als ieder ander medicijn					x	een rationele discussie voeren
all uncertainties			x	SWOT analysis	x	produkt niet zelf op de markt brengen maar dmv grote partijen						

Nanophamaceuticals						
GSK						
	search	activity	**select**	activity	**implement**	activity
economic uncertainty	x	scouten voor nieuwe ontwikkelingen: praten met universiteiten, onderzoekscentra, spin offs etc over samenwerkingsmogelijkheden (bijv Philips --> target drug delivery)	x	analyses doen voor de cost of goods, cost effectiveness en vraagprijs	x	in alle transparantie met elkaar praten over de ontwikkeling
	x	andere insituten bezoeken en gebruik maken van contacten waarbij je info krijgt over technologieën --> info doorgeven aan GSK				
	x (crisis)	veel strakke keuzes maken over wat je wel en niet gaat doen en vooruitdenken				
technological uncertainty	x	scouten voor nieuwe ontwikkelingen: praten met universiteiten, onderzoekscentra, spin offs etc over samenwerkingsmogelijkheden (bijv Philips --> target drug delivery)			x	gebeurt nog niet, maar interviewee zou graag meer controle hebben op het goed gebruik vh medicijn.
	x	andere insituten bezoeken en gebruik maken van contacten waarbij je info krijgt over technologieën --> info doorgeven aan GSK				
	x	vantevoroen goed bedenken wat je qua veiligheid zal kunnen bewijzen en wat je dus gaat selecteren				
	x	in samenwerkingsverband onderzoek doen				
social uncertainty		vraaggestuurd zijn: heel erg gericht zijn op de medical need, onderzoeken en invullen wat de markt nodig heeft			x	artsen betrekken bij het onderzoek
					x	in alle transparantie met elkaar praten over de ontwikkeling
regulatory uncertainty	x	laten weten dat GSK het niet eens is met het beleid dmv alle contactmomenten die interviewee heeft met de overheid en lezingen.(belastingaftrek hebben MKBs niks aan)			x	overleggen met overheden en in regulaire platforms wat nodig zal zijn voor goedkeuring v e produkt. GSK is betrokken bij EFPIA (nauwe samenwerking met eur. Registr. Autoriteiten en de FDA)
					x	Met TI-farma Escher zoeken naar alternatieve ontwikkelingstrajecten --> fase 3 korter + voorlopige vergoeding, fase 4 beter maken
all uncertainties	x	vanaf het begin heel marktgericht denken --> weten dat er een medical need moet zijn, klinisch onderzoek verschil moet tonen voor goedkeuring en vergoeding				

	search&select	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty			x	duidelijk naar voren brengen wat het product voor verschil maakt tov bestaande technologie qua kosten en gezondheid	x	hoge investeringen in samenwerkingsverbanden vanuit GSK voor de komdende jaren
			x	vroegtijdig met overheid praten over ontwikkelingen en wat nodig is om verdediging zo optimaal mogelijk te maken (vanaf 1ste fasen klin onderzoek). GSK weet inmidd wat nodig is maar laat het toch weten aan benodigde instanties om hun reactie te peilen	x	kijken vanuit de eigen sterktes en competitie in de gaten houden --> dmv professionele bureaus en interne analisten. Die houden in de gaten of anderen patenten aanvragen/licenseren. Ook abbonement op patentbueaus die gegevens verschaffen.
technological uncertainty						
social uncertainty	x	alleen die innovatie kiezen die duidelijk meerwaarde biedt--> risico's moeten in evenwicht staan met therapeutische benefit --> ook hierbij aard vh ziektebeeld meenemen	x	op het moment dat er een concrete ontwikkeling is, dan zal GSK pas verdedigen waarom hiervoor gekozen is en transparant zijn over de voordelen en risico's	x	sentimenten vanuit de maatschappij, die bijv. op internet tot uiting komen, in de gaten houden
regulatory uncertainty	x	alleen die innovatie kiezen die duidelijk meerwaarde biedt--> risico's moeten in evenwicht staan met therapeutische benefit --> ook hierbij aard vh ziektebeeld meenemen	x	vroegtijdig met overheid praten over ontwikkelingen en wat nodig is om verdediging zo optimaal mogelijk te maken (vanaf 1ste fasen klin onderzoek). GSK weet inmidd wat nodig is maar laat het toch weten aan benodigde instanties om hun reactie te peilen		
			x	het risico nemen en zo goed mogelijk onderzoek doen		
all uncertainties						

In vivo med hulpmiddel						
Xpand						
	search	activity	**select**	activity	**implement**	activity
economic uncertainty	x	inzetten van studenten voor onderzoek				
	x	vanaf het begin bekijken waar een markt voor zal zijn, daarna hier geen onzekerheid meer over			x	dierproeven in China laten uitvoeren
					x	technologie demonstreren zodat hij gekocht wil worden door groot bedrijf --> in contact komen met groot bedrijf, publiceren, website
					x	niet noemen dat het nanotechnologie is om moeilijkheden te vorokomen i.e. meer veiligheidsonderzoek
technological uncertainty	x	kennis over biologische processen in het lichaam --> het lichaam zal de nanoparticles zelf verwijderen door het afweersysteem en kennis van de stof --> lichaamseigen stof			x	technologie demonstreren zodat hij gekocht zal worden door groot bedrijf
	x	onderzoek				
	x	meedoen aan onderzoeksprjecten in Eur. ---> hulp vragen aan betrokkenen				
	x	inzetten van studenten voor onderzoek				
social uncertainty						
regulatory uncertainty					x	gebruik maken van het feit dat de individuele stoffen een CE markering hebben
					x	niet noemen dat het nanotechnologie is om moeilijkheden te vorokomen i.e. meer veiligheidsonderzoek
all uncertainties						

	search& select	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x	samenwerking met andere laboratoria en Universiteiten in de wereld voor kennis en apparatuur	x	het product zo gebruiksvriendelijk en goedkoop mogelijk maken --> onderzoeken vóór de clinical trials	x	beste technologie maken maar ook zo gebruiksvriendelijk mogelijk maken
	x	grants voor onderzoeksprojecten en investeringen vanuit Xpand zelf			x	concurrenten in de gaten houden dmv websites, conferenties,
					x	het in huis hebben van veel verschillende soorten kennis en
			x	geheimhouden van je idee totdat je een patent hebt		
technological uncertainty	x	samenwerking met andere laboratoria en Universiteiten in de wereld voor			x	onderzoek
					x	het in huis hebben van veel verschillende soorten kennis en
social uncertainty			x	het product zo gebruiksvriendelijk en goedkoop mogelijk maken --> onderzoeken vóór de clinical trials	x	beste technologie maken maar ook zo gebruiksvriendelijk mogelijk maken
			x	contact houden met artsen over de ideeën mbt technologieën		
regulatory uncertainty						
all uncertainties					x	vertrouwen op de ervaring die er

In vivo med devices												
MyLife Technologies												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty			x	keuze obv benadering vanuit klanten/co-developers	x	zoeken naar partners/co-developers	x	zowel ontwikkeling aanhouden van medicijn- als diagn applicatie	x	subsidie aanvragen/financiering proberen binnen te halen	x(vergoeding)	aantonen dat het product werkt
			x	aanvragen van financiering/valorisatie-grant fase 1	x	uniek sellingpoint creëren door ontwikkelen van de technologie	x	weten dat je keuze moet maken hoe de technologie toe te passen (medicijn/diagnostiek)	x	website maken over de etchnologie+bedrijf om nieuwe partners te vinden	x	instrumenten vanuit de overheid aangrijpen
			x	onderzoek wat je markt en klanten worden --> hoe dichter bij de markt te komen--> dit onderzoek evalueren			x	je onderzoek naar buiten brengen (dmv artikel) om potentiële klanten te vinden	x	strategisch kiezen welke potentiële klanten je wil bereiken --> alleen in NL bladen publiceren	x	de utilisatie van je technologie duidelijker benadrukken en daarom je visie helder hebben en sterk formuleren
			x	proeven uitzetten voor de applicatie & markt in de gaten houden			x	samenwerken				
			x	subsidie aanvragen, valoriasatiefase 2, networking			x	marktanalyse laten uitvoeren door onpartijdige partij --> niks aan gehad!				
			x	kosten/baten analyse								
			x	trendspotting								
			x	een breed inzetbare technologie ontwikkelen								
technological uncertainty	x	samenwerking in onderzoek doen	x	kosten/baten analyse	x	zoeken naar partners/co-developers	x	vervaardigen van de technologie	x	dierproeven		
	x	conferenties bezoeken om academische contacten te leggen					x	onderzoek doen				
	x	specificaties vaststellen om een efficiënt product te maken					x	samenwerken				
							x	marktanalyse laten uitvoeren door onpartijdige partij --> niks aan gehad!				
social uncertainty			x	keuze obv benadering vanuit klanten/co-developers			x	zowel ontwikkeling aanhouden van medicijn- als diagn applicatie	x	website maken over de technologie+bedrijf om nieuwe partners te vinden	x	aan de maatschappij het belang v onderzoek naar de toepassing van nanotechnologie toelichten
			x	onderzoek wat je markt en klanten worden --> hoe dichter bij de markt te komen --> dit onderzoek evalueren			x	je onderzoek naar buiten brengen (dmv artikel) om potentiële klanten te vinden			x	de term 'nano' weglaten als je weet dat het geen risico omvat
			x	proeven uitzetten voor de applicatie & markt in de gaten houden			x	scouten en netwerken om potentiële klanten te vinden			x	regels, wetten en toetsen naleven
			x	subsidie aanvragen, valoriasatiefase 2							x	voldoen aan de veiligheidseisen die met de huidige technieken bepaald kunnen worden. En procedures gebruiken die daarvoor geschikt zijn
			x	trendspotting								
regulatory uncertainty			x	onderzoeken hoe een technologie volgens de regelgeving op de markt te krijgen	x	future scenarios maken					x	juiste beleid vormen door het gesprek te zoeken met de juiste partijen daarin (bijv RIVM)
											x	met de overheid in gesprek gaan en vragen stellen hoe je succesvol een projectvoorstel kan indienen, wat zijn de criteria enz..
all uncertainties	x	niet te snel een BV worden, eerst in een incubator omgeving zitten om te ontwikkelen		SWOT-analyse wordt gedaan door de valorisatie-grant commissie obv de aangeleverde data								

Med device in vitro						
Philips magnotech						
	search	activity	**select**	activity	**implement**	activity
economic uncertainty	x	tijdens technologisch onderzoek heroverwegingen maken mbt de technologie obv industrialisatie mogelijkheden	x	kiezen voor een breed inzetbare technologie	x	marktstudies doen, met verschill partijen praten over mogelijkheden, met potentiele gebruikers praten --> heel erg vraaggestuurd
	x	deelcomponenten laten aanleveren	x	samenwerkingsverband zoeken, zowel op technisch gebied, als qua marktkanalen	x	voordat het ene produkt op de markt is al kijken naar vebeteringen
	x	gebruik maken van subsidies om samenwerkingsverbanden wat ruggesteun te geven			x	bewijzen: patientvriendelijker product met zelfde kwaliteit van de metingen als bestaande methode
		strategic positioning: eigen sterktes in kaart brengen en ontwikkelingen in de markt bekijken --> exploratief onderzoek starten om te kijken hoe je als Philips daar een rol kan spelen --> conferenties bezoeken, met verschillende partijen praten, universiteiten en start-ups bezoeken				
technological uncertainty	x	onderzoeken wat er met de technologie kan, als op het gebied van de toepassing --> waar liggen kansen			x	verificatiestudies doen met prototypes, clinische validatie om CE markering te krijgen
	x	techn onderzoek doen				
	x	conferenties bezoeken om info in te winnen				
	x	conferenties bezoeken om mensen uit verschillende disciplines te ontmoeten --> netwerken (bij nano verschill disciplines				
	x	veel samenwerken voor complementaire velden van expertise				
social uncertainty	x	vanaf begin vaststellen dat je op de gezondheidswereld wilt richten: wat hebben artsen/patiënten nodig			x (verschuiv arts-patient relatie)	toepassen in een gecontroleerde setting (ziekenhuis) en over de wensen voor de toekomst nadenken
	x	onderzoeken wat er met de technologie kan, als op het gebied van de toepassing --> waar liggen kansen			x	bewijzen: patientvriendelijker product met zelfde kwaliteit van de metingen als bestaande methode
	x	trendwatching: gericht op grote trends				
regulatory uncertainty					x	verificatiestudies doen met prototypes, clinische validatie om CE markering te krijgen
all uncertainties	x	onzekerheden en risico's van te voren in kaart brengen en die ontwikkeling als eerste kiezen waar niet alle onzekerheden groot zijn			x	je krijgt steeds meer kennis over de technologie, markt, alle gebieden --> meer toekomstgericht denken voor nieuwe mogelijkheden

	search& select	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x	patenten schrijven	x	businessplan schrijven in de Health incubator waar het project naartoe is verschoven waar meer economische kennis en kunde aanwezig is	x (competition)	andere technologien en applicaties in de gaten houden dmv conferenties, benchmarking.
			x	technologie op conferenties naar buiten brengen (en dmv publicaties) om mogelijke klanten te vinden (need vinden)	x (indien slecht gaat)	op kosteneffectieve manier onderzoek doen en ontwikkelen
			x	die toepassingen selecteren waar al een vergoedingsmodel voor bestaat, om risico vd business case te verkleinen		
technological uncertainty						
social uncertainty	x	zoeken naar toepassingsgebied waar je grote meerwaarde kan bieden	x	businessplan schrijven in de Health incubator waar het project naartoe is verschoven waar meer economische kennis en kunde aanwezig is	x	eigen koers varen en op heel consistente wijze objectieve informatie geven (naar de pers toe)
	x	onderzoeksvoorstel schrijven om subsidie aan te vragen: beoordeling geeft aan of je op het goede pad bent en subsidie wordt alleen toegekend als er maatsch nut is	x	technologie op conferenties naar buiten brengen (en dmv publicaties) om mogelijke klanten te vinden (need vinden)	x	transparant zijn en regelmatig in wetensch en populaire literatuur verschijnen
regulatory uncertainty			x	op tijd met de FDA spreken over je plannen en hoe het beste klinische studies op te zetten		
all uncertainties					x	stage gate approach

Med devices in vitro												
Micronit												
	search	activity	**select**	activity	**implement**	activity	**search & select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x	vooruitdenken: wat gaat de klant nodig hebben	x	verbeteren van de technologie	x	verbeteren van de technologie						
	x	conferenties bezoeken & mensen spreken	x	subsidie aanvragen	x	expertise ontwikkeld in een verbetering vd technologie (coating)						
	x	klant-vragen gebruiken & samenwerking met klanten	x	technologie/markt match doen voor potentiele klant	x	klanten service						
	x	nieuwe techniek uit iegen initiatief aanbieden aan klanten	x	portfolio overzicht	x	investeerders zoeken						
	x	resource acquisition (AIO)	x	prijs + productie kosten inschatten	x	lancering dmv nieuwsbrief, conferenties, flyers, beurzen						
					x	naamsbekendheid proberen te vergroten						
technological uncertainty	x	promotie-onderzoek	x	verbeteren van de technologie	x	expertise ontwikkeld in een verbetering vd technologie (coating)						
	x	vrij spel qua onderzoek --> technology push	x	technologie/markt match doen voor potentiele klant	x	houden aan arbo-wetgeving en maken v eigen procedures voor veilig werken						
	x	samenwerkingsprojecten	x	multitasken van medewerkers	x	incremental innovations						
	x	conferenties, contact met research labs	x	wekelijkse bespreking met research groep --> samen kiezen wat te onderzoeken								
	x	resource acquisition (AIO, stagiaires)										
social uncertainty	x	vooruitdenken: wat gaat de klant nodig hebben	x	wekelijkse bespreking met research groep --> samen kiezen wat te onderzoeken	x	expertise ontwikkeld in een verbetering vd technologie (coating)						
	x	conferenties bezoeken & mensen spreken										
	x	klant-vragen gebruiken & samenwerking met klanten			x	lancering dmv nieuwsbrief, conferenties, flyers, beurzen						
	x	nieuwe techniek uit iegen initiatief aanbieden aan klanten										
	x	onderzoeksprojcten samen met research labs										
regulatory uncertainty			x	ook richten op de analytische wereld (waar het niet FDA approved hoeft te zijn)								
all uncertainties					x	face gate approach bij grote klantprojecten						

Medical devices in vitro												
Lionix												
	search	activity	**select**	activity	**implement**	activity	**search& select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x	marktonderzoek doen d.m.v. technologische ontwikkelingen in de gaten houden (d.m.v. conferenties, websites etc)	x	technologie gekozen waar weinig concurrenten zijn	x	vergoeding voor de klant van belang --> Lionix doet er zelf niets mee					x	contacten up to date houden --> obv wat je hoort marktanalyse doen
	x	alleen in grote R&D projecten stappen als er potentiële klanten in zitten	x	proberen te onderscheiden van concurrenten die er zijn (bijv door breder en oplossingsgerichter te zijn)	x	outsourcing etc voor de klant erg belangrijk --> verkopen vh produkt aan een groot bedrijf (met name in farma wereld)					x	bij crisis oid kunnen er minder projecten worden gedaan door minder investeringen
	x	samenwerkingsverband met de Universiteit										
technological uncertainty	x	onderzoek doen			x	werken aan teambuilding						
	x	samenwerkingsverband met de universiteit										
social uncertainty	x	marktonderzoek doen d.m.v. technologische ontwikkelingen in de gaten houden (d.m.v. conferenties, websites etc)	x	technologie gekozen waar weinig concurrenten zijn	x	de consument voldoende informeren dmv objectieve informatie (gebeurt wel door Rath. Inst. en op Eur niveau)						
	x	netwerk gericht zijn, bijv door aan te sluiten bij Biofarmind	x	proberen te onderscheiden van concurrenten die er zijn (bijv door breder en oplossingsgerichter te zijn)								
	x	alleen in grote R&D projecten stappen als er potentiële klanten in zitten										
regulatory uncertainty											x	nieuw innovatiebeleid: mee bemoeien dmv deelname aan topsectoren, lobbyen (mbv Biofarmind, overheden beïnvloeden
all uncertainties												

In vitro medical device						
Medimate						
	search	**activity**	**select**	**activity**	**implement**	**activity**
economic uncertainty	x	marktonderzoek doen			x	samenwerking voor verkrijgen v bepaald deel vd technologie
	x	samenwerking in onderzoek voor belangrijk deel vd technologie			x	inkopen van onderdelen
					x	het niet beter willen doen dan de benodigde specs --> manager controleert hoever het onderzoek is
					x	technologie verkopen aan groot bedrijf
					x	(vergoeding) --> richten op Amerika waar de vergoedingsstructuur niet ze 'heftig' is als in Europa
technological uncertainty	x	onderzoek doen	x	onderzoek doen	x	samenwerking voor verkrijgen v bepaald deel vd technologie
	x	proefschrift			x	tijdig denken aan alternatieve stoffen
social uncertainty	x	marktonderzoek doen			x	zorgvuldige gebruiksaanwijzing maken
regulatory uncertainty						
all uncertainties			x	bedrijf opstarten om niet alleen te richten op het technologisch deel, maar ook het economisch en maatschappelijk etc --> mensen voor in dienst	x	focus houden op humane toepassing; verbreden dmv spin-off, licenties en samenwerking

economic uncertainty	**search& select**	**activity**	**select& implement**	**activity**	**all phases**	**activity**
	x	trend watching	x	concurrentie-analyse (welke technologieën en wat kunnen ze wel/niet) --> dmv scannen van internet	x	voor vergoeding: validatiestudies, certificeringen, effectiviteitsstudies. Belangrijk voordeel = kosten gaan omlaag! En kwaliteit v leven verhoogt
	x	inspelen op veranderingen in de markt en politiek dmv de technologie	x	(Europese) subsidie aanvragen	x	Zorgverzekeraar in Raad van Advies en als aandeelhouder
					x	gebruik maken van goedkope inhuurkrachten (stagiaires)
					x	strategisch bekijken wat je in huis wil en kan hebben (appropraite project structure)
					x	zsm op de markt proberen te komen en gebruik maken van first mover advantage --> realiseren mbv aandeelhouders en reeds onderhandelingen met distributeurs in buitenland.
technological uncertainty					x	En richten op grote markt = grote volumes = lage prijs
	x	het onderzoek richten op patientgroepen	x	concurrentie-analyse (welke technologieën en wat kunnen ze wel/niet)	x	medisch gecertificeerd produkt maken -> aan benodige eisen voldoen
social uncertainty						
	x	het onderzoek richten op patientgroepen			x	Een Raad van Advies erbij betrekken = patientverenig, specialisten, zorgverzekeraar; en expertgroepen = key opinion leaders
	x	trend watching			x	Zorgverzekeraar in Raad van Advies en als aandeelhouder
regulatory uncertainty	x	inspelen op veranderingen in de markt en politiek dmv de technologie				
all uncertainties					x	medisch gecertificeerd produkt maken --> duidelijk beeld krijgen van de benodigde
	x	analyse vd stoffen, markt (potentie), prijs, business case en haalbaarheid	x	focus op interne communicatie en organisatie want steeds specialistischer --> implementatie v beoordelingssystemen, functioneringsgesprekken, ISO certificatie, regulatory affairs; mgt team meetings en maken v businessplan		

Expert												
Ir. J. G. Hanstede												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select&implement**	activity	**all phases**	activity
economic uncertainty											x (overheid)	meer nadruk leggen op het maatschappelijk nut
											x (SMEs)	op het juiste moment de juiste expertise in huis halen. En op een gegeven moment duidelijk hebben wat je eerste klant (groot bedrijf) wil --> onderzoeken wat maatschappij wil, advies inwinnen bij grote bedrijven, op tijd met je 1ste klant praten
											x (SMEs)	actiever zoeken naar contacten (in de farma wereld) --> biofarmind organiseerd hiervoor ook network bijeenkomsten
											x (grote bedrijven)	samenwerkingsverband aangaan met klein innovatief bedrijf-->
technological uncertainty											x (overheid)	meer nadruk leggen op het maatschappelijk nut
											x (overheid)	publiek-private samenwerking
social uncertainty											x	overheid moet op het juiste niveau met de maatschappij communiceren
											x	niet het contact verliezen met de maatschappij en met alle spelers blijven communiceren
											x	duidelijk vaststellen waar de voordelen en risico's zitten en daar transparant over zijn --> weten waar nog onderzoek gedaan moet worden
regulatory uncertainty			x (bedrijven)	vroeg met autoriteiten praten over ontwikkelingen om zsm op de markt te komen. Tip: in Amerika is een org. Die richtlijnen binnen 2 weken opstelt --> ook in NL opzetten					x (bedrijven)	leren hoe om te gaan met de vereisten vanuit de overheid voor vergoeding vh product	x	goede samenwerking tussen ministeries om geen verwarring te veroorzaken voor bedrijven
all uncertainties												

Expert regulations												
Sabina Hoekstra												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty											x	onderzoeksprogramma's instellen, zowel op Europees als nationaal niveau.
technological uncertainty											x	oprichten NET werkgroep --> nanotechnologie
											x	NET werkgroep schrijft rapport nav analyse over wetgeving en ontwikkelingen mbt nanomed devices
social uncertainty											x	praten met allerlei belangengroepen. Organiseren van bijeenkomsten om mening van mensen te vragen (zowel formeel als informeel)
											x	naar buiten treden
											x	de beeldvorming genuanceerd naar buiten brengen
											x	voorlichtingsbladen (EC) en publicaties voor breed publiek (lidstaten)
regulatory uncertainty											x	NL heeft in 2004 onderzoek naar geschiktheid vd wetgeving v geneesmidd+med hulpmidd op de agenda gezet van de EU
											x	oprichten NET werkgroep --> nanotechnologie
											x	NET werkgroep schrijft rapport nav analyse over wetgeving en ontwikkelingen mbt nanomed devices
											x	EMA richt Innovation Task Force op
											x	besluit NET werkgroep: alleen aanpassing wetgeving mbt vrije nanodeeltjes
											x	NET werkgroep wil vloeiende overgang tussen geneesmidd en med hulpmidd wetgeving
											x	wens vanuit gezamenlijke lidstaten voor 1 Europese club die beslist over grensproducten (bijv converging technologies)
all uncertainties											x	vroegtijdig een onderwerp/ontwikkeling goed bekijken (vb = NET werkgroep)

Notified Body												
BSI Group												
	search	activity	select	activity	implement	activity	search &select	activity	select& implement	activity	all phases	activity
economic uncertainty					x (bedrijven)	BSI maakt de eisen niet zo zwaar dat innovatiekracht verloren gaat					x	veel aandacht vanuit overheid aan behouden van innovatiekracht: projecten, rapporten en NET Werkgroup van de EC
					x(bedrijven)	bedrijven brengen in een aantal landen hun prod gecontroleerd op de markt om benodigde info te verzamelen voor volledige vergoeding					x	lobby vanuit de farma industrie naar de EC om med. Device wetgeving niet teveel weg te gooien ivm innovatiekracht
											x (bedrijven)	kleine farma bedrijven proberen hun prod viable te maken obv venture capital om opgekocht te worden door groot bedrijf
											x(vergoeding)	BSI adviseert bedrijven klin studies met elkaar te combineren voor zowel CE markering als vergoeding
											x	BSI geeft training aan bedrijven
technological uncertainty					x	BSI neemt zeer hoog opgeleide mensen in dienst voor audits en dossierbeoordelingen, met jarenlang werkervaring op spec gebied en worden losgesteld van commerciële belangen					x	veel aandacht vanuit overheid aan behouden van innovatiekracht: projecten, rapporten en NET Werkgroup van de EC
					x	mensen inzetten op nano cases die eerder met vergelijkbare technologieën hebben gewerkt					x	praten over de kwestie of nanotechn als risicoklasse gezien moet worden (vanuit NL en NET werkgroep)
					x	BSI vergelijkt met de state of art: basisveiliggheid, korte termijn veiligheid in klinische studies die voor innovatieve prod altijd gedaan moeten worden					x	ook in med device wetgeving QP bevoegdheid instellen (gevolg: rem tot innoveren)
					x	argumenteren waarom wel/niet toelaten op de markt van een produkt					x	BSI adviseert bedrijven klin studies met elkaar te combineren voor zowel
					x	BSI valideert de klinische bewijsvoering en onderbouwing vd claims					x	wetgeving wordt aangepast: risicobeoordelingsmodel meer obv
					x	lange termijn effecten in de gaten houden					x	frequent contact met fabrikant en ook de subcontractors voor een beter voorbereide beoordeling
					x	in geval van vrije nanoparticles --> zelfde soort tests vereist als bij geneesmiddelen. BSI zet mensen in me meer dan gemiddeld ervaring van geneesmiddelen						
					x (bedrijven)	grote farma bedrijven investeren pas als voldoende bewijs is geleverd						
					x(overheid)	trend is dat de overheid meer toezicht wil op het op de markt brengen van innovatieve produkten						
social uncertainty					x	meer klinische studies en data nodig voor innovatieve produkten door evolutie in visie van wat veilig is (discussie = wat wil je ermee bereiken en hoe?)						
					x	evolutie in visie op acceptabele risico's: beoordelaars confronteren ontwikkelaars met hun eigen gevoel over het produkt						
					x	alles wat in het publieke domein is wordt meegenomen: literatuurstudies, conferenties, websites, kranten						
					x	meepraten in het debat zoals EC over benodigde waarborgen voor de maatschappij						
regulatory uncertainty					x (bedrijven)	BSI stelt hoge eisen bij hun beoordeling (dat wil de industrie ook)					x	overheid besteed veel aandacht praten over innovatie en bij elkaar brengen van regelgeving van med device en farma werelden; ook vanuit de farma industrie is hierover een debat geweest + vanuit de HMA
					x (bedrijven)	beoordelaars van BSI zullen niet anders kijken naar nano als andere geneesmiddelen					x	overheid: in de EC praten over toekomstige wetgeving met verschillende stakeholders
					x (bedrijven)	meer klinische studies en data nodig voor innovatieve produkten door evolutie in visie van wat veilig is					x	lobby vanuit de farma industrie naar de EC om med. Device wetgeving niet teveel weg te gooien ivm
					x	argumenteren waarom wel/niet toelaten op de markt van een produkt					x	VWS, IGZ en CBG praten veel samen
											x	praten over de kwestie of nanotechn als risicoklasse gezien moet worden (vanuit NL en NET werkgroep)
											x	ook in med device wetgeving QP bevoegdheid instellen (gevolg: rem tot innoveren)
											x	BSI geeft training aan bedrijven
all uncertainties												

MEB												
	search	activity	**select**	activity	**implement**	**activity**	**search&select**	activity	**select&implement**	activity	**all phases**	activity
economic uncertainty					x (voor bedrijven)	weet goed wat wel en niet nodig is qua studies voor approval						
technological uncertainty					x	geen toestemming geven voor klinische toepassing						
					x	richtlijnen opstellen/aanpassen						
					x	beschermingsmechanisme van het lichaam zelf mee laten wegen bij besluit						
					x	toekomstscenario's bedenken voor zover het kan. En voor handen hebben van een pakket aan onderzoeken en guidelines (indien nodig)						
					x	voor een groter deel dan nu gebeurt de fysisch-chemische eigenschappen van de nanodeeltjes beschrijven						
					x	case-by-case benadering van deeltjes door verschillend karakter en eigenschappen en NIET doordat het 'nano' is						
					x	goed op de mate van verspreiding/verdeling letten (die						
					x	mbt coating --> goed onderzoek doen door minder goede voorspelbaarheid van de eigenschappen van het gecoate						
					x	risk-benefit en kijken wat de potentiële schade is voor de patiënt						
					x	potentiële risico's opschrijven in een risk-mgt plan en in een wetenschappelijke bijsluiter						
					x	aanbevelingen doen over de veiligheid. Indien heel onzeker produkt: arts moet register bijhouden zodat snel kan worden gehandeld als zich iets vorodoet						
					x	CCMO regelt/bepaalt bennodigde testen mbt mogelijke risico's voordat het onderzoek op mensen mag worden toegepast						
					x	Denk kritisch na over de veiligheid						
social uncertainty					x	risk-benefit en kijken wat de potentiële schade is voor de patiënt						
					x	potentiële risico's opschrijven in een risk-mgt plan en in een wetenschappelijke bijsluiter						
					x	aanbevelingen doen over de veiligheid. Indien heel onzeker produkt: arts moet register bijhouden zodat snel kan worden gehandeld als zich iets voordoet						
regulatory uncertainty					x (voor bedrijven)	weet goed wat wel en niet nodig is qua studies voor approval						
all uncertainties												

CVZ												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty					x	noodzakeljkheid' als criterium voor vergoeding						
					x	kosteneffectiviteit' als criterium voor vergoeding						
					x	bezuinigen op basispakket--> meer gaan letten op 'meerkosten' die nieuwe techn oplevert						
					x	het vergoedingssysteem snel optimaliseren: toetsingssysteem zo helder en strkt mogelijk toepassen						
technological uncertainty					x	eisen dat de effectiviteit bewezen is						
					x	voorlopige/voorwaardelijke vergoeding geven (voornamelijk aan med hulpmidd door slechtere effectiviteitsstudies)						
					x	voor med hulpmidd dezelfde eisen stellen als voor						
					x	gastspreker uitgenodigd bij CVZ om informatie te geven over nanotechnologie en de stand van zaken						
					x	voorwaardelijke toelating alleen voor ziekenhuiszorg om goed gegevens te kunnen verzamelen						
					x	vertrouwen op risk-benefit afweging van het CBG en notified body						
social uncertainty					x	bij beoordeling meenemen of de technologie al in praktijk bekend is/omarmd word door artsen						
					x	uitvoerbaarheid' als criterium						
					x	praten met alle belanghebbende organisaties over o.a. ethische kwesties en als laatste stap het advies laten beoordelen door 'commissie van wijze mannen en vrouwen' met expertise op verschillende gebieden						
regulatory uncertainty					x	rekening houden met wat mogelijk is qua onderzoek voor med hulpmidd en met fabrikanten meedenken hoe voldoende onderzoek te doen						
					x	gastspreker uitgenodigd bij CVZ om informatie te geven over nanotechnologie en de stand van zaken						
all uncertainties												

VWS												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x (bedrijven)	overheid financiert grote fundamenteel onderzoeksprojecten			x (bedrijven)	instellen 'voorlopige vergoeding' voor geneesmiddelen en wordt ook gedacht voor bepaalde med hulpmiddelen					x	meer nadruk leggen op doelmatigheid vh product om vergoeding te krijgen --> bezuiniging en meer drive voor bedrijven om écht te innoveren
	x (bedrijven)	ELI ondersteunt ook meer produktgericht onderzoek (maar alleen als extra toevoeging)									x	
technological uncertainty					x	CBG beoordelingen laten doen obv gegevens en ervaring. Nanomedicine: zoveel mogelijk de zekerheden en onzekerheden te definiëren obv wetensch onderzoek					x	toepassen van algemene wet- en regelgeving
					x	gegevens verzamelen om kennis op te bouwen --> kwestie van tijd					x	regelmatig organiseren v workshops e.d. om met bedrijfsleven, wetenschap en overheid te praten over ontwikkelingen
					x	onderzoeken of de regelgeving/eisen voor veiligheidsonderzoek wel goed zijn (ook onderzoeken bij andere categorieën mensen (kinderen, ouderen, vrouwen)					x	richtlijnen of regelgeving worden aangepast op het moment dat er iets ergs gebeurt --> overheid is alert
											x	meer nadruk leggen op doelmatigheid vh product om vergoeding te krijgen --> bezuiniging en meer drive voor bedrijven om écht te innoveren
											x	invasieve medischie hulpmiddelen (nanomed) in hoogste risicoklasse plaatsen
											x	onderzoek en ontwikkelingen toestaan
social uncertainty											x	maatschappij informeren via websites en er is een brede maatschappelijke discussie geweest
regulatory uncertainty					x	instellen 'voorlopige vergoeding' voor geneesmiddelen en wordt ook gedacht voor bepaalde med hulpmiddelen					x	regelmatig organiseren v workshops e.d. om met bedrijfsleven, wetenschap en overheid te praten over ontwikkelingen
											x	richtlijnen of regelgeving worden aangepast op het moment dat er iets ergs gebeurt --> overheid is alert
											x	praten over convergentie van de regelgeving van de farma en med hulpmidd industrie.
all uncertainties												

Ministerie ELI												
	search	activity	**select**	activity	**implement**	activity	**search& select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty	x	overheid levert financiele bijdrage aan fundamenteel onderzoek			x	financiële bijdrage dmv fiscale maatregel en innovatiebox in het belastingsysteem						
technological uncertainty											x	samen met meerdere ministeries invulling geven aan kansen en risico's
											x	vertrouwen op signalen vanuit allerlei instanties (Rath, RIVM, I&M, VWS) die in een projectgroep worden gecommuniceerd --> netwerk van belang
											x	risico analyse en techn assessment in Nanonext project opnemen
											x (bedrijven)	MKB vraagbaak opgezet waar bedrijven terecht kunnen met vragen over
											x	onderzoek toestaan om kansen te benutten maar ook inzetten op de onzekerheid rondom de risico's dmv onderzoek en communicatie
											x	onderzoek toestaan om kansen te benutten maar ook inzetten op de onzekerheid rondom de risico's dmv onderzoek en communicatie
social uncertainty											x	de burger en bedrijven informeren via de website van de overheid (transparantie overeind houden) en via de klankbordgroep waarbij verschill. instanties zijn betrokken --> publiceren ook
											x	Commissie Maatschappelijke Dialoog (onafhankelijke comm) heeft veel projecten gedaan over nanotechnologie: wat weet de maatschappij en er is geprobeerd bekendheid te
											x	op de site doorverwijzen naar andere instanties en informatie op niveau van leerlingen aanbieden --> informatie toegankelijk maken voor zo breed mogelijk publiek
regulatory uncertainty											x	bij probleemsignalering veroorzaakt door nieuw beleid zoeken voor oplossingen
											x	uiteenzetting gemaakt in een brief aan de voorzitter van de tweede kamer over de stand van zaken van nanotechnologie.
all uncertainties												

IGZ												
	search	activity	**select**	activity	**implement**	activity	**search &select**	activity	**select& implement**	activity	**all phases**	activity
economic												
technological uncertainty					x	op product en toepssaingsniveau erop toezien dat aan de wet wordt voldaan						
					x (indien)	met het veld optrekken en samen bekijken wat het probleem is en hoe ieder daarin staat						
					x (indien)	de issue problematiseren binnen het departement en aankaarten bij ketenoverleg. Dus dat kan via 2 routes: de beleidsdirectie, of andere partners en met name het CBG						
social uncertainty					x	signalen worden meegenomen om adequaat met de burger te kunnen communiceren en dit mogelijk te bespreken met de beleidsafdeling. Alles wordt eerst altijd intern besproken.						
regulatory uncertainty					x	de issue problematiseren binnen het departement en aankaarten bij ketenoverleg. Dus dat kan via 2 routes: de beleidsdirectie, of andere partners en met name het CBG						
					x (indien)	goed kijken of het huidige regelgevingssysteem nog past dmv wereldwijde samenwerking. Problematiseren in Brussel, binnen lidstaten moet het worden geproblematiseerd, EC zal onderzoeken dan of de huidige regelgeving nog past.						
all uncertainties												

OMS												
	search	activity	**select**	activity	**implement**	activity	**search& select**	activity	**select& implement**	activity	**all phases**	activity
economic uncertainty					x	kosteneffectiviteit wordt door de OMS inmiddels meer meegenomen dan eerder						
technological uncertainty					x	OMS pleit voor meer/betere gegevens mbt medische effectiviteit, met name voor med hulpmiddelen (vaak geen direkt vergelijkend onderzoek)						
					x	OMS pleit bij voorlopige vergoeding dat vooraf goed wordt vastgesteld welke gegevens er uiteindelijk moeten zijn						
					x	OMS pleit voor voorlopige vergoeding in geval van techn onzekerheid						
social uncertainty					x	kosteneffectiviteit wordt door de OMS inmiddels meer meegenomen dan eerder						
					x (arts-patient relatie)	in de richtlijnen erop letten dat soms meer instructies nodig zijn voor de patient.						
					x	bij opstellen richtlijnen patientverenigingen erbij betrekken						
regulatory uncertainty					x	denken over verbetering vd besluitvormingswijze door opkomst van complexere en individuelere technologieën						
					x	beoordelen met medisch specialist of de bestaande richtlijn nog goed is of (gedeeltelijk) moet worden aangepast						
					x	OMS maakt afspraken met kwaliteitsinstituut dat eraan komt hoe gegevens centraal verzameld kunnen worden --> procedure maken						
all uncertainties												

VMDB												
	search	activity	**select**	activity	**implement**	activity	**search& select**	activity	**select& implement**	activity	**all phases**	activity
economic												
technological uncertainty											x	patientverenigingen in het buitenland en met de wetenschapp. wereld. --> op de hoogte blijven en meewerken aan onderzoek bijv enquetes
social uncertainty											x	obv investeringen doet de VMDB een project over 'zelfmanagement en dialoog'.
											x	visie dat je mee moet met ontwikkelingen in de maatschappij door toename van technologische mogelijkheden
											x	Medimate uitgenodigd voor een presentatie op een ledendag
											x	wensen vanuit patienten worden duidelijk op ledendagen, via een ledenblad waarin patiënten zelf schrijven
											x	VMDB is betrokken vij het Kenniscentrum bipolaire stoornis, waar ontwikkelingen als de litiummeter worden besproken met verschillende leden (academisch en zorg instellingen) en hoe dit zal moeten worden toegepast (hoe maakt arts overweging, wat is er vanuit de patient nodig)
											x	patient informeren via website
											x	contacten onderhouden met patientverenigingen in het buitenland en met de wetenschapp. wereld. --> op de hoogte blijven en meewerken aan onderzoek bijv enquetes
											x	mbv investeringen vanuit farma bedrijven kwalitatief onderzoek opzetten --> marktonderzoek waar zowel de farmaceut als de VMDB iets aan heeft --> VMDB kan daarmaa naar de behandelaren / VWS toe (contact met de overheid is wel moeilijker)
regulatory uncertainty												
all uncertainties												